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I, Dr. Georg Zeit, of Falkenweg 2,40764 Langenfeld / Federal Republic of Germany, being authorised by the Applicant/Nominated Person in respect of Application No 15760/92 state the following:-

The Applicant/Nominated Person has entitlement from the actual inventor(s) as follows:-

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DATED this 19 th day of August 1993

Dr. Georg Zeit

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IMPROVED RETARD SYSTEMS FOR DELAYED RELEASE OF MEDICAL AND/OR BIOLOGICAL VALUABLE SUBSTANCES FROM A DEPOT-CARRIER MATERIAL

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(57) Claim

1. A composition for preparing a sustained release formulation, which composition comprises a pharmaceutically or biologically active substance, a carrier material of at least one oligomer and/or polymer of a lower hydroxycarboxylic acid and cross-linker components prepared from olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

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(54) Title: IMPROVED RETARD SYSTEMS FOR DELAYED RELEASE OF MEDICAL AND/OR BIOLOGICAL VALUABLE SUBSTANCES FROM A DEPOT-CARRIER MATERIAL

(54) Bezeichnung: VERBESSERTE RETARD-SYSTEME FÜR DIE ZEITVERZÖGERTE FREIGABE MEDIZINISCHER UND/ODER BIOLOGISCHER WERTSTOFFE AUS EINEM DEPOT-TRÄGERMATERIAL

(57) Abstract

A first embodiment of the invention concerns the use of radically reactive crosslinking components based on olefinically unsaturated esters of low hydroxycarboxylic acids and/or their oligomers to modify depot materials, in particular retard systems, containing medical and/or biological valuable substances admixed with a carrier material, for the delayed release of the active substances. The crosslinking agents are present as polymer compounds in the application form of the retard system and may be distributed uniformly or non-uniformly in the retard system or depot material. The invention also concerns retard systems containing medical and/or biological valuable substances and based on oligomer and/or polymer compounds of low hydroxycarboxylic acids as carrier material providing delayed release of the active substances. The invention is characterized in that these retard systems or depot materials are modified with polymer compounds of olefinically unsaturated esters of low hydroxycarboxylic acids and/or their oligomers.

(57) Zusammenfassung

Gegenstand der Erfindung ist in einer ersten Ausführungsform die Verwendung von radikalisch reaktiven Vernetzerkomponenten auf Basis olefinisch ungesättigter Ester niederer Hydroxycarbonsäuren und/oder deren Oligomeren zur Modifizierung von Depot-Materialien, insbesondere Retard-Systemen, die medizinische und/oder biologische Wertstoffe in Abmischung mit einem Trägermaterial bei zeitverzögerter Wirkstoffabgabe im praktischen Einsatz enthalten. Die Vernetzer liegen dabei in der Applikationsform des Retard-Systems als Polymerverbindungen vor und können dabei in weitgehend homogener oder auch ungleichmäßiger Verteilung im zu applizierenden Retard-System beziehungsweise Depot-Material angeordnet sein. Gegenstand der Erfindung sind weiterhin medizinische und/oder biologische Wertstoffe enthaltende Retard-Systeme auf Basis von Oligomer- und/oder Polymerverbindungen niederer Hydroxycarbonsäuren als Trägermaterial mit verzögerter Wirkstofffreigabe, wobei das Kennzeichen der Erfindung darin liegt, daß diese Retard-Systeme beziehungsweise Depot-Materialien mit Polymerverbindungen aus olefinisch ungesättigten Estern niederer Hydroxycarbonsäuren und/oder deren Oligomeren modifiziert sind.

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IMPROVED RETARD SYSTEMS FOR DELAYED RELEASE OF MEDICAL AND/OR BIOLOGICAL VALUABLE SUBSTANCES FROM A DEPOT-CARRIER MATERIAL

The invention relates to a continuation in the development in the field of sustained release systems of active substances, more particularly in the area of medicinal and/or biological valuable materials from a carrier material. Combination materials of this kind are the subject matters of numerous more recent investigations and printed publications - that is in both the fields of pharmaceutical auxiliary materials and of biological preparations, for example crop protection chemicals. They are designated by terms such as retard systems, depot or slow release materials, respectively, or quite generally as mixtures of active substances providing a sustained release of the valuable materials.

Depot materials of this kind usually consist of a carrier with or without any action by its own, in which the active substance the release of which is to be sustained has been incorporated. In the literature of the most recent years particular attention has been given to polymer compounds based on polyesters of lower hydroxycarboxylic acids as carrier materials, more specifically those having from 2 to 6 carbon atoms in the hydroxycarboxylic acid molecule. Carrier materials of this kind on their part are prone to undergo hydrolysis and are subject to biological degradation mechanisms. Here the corresponding polyesters derived from glycolic acid, lactic acid and/or hydroxybutyric acid and having a comparably restricted molecular weight may be of particular importance.

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Among the more recent pertinent literature, reference may be made, for example, to U.S. Patent No. 4,011,312, which discloses solid formulations of copolyesters of glycolic acid and lactic acids having molecular weights of below 2,000 as a carrier material in admixture with antibiotically active substances such as tetracycline, neomycin and further antibiotics for the treatment of bovine mastitis at room temperature or body temperature. The preparation of lower molecular weight poly(ß-hydroxybutyrate) and the use thereof as a solid carrier material for the formulation of matrix retard tablets containing a pharmaceutically active substance has been described in "Die angewandte makromolekulare Chemie" **161** (1988), 1-8 (No. 2604). Upon the investigation of the release kinetics it has been shown in the case presented here that the amount released of the active ingredient is highly dependent on the molecular weight of the PHB fraction, the retardation in the release of the active substance being increased with the decrease in the molecular weight.

Numerous investigations deal with the use of resorbable polyesters based on glycolic acid/lactic acid as a carrier material for the sustained release of the active substance when used in combination with medicinal valuable materials, crop protection agents and the like. Reference may be made, e.g., to D. L. Wiese *et al.* in: "Drug Carriers in Medicine", Academic Press, London 1979, pp. 237-270, and to the literature quoted therein re retard forms of drugs; R.L. Kronenthal, Polym. Sci. Technol. 1975, **8** (Polym. Med. Surg.), 119-137.

The manner of the release of the active substance is affected, on the one hand, by the interaction between the active substance and the carrier material while, on the other hand, it highly depends on the structure and the properties of the usually polymeric carrier material. For example, the active substance may have been micro-encapsulated in the

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polyesters of the type mentioned, it may have been embedded in the polymer matrix, or it may be bonded to the terminal groups.

Thus, the release of the active ingredient proceeds via different mechanisms depending on the given kind of formulation. In the case of encapsulated active substances the diffusion of the active substances through micropores in the envelope plays an important role. If the active substances are dispersed or dissolved in a solid polymer matrix, the release of the active ingredients is governed by the diffusion through the matrix or by the hydrolytic erosion of the matrix or by a combination of these parameters. Nevertheless, the considerations of the usability of such a depot system include deliberations on how the concerned substance mixture is to handle. The depot material should be storage-stable under normal conditions of storage, should be sufficiently solid and, thus, dispensable in portions, should not undergo clogging during the actual conditions of manufacture, transportation and storage, should exhibit a sufficient stability to an inevitable access of moisture and the like.

In consideration of these numerous demands which are difficult to reconcile with each other, it is not amazing that to date a use of retard systems and/or depot materials based on body-resorbable polyesters of lower hydroxycarboxylic acids have not been known in practice.

It is the object of the invention to advance the development of retard systems and/or depot materials of the described type in such a way that the final product to be put into use may be optimally adapted to the respective case of application. The invention provides the elements described in detail hereinbelow for composing the depot material in a sense of a module system, which elements then will provide a degree of freedom so far unknown for configuring the combination of properties

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concretely required to be manifest in the final product in response to the respective actual profile of demands.

Subject Matter of the Invention

The invention relates to the concomitant use of free radical-reactive components based on olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof for modifying depot systems, and especially retard systems, which contain medicinal and/or biological valuable materials in admixture with a carrier material in a sustained release of the active substance(s) in practical application. Said reactive components are present as polymer compounds in the application form of the retard system and may be provided in the retard system or depot material to be applied in a largely homogeneous as well as in a non-uniform distribution.

The invention further relates to retard systems which contain medicinal and/or biological valuable materials and have been based on oligomer and/or polymer compounds of lower hydroxycarboxylic acids as carrier materials providing a sustained release of the active substance, the invention being characterized in that said retard systems and/or depot materials have been modified with polymer compounds prepared from olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof. These olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof which do form polymer compounds within the scope of the teaching of the invention will be designated, for the sake of simplicity, also as "cross-linkers" or "cross-linker components" within this description of the invention.

Accordingly, there is provided according to a first embodiment of the invention a composition for preparing a sustained release formulation, which composition comprises a pharmaceutically or biologically active substance, a carrier material of at least one oligomer and/or polymer of a lower hydroxycarboxylic acid and cross-linker components prepared from olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

According to a second embodiment of the invention there is provided a sustained release formulation prepared from the composition of the first embodiment.

According to a third embodiment of the invention there is provided a method of preparing a composition used in a sustained release formulation, which method comprises reacting cross-linker components which are reactive via free radicals, said components based on olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

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Details of the invention

In the following, the system of the teaching according to the invention will be described by means of carrier/valuables mixtures which are designed to be used with humans and/or animals and contain antibiotically active substances - and more particularly so-called broad-spectrum antibiotics - in a carrier material which has been derived from lower hydroxy-carboxylic acids - especially from lactic and/or glycolic acids - and is resorbable by the body. The combination material which is described in detail by way of example hereinbelow is rendered tissue-compatible so that its incorporation in a living body will be possible. Said material is of particular importance as a retard system which releases an antibiotic with some retardation and sustains said release for a sufficiently long period upon implantation of the multi-component material described according to the invention into human or animal living tissue. Thus, this retard material within the scope of the invention is suitable for wound disinfection upon surgery as an auxiliary material which is resorbable by the body. Thus, this material is capable of replacing all of the non-resorbable auxiliary means as conventional to date which, for example, ensure a sustained antibiotics release from solids inserted in the surgery region, but which in turn will have to be removed from the human or animal body.

The illustration of the invention by way of the concrete example as decribed here does not imply any restriction of the teaching according to the invention towards this definite direction. By way of said example there are rather explained only the combinatory elements of acting according to the invention which, to the effect, are applicable to other fields of application in the same manner. Thus, more particularly, within the scope of the invention, there may be given any option with respect to the valuables to be released. For

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example, important further valuable materials for implantation in the living organism include cytostatics, hormones, insulin, cortisone and the like. Adjustably high local concentrations of the active ingredient are attainable over an extended period of time with a simultaneous reduction in the total stress on the organism by embedding the respective depot material(s) in the region concerned by the disease or in any other freely chosen region.

The area of application of the retard systems according to the invention in the medical and/or veterinary field, however, is not limited to valuables-containing substance mixtures for a direct implantation into living tissue: The invention likewise includes valuables-containing admixtures that are suitable for any topical administration to human or animal. The term "topical administration" is intended to comprise the application of valuable materials to mucosa regions as well as the so-called transdermal administration of valuable materials by applying the pertinent preparation to selected areas of the outer skin. In all of these cases the substance mixtures of the kind according to the invention are distinguished by the possibility of that the retarded release of valuable is adjustable. This, for example, allows the successful application of valuable materials to the living organism over a pre-determinable period of time at delivery concentrations which are also to a large degree freely pre-determinable. In any particular case it will be necessary, of course, to examine and determine the interactions between the structural elements of the retard system within the scope of the teaching according to the invention and the valuables to be released therefrom, as well as the interaction between the living body and the retard system at the site of application thereof. Nevertheless, the great freedom in the selection of the structural elements in composing the retard systems defined according to the invention in cooperation with the comparably great freedom in combining

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said structural elements provides new possibilites for the time-controlled release and application of virtually any optional valuable material.

More particularly, the teaching of the invention is suitable for improvements in the field of the so-called bioadhesive preparations of active ingredients. These are known to be systems which exhibit an increased adhesive strength due to an interaction of functional groups or functional regions, respectively, on the surface of the administered active substance mixture with mucosa regions of the body with the participation of body liquid and, thus, for example, possess an extended residence time in the gastrointestinal tract. As to the term of "bioadhesive preparations of substances", there is referred to, e.g., Herve Tournier *et al.*, "New Bioadhesive Polymers for Topic Mucosal Dosage Forms", Proceed. Intern. Symp. Control. Rel. Bioact. Mater. **15** (1988), Controlled Release Society, Inc., No. 237, pp. 418/419, and the literature quoted therein.

The teaching of the invention comprises a variety of concrete substance mixtures, depending on the concrete realization of the retard system and the adjustment thereof to the parenteral, enteral or other topical application. All of these different substance mixtures, however, are governed by the uniform principles of the invention as discussed in detail hereinbelow.

<u>The carrier material for the sustained release of the active substance(s)</u>

The preferred carrier materials within the scope of the teaching according to the invention are to be defined as oligomer and/or polymer compounds of hydroxycarboxylic acids having from 2 to 6 carbon atoms, among which the corresponding hydroxycarboxylic acids having from 2 to 4 carbon atoms are of particular importance. The respective compounds of glycolic

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acid and/or lactic acid are compounds of the kind concerned here, which are not only readily accessible on a commercial scale; the selection and mutual adjustment of these components play an important role, due to the different stabilities thereof to hydrolytic influence. The term of the lactic acid derivatives includes the respective components of any steric configuration, i.e. D-, L- and/or DL-forms including the racemates. The period of the decomposition of the polymer compound under the hydrolytic action of metabolic sources is determined in a *per se* known manner by appropriately selecting the polyester-forming molecular module(s). Thus, polyglycolic acid is known to be decomposed by hydrolytic degradation within a few days, whereas the decomposition time of poly-DL-lactide may be within the range of from weeks up to some months.

In recent pertinent publications, accordingly, for polymer materials of the kind as concerned here crucial importance is attached to an adjustment of pre-determined degrees of polymerization which, if possible, are uniform. Reference may be made, for example, to EP-A1-0 244 114 and to EP-A2-0 299 730. Here it is attempted to put up with the multiform requirement profile of the depot material by the choice and adjustment of selected parameters of the polyester-based carrier material.

The teaching according to the invention, by way of the concomitant use of the above-defined cross-linker components - which will still be described in detail hereinbelow - as an integral constituent of the depot material, allows a largely free variation of the carrier concerned here which has been derived from lower hydroxycarboxylic acids, especially lactic and/or glycolic acids. More specifically, when the bulk component of the carrier substance is to be selected, the teaching according to the invention, allows said bulk component to be determined such as to effect an optimization of the sustained release of valuables under the respective conditions of appli-

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cation. Further elements of the requirement profile of the depot material as demanded altogether are generated or satisfied, respectively, in a manner still to be described by the cross-linker components as concomitantly used.

Thus, suitable carrier materials for the teaching of the invention quite generally are oligomers and/or polymers of lower hydroxycarboxylic acids having a tough-viscous to solid consistency at room temperature. More particularly, oligoesters having average molecular weights within the range of from about 200 to 5,000 may be suitable, wherein preferred oligoester materials have average molecular weights within the range of from about 300 to 2,000.

In the course of the work which the invention has been based on it has surprisingly been shown that, in combination with antibiotics, release rates convenient in practice of the active substances can be achieved, when the bulk mass of the carrier substance is composed such as to have been based on so-called bone waxes like those described in the printed publications DE 32 29 540, DE 37 16 302 and DE 38 25 211, the disclosures of which printed publications re the nature of the tough-viscous to solid waxy polyester oligomers are incorporated by reference in the present disclosure in the context of developing the carrier material providing a sustained release of the active substance.

DE 32 29 540 describes resorbable waxes for mechanically stopping of the blood on endogenous hard tissue from said lower hydroxycarboxylic acids, more particularly the glycolic acid and/or the lactic acid. These waxes, due to their structures, are degradable by endogenous metabolic mechanisms, where the rate of degradation is controllable in a *per se* known manner. Oligomers of glycolic acid are decomposed faster than those of lactic acid by the endogenous metabolism. The preferred waxes

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exhibit average molecular weights within the range of from about 200 to 1,500, and more specifically within the range of from about 300 to 1,000.

For controlling the average molecular weight of said polyester oligomers it is proposed to concomitantly use monofunctional and/or polyfunctional alcohols or carboxylic acids. Then an average molecular weight can be pre-determined in a *per se* known manner by choosing suitable mixing ratios of the oxycarboxylic acid and the additional monofunctional and/or polyfunctional component(s). The resulting reaction products still contain some amounts of the starting components employed.

DE 37 16 307 describes the advanced optimization of these waxy polyesters. Here, it has been described, more particularly, that quite a definite trifunctional alcohol, viz. glycerol, is employed for adjusting the average molecular weight. The combination of glycerol with oligoesters of lactic acid and/or of glycolic acid results in degradable wax-like components of the type mentioned, which when implanted into tissue of the living body are distinguished by a well pronounced compatibility with the body. In order to exclude any undesirable tissue damage, a purification of the degradable wax may be provided to remove unreacted carboxyl groups.

The body-resorbable tough-viscous to solid waxes of the DE 38 25 211 which have been based on oligomers of glycolic acid and/or lactic acid, eventually, are distinguished by a content of body-compatible salts of organic and/or inorganic acids, which salts have been formed by the reaction until completion of the free carboxyl groups possibly present in the oligomer wax and/or have been incorporated in the wax in a homogeneous distribution as added salts. Particularly suitable as admixed components are, more particularly, alkali metal, alkaline earth metal and/or aluminum salts, among which the

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salts of sodium, calcium and/or magnesium are of particular importance.

In a preferred embodiment of the invention, oligomeric waxes of the range of comparably low molecular weights are employed as the carrier materials. Waxes of this kind exclusively based on glycolic acid as the lower hydroxycarboxylic acid undergo a rapid decomposition so that only a comparably low period of the sustained release of the valuables can be assured. This may be deliberately utilized within the scope of the module principle according to the invention under some partial aspect: The incorporation in the retard system of such proportions of glycolic acid-based wax results in releases of valuables in controllable amounts in the initial phase of the period of action. Thus, in surgical practice it may be desirable to assure a local availability of a comparably high cocentration of antibiotics. The addition of adequate amounts of some rapidly decomposing glycolic acid wax filled with the pre-determined antibiotic would satisfy this need.

Then, however, a glycolic acid-based wax is no longer suitable for the release of an antibiotically active substance over an extended period of time - for example over the subsequent period of from two to four weeks - . Applicants' investigations have shown that quite especially here lactic acid waxes having comparably low molecular weights are distinguished by providing the required profile of valuable-release. Thus, lactic acid oligomers having average degrees of oligomerization of from about 6 to 20 lactic acid units per molecule, and especially those comprising from about 8 to 15 lactic acid units per molecule, are particularly suitable for assuring a local uniform release of antibiotics for the period of from about 1 to 4 weeks after implantation into living tissue. For this application, appropriate lactic acid waxes can be prepared in a particularly simple manner by the

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concomitant use of, especially polyfunctional, alcohols within the scope of Applicants' cited German protective rights. Thus, the glycerol esters of lactic acid having an average of from 3 to 5 lactic acid units per oligoester moiety, which are especially mild to the body, can be used with particular advantage. As to a use of ethyleneglycol, the indications relating to the average molecular weights of the oligolactic acid moieties are to the effect applicable.

Investigations on the degradation behavior of oligoesters of the kind described here revealed that the respective lactic acid-based glycerol waxes may possess considerable resistance to the hydrolytic degradation so that the absorption thereof in the living organism may take substantially more time than the sustained release period of the pharmacologic valuable material. This fact is irrelevant to the usability of this carrier material within the objective according to the invention. If in an individual case this retarded degradation of the carrier material based on lactic acid/glycerol is considered to be detrimental, then opposite controls may be used by means of further determinative elements of the invention which are constituted, more specifically, by a binary mixture of glycolic acid-based and lactic acid-based proportions of wax and which will still be described hereinbelow.

The comparably low molecular weight waxes of the kind described here, and more particularly those lactic acid-based waxes, however, fail to comply with important further requirements of the quality of such a depot material in as far as, more specifically, questions of handling, non-tackiness, storage stability and the like are concerned. This drawback inherent to said waxes is insignificant to the teaching according to the invention in its entirety. It will be compensated by the concomitant use of the previously defined cross-linker components in the way still to be explained hereinbelow.

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The contemplations set forth with respect to the selection and nature of certain preferred carrier materials for the immediate implantation into living tissue may be applicable also to listing retard systems for the enteral and/or other topical application. However, here the respective ranges of possible suitable representatives of the carrier material within the scope of the invention are reasonably enlarged. This may be illustrated by way of the following example: Upon an oral application, the presence of free carboxyl groups in the carrier material is not only tolerable; for the mechanism of the bioadhesion, the interaction of the mucosal areas with functional carboxyl groups on the surface of the administered multicomponent mixture rather is a known and important mechanism leading to a sustained bonding of the applied multicomponent mixture to the respective mucosal areas. Thus, carboxymethyl cellulose and/or polymer or copolymer compounds of acrylic acid and/or meth. rylic acid having free carboxyl groups are important known polymeric carriers for bioadhesive preparations of active substances of the kind as concerned here.

According to the invention, by way of appropriately designing the carrier material, this known mechanism for the mucosal interaction can be complied with by using monovalent and/or preferably polyvalent carboxylic acids for the regulation of the average degree of oligomerization of the hydroxycarboxylic acid esters. Then, the resulting oligomer molecule is characterized by the presence of terminal carboxyl groups which upon the application in the finished product may enter into the bioadhesive interaction with the mucosal areas. Here, physiologically acceptable representatives are especially suitable as the molecular weight-controlling carboxylic acid, among which the so-called edible acids are to be mentioned as example which are known to include the range of mono- and polyvalent carboxylic acids.

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Then, as to the question of the stability to hydrolytic degradation, the deliberations set forth above in the context of the selection of the defined hydroxycarboxylic acids for synthesizing the oligomeric carrier materials are to the effect applicable in the same manner.

The cross-linker components employed according to the invention

The components of active ingredients described as cross-linker components in the following are free radical-reactive components which preferably are polyfunctional and can be reacted via olefinic double bonds to form polymer compounds. In the ready-to-use depot material the reactive cross-linkers have been converted into the corresponding polymer compounds by polymerization and/or cross-linking and, in these forms, determine important material properties of the depot material. They have particular importance *inter alia* for the sufficient consolidation of the total composition which contains the carrier materials based on tough-viscous to waxlike oligomer compounds as the major component. Surprisingly it has been shown that soft waxes may be turned into sufficiently solid, non-tacky or even tack-free materials by already comparably low amounts of such reactive constituents. More specifically, an *in situ* curing of the reactive cross-linker components in admixture with the respectively selected wax-based carrier material will lead to combination materials which possess the whole spectrum of the demanded application-technological properties. Also here the modular working principle of the invention includes a plurality of concrete embodiments of the final product which will still be discussed hereinbelow.

The reactive cross-linkers provided according to the invention and/or the polymer compounds formed thereof by way of reaction are based on olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof. In this

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manner also here the degradation of the implanted polymer compounds and the resorption of also this material component can be assured.

Suitable for the use as cross-linker components, more particularly, are polyfunctional components of the reported kind which comprise more than one functional olefinic group in the molecule. Especially suitable are di- to tetrafunctional olefinically reactive hydroxycarboxylic acid derivatives which should be comprised of at least a substantial proportion of the cross-linker components.

Preferred cross-linkers within the teaching according to the invention are esters and/or oligoesters of lower polyfunctional alcohols or carboxylic acids with lactic acid and/or glycolic acid, which in addition have terminal olefinically unsaturated groups. Here again particularly suitable are cross-linker components derived from lower di- to tetrahydric alcohols, and more specifically from ethyleneglycol and/or glycerol, which have been olefinically substituted in the terminal positions with acrylic acid and/or methacrylic acid moieties - designated as (meth)acrylic acid moieties within this description of the invention.

Reactive components of the kind mentioned here have been described in detail, for example, in DE-A1 32 04 504 and DE-A1 32 29 635. In these references, more specifically, there have been provided (meth)acrylate compounds having terminal (meth)acrylic acid moieties on an oligomer chain of hydroxycarboxylic acids, said compounds being slow-evaporating and liquid to solid at room temperature, wherein the polyester oligomers have an average molecular weight within the range of from 200 to 600. The polyfunctional (meth)acrylic acid esters of this kind are intended to be used as surgical binder systems for bonding endogenous hard tissue, if desired together with

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plastics and/or metal. Compounds of this kind are a suitable example for cross-linkers within the scope of activities according to the invention.

However, reactive cross-linker components are not limited to (meth)acrylic acid esters of the described kind. The introduction of reactive olefinic groups into an ester molecule concerned according to the invention may be effected in any optional *per se* known manner. Reference may be made here only by way of example to the known introduction of terminal olefinic groups into basic structures containing carboxyl groups. Then, to the effect, the same considerations are applicable as those already set forth in the context of those carrier materials which in one preferred embodiment are oligomers terminated with hydroxyl groups, while they have been formed as corresponding carboxyl group-terminated compounds for certain intended uses - for example for bioadhesive materials - . One class of cross-linker components which are especially important for use in the living human and animal organism is constituted by the reaction products of glycerol esters of lactic acid and/or oligo-lactic acids modified with terminal (meth)acrylic acid moieties. Here, in addition to or in the place of lactic acid, also glycolic acid moieties may have been incorporated in the cross-linker molecule. In a preferred embodiment, these cross-linkers, as a random average, contain at least two olefinically unsaturated terminal groups, among which cross-linker components which have been completely reacted with (meth)acrylic acid and/or the reactive derivatives thereof are a particularly interesting class of cross-linker components within the teaching according to the invention. These cross-linkers comprising, as a random average, from 2 to 3 olefinic terminal groups per one mole of glycerol, in one important embodiment may contain from 3 to 12 moles of lactic acid moieties, and especially from 3 to 6 moles of lactic acid

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moieties, as a random average per one mole of glycerol. Reactive glycerol derivatives having a molar ratio of glycerol/lactic acid/(meth)acrylic acid of about 1/4/3 are highly effective cross-linker components, which when admixed in an amount of, for example, from 1 to 5% by weight - relative to the weight of the non-reactive carrier material - are capable of reshaping a tough-viscous or soft waxy carrier in its physical nature so that it satisfies the requirements according to the invention.

The following deliberations, more particularly, are relevant to retard systems to be implanted into the living body: Here the teaching according to the invention intends to provide material mixtures which with respect to all components thereof have been optimized to body compatibility. This deliberation may be especially important with respect to the cross-linker components.

The cross-linkers are systems susceptible to undergo a reaction via free radicals. Such systems, in order to safely exclude an undesirable premature reaction, require the concomitant use of radical inhibitors. More particularly, such radical inhibitors are also needed already in the preparation of the free radical-reactive systems - i.e., e.g., the polyfunctional (meth)acrylate esters. It is just the high gelling tendency of the polyfunctional (meth)acrylic acid esters of the kind involved here that demands the use of highly efficient inhibitors already in the production process. In accordance with one essential feature of the invention the concomitantly used cross-linker components are free from inhibitors which as to kind and/or amount are undesirable and would be left from the production, storage and/or processing of the polyfunctional components.

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One particularly important example for a suitable inhibitor within the activities according to the invention is constituted by tocopherol compounds and, among these, more specifically, α-tocopherol and, thus, vitamin E.

The use of physiologically compatible tocopherol compounds, and more specifically of vitamin E, as application inhibitor, but optionally also already as a preparation inhibitor, in connection with polyfunctional (meth)acrylic acid compounds is in detail the subject matter of Applicants' older application DE 39 39 161, the disclosure of which older protective right is hereby incorporated by reference in the disclosure of this invention.

Within the scope of the teaching according to the invention, relevant to the cross-linker components may be also that part of the disclosure of the quoted older application DE 39 39 161 which describes the use of olefinically reactive (meth)acrylic acid esters which are free from solvents, and more specifically of residual amounts of solvents left from the production. Accordingly, also according to the invention in the preferred embodiment, in the preparation of the cross-linker components there is *a priori* used no solvent, more specifically no physiologically questionable solvent. In this context reference is made at the same time to the disclosures of Applicants' printed publications DE-A1 38 43 854, 38 43 938, 38 43 930 and 38 43 843.

The mixing ratios between the carrier material, on the one hand, and the cross-linker components and/or the polymer components formed by the reaction thereof, on the other hand, may vary within wide limits. They are in detail governed by a plurality of parameters, among which the following may be mentioned in particular: Nature of the carrier material, especially its physical nature at room temperature and at the

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application temperature, profile of requirements set for the quality and nature of the depot material upon storage and application, reactivity and individual nature of the cross-linker components and/or of the polymer components formed by the reaction thereof, as well as the profile of requirements set for the final material in view of the intended use. More particularly, as to the last item it will be readily conspicuous that materials to be implanted into a living organism to release pharmaceutical compositions will have to meet requirements different from those set for a depot material to be used for the sustained release of biologically active substances, for example, in the agricultural sector. As far as the mixing ratios are concerned of the non-reactive carrier material, on the one hand, and the reactive carrier components, on the other hand, in general there will be applicable that the cross-linker components will comprise not more than half of the entire system. In a preferred embodiment distinctly lower amounts of cross-linker components will be used. More specifically, the modifying and at least partially reacted cross-linker components may be present in the mixture in proportions of from about 0.5 to 40% by weight, and preferably in proportions of from about 1 to 10% by weight - % by weight here relative to the sum of carrier material and cross-linker components. For a use of the retard systems according to the invention in the medicinal sector, and especially for the implantation into the living tissue, proportions of the cross-linker components of at most about 10% by weight may be preferred. As has already been mentioned, here good results are obtained with mixing ratios of up to 5% by weight, and especially by using mixtures containing from about 2 to 5% by weight of cross-linker components. This is more particularly applicable to the use of compounds exhibiting a comparably high cross-linking activity, for example those of the kind of the three-functional (meth)acrylic acid esters of the hydroxyl-terminated glycerol/lactic acid esters or oligoesters.

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The various embodiments of the retard systems

It is difficult to safely predict the release behavior of retard systems - which fact has already been adverted to in the introduction - because a variety interaction parameters will affect the ultimate activity of the system. It is a particular advantage of the teaching according to the invention that it provides the chance to effect an optimization towards the profile of requirements set for the individual case by means of varying the concrete embodiment of the system. This will be understood from the following contemplations:

The major portion or at least an essential portion of the depot material is usually comprised of the carrier material as described hereinbefore. The time-control of the release mechanism can be influenced by means of the selection of the components forming the oligomer and/or polymer components and the release characteristics dependent thereon. This is applicable already to uniform types of compounds definitely selected and composed with respect to the constitution thereof. A further modification ensues from the use of carrier materials having an at least binary composition combining different wax or resin types. For example, here oligomer and/or polymer compounds adapted to undergo a comparably fast degradation, on the one hand, are used in combination with compounds, on the other hand, that are subject to a slower degradation. A further option of exerting influence is provided by the definite manner of how to mix such different components of the carrier material. It covers the whole range from homogeneous mixtures through types of mixtures which combine delimited sectors of a material having a pre-selected definite composition with corresponding sectors of a material having a different composition and, hence, a different degradation behavior. The form presented here, for example, may control a porosity being formed in practical use, i.e. the permeability of a block comprising

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carrier material composition to a permeation of body liquid and/or permeation of cell growth. Eventually, also a layer-like arrangement of the various components of the carrier material may be taken into consideration to form a primarily continuous material block which in practical use would comply with definite characteristic requirements, due to the different degradation rates of the individual layered blocks.

The modifications outlined here which are due to the respective modification of the carrier material are substantially extended by the concomitant use according to the invention of the cross-linker components. Applicable are, to the effect, the indications given above also to the substance mixtures composed of carrier material and cross-linker components. Thus, in one embodiment carrier material and cross-linker components - together with the valuable materials - may be present as a largely homogeneous mixture. Nevertheless it is also possible that the cross-linker components and/or the polymer compounds resulting therefrom are present, for example, in a layerwise arrangement in the retard system so that, at least to a large extent, regions free from cross-linkers of the valuable-carrier mixture are interspersed and/or enclosed by regions occupied by material comprising reacted cross-linker components. Cross-linker components need not be combined with all of the carrier materials. Thus, for example, as release-retarding carriers there may be especially suitable those types of lactic acid oligomers which are in a tough-viscous state at room and/or application temperature and are interspersed with cross-linker components within the scope of the invention and are fixed such as to be dimensionally stable, for example for the reason of improved handling. Combination materials of this kind may then be mixed with further carrier materials - for example those based on types of polymers having higher molecular weights or the glycolic acid oligomers and/or polymers which anyway are obtained in the solid state.

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The possibilities as enumerated here elucidate the following: Due to the cross-linker components and the possibility provided thereby of influencing the nature of the material of those regions of the depot material which are determined by the cross-linker components and/or the polymer compounds produced thereby, it is possible for the first time, more particularly, to put into the intended use that region of comparably low molecular weight carrier materials of the type here concerned of hydroxycarboxylic acid oligomers; in many cases it is just these carrier materials having comparably low molecular weights which in many cases exhibit the desirable retarded release characteristics. Hindrances to the regenerative cell growth can be reliably excluded by that the individual regions of the respective carrier materials - for example those based on lactic acid - are kept small. The depot material stabilized according to the invention may be introduced as a finely granular matter or even as a powder into the tissue regions concerned, or it may be employed in topical application forms; however, it is as well possible to fix larger three-dimensional forms, for example in the shape of plates, rods, spheres or in any other optional three-dimensional form in the living tissue and, due to the concrete decay characteristics of such an enlarged volume unit in the living organism, with certainty to exclude undesirable delays of the regenerating cell growth.

Curing of the cross-linker components

In conjunction with just the contemplations as discussed last re the possible variety of the depot materials to be designed according to the invention, it will be intelligible that there is also a multiplicity of possible approaches for converting the cross-linker components defined according to the invention into their polymer compounds. Thereby it is possible to realize an adaption to the particular circumstances and to reliably attain the main object of providing a depot material

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which in practical use makes the valuable materials available in intact conditions.

Investigations conducted by Applicants have shown that in an obviously broad range of concrete carrier/valuables mixtures it is possible to admix cross-linker components to form a homogeneous mixture and to allow an *in situ* reaction without thereby inducing a substantial damage or deterioration to the valuable material. In this simplest embodiment of the materials according to the invention the modifying polymer compounds have then been prepared *in situ* from the radical-reactive cross-linker components in admixture with at least one portion of the depot material based on carrier/valuable material. Thus, mixtures of active materials of glycerol/lactic acid-based oligomers as carrier material and aminoglycoside antibiotics may be prepared by melting the carrier material at comparably low temperatures and suitably introducing the valuables to form a homogeneous mixture. For example, temperatures of below or at least within the range of about 70 °C are in fact sufficient for melting said carrier materials. Within the same temperature range, low amounts, for example from 1 to 5%, and especially from 2 to 4% by weight, of cross-linker components based on glycerol/lactic acid/(meth)acrylic acid can be admixed to form a homogeneous mixture. The *in situ* cross-linking of the cross-linker components is successfully accomplished by means of a free radical-initiated reaction, whereby the corresponding polymer compounds are formed which then are crucially involved in determining the ultimate phenotype of the depot material designed to release pharmaceutical compositions. For example, shaped articles may be produced which are largely tack-free in the dry state and may be subjected to further comminution, if so desired.

If it appears that there may be some danger of interactions to take place between the particular valuable material

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and the cross-linker components employed according to the invention that would cause the characteristic of the valuable material to be impaired, then the principle according to the invention nevertheless may be applied without efforts: In such a case, the carrier/valuables mixtures are converted into some predetermined particulate form and then provided with an envelope containing cross-linker components within the scope of definition according to the invention. Here again mixtures of carrier material and cross-linker components can be employed which, however, now are free from valuables within the envelope region. The carrier material used in this case may be the same as or different from the carrier material used in the interior region for the valuable to be released. In the subsequent curing step there cannot take place any substantial interaction of the cross-linker components with the valuable material embedded in the core. The two embodiments presented here are just to be understood as examples. They may be employed separately from each other or also in combination with each other, with further concrete embodiments being derivable for the concrete design of a particular depot material, to the effect, from the numerous possible combinations as described hereinabove.

In one preferred embodiment for the teaching according to the invention the initiation of the reaction can be performed under conditions which exclude any physiologically undesirable components from being introduced into the ultimate product. Hereto, reference is made to the indications set forth in the Applicants' older German Patent Application P 40 37 516, the pertinent disclosure is hereby incorporated by reference in the disclosure of the present invention.

In said older Application P 40 37 516 there have been described degradable high-strength materials and shaped articles for the implantation into human and animal organisms,

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which materials have been composed of cured (meth)acrylic acid esters of polyfunctionally hydroxy-terminated oligomers of lower hydroxycarboxylic acids. They are characterized in that, *inter alia*, they are substantially free from reaction aids and/or other additives resulting from the production (contaminants of the active substances) which are undesirable with respect to kind and/or amount, since here, more particularly within the production procedure, there has been effected an adjustment - with respect to kind and amount - between the inhibitors of the polyfunctional (meth)acrylic acid esters and the initiators and/or starter systems, respectively, as optionally used for cross-linking same. Curing is to be effected either by radiation curing - especially using UV radiation - or by using starter systems which have substantially been based on body-compatible components or have at least been restricted as to kind and amount so that the residual matter released upon the degradation does not give rise to any physiological problems.

Within the scope of radiation curing there may also be taken into consideration, in addition to curing by UV light as already mentioned, the use of any other reaction-inducing types of radiation, among which, for example, laser beams, X-ray or γ-rays may be mentioned. Any concomitant use of *per se* known initiators is possible; in this context, reference is made, for example, to the printed published indications in Encyl. Polym. Sci. and Eng. (2nd edition), Volume **11**, 187-207, and pertinent commercial products, available, e.g., from the companies Merck, Darmstadt (DE), and Ciba-Geigy (Switzerland).

According to the invention, what is especially possible is also curing the reactive material in a *per se* known manner by a chemically induced free radical-initiated polymerization. If here known auxiliary agents are intended to be employed, the following may serve to facilitate the selection of reaction

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aids: In prior art there is known a multiplicity of redox systems based on peroxidic compounds which are used in combination with reducing agents and/or metal compounds of such metals that may occur in several valency states. In this context reference is made, for example, to the survey presented in PROGRESS IN POLYMER SCIENCE, Vol. 8, Pergamon Press, Oxford-New York, 1982, pp. 61-131, and the voluminous primary literature referred to therein.

In the selection of suitable redox systems which do not give rise to any substantial physiological doubts with respect to kind and amount of the residual materials remaining in the reacted material, the following state of facts is particularly beneficial for the activities within the scope of the invention. Reactant systems which physiologically are comparably safe, have been described in prior art especially in connection with aqueous polymerization systems. The material to be cross-linked according to the invention is *per se* an anhydrous system. However, due to its oligomeric structure derived from lower hydroxycarboxylic acids, the solubility ratio is frequently assured within the scope of the invention also for those compounds which are otherwise employed in the aqueous systems. Thus, it will be possible to accomplish a really homogeneous distribution of physiologically largely acceptable activator systems also in the anhydrous reaction phase of the polyfunctional (meth)acrylic acid esters or of the admixtures thereof with the carrier materials, so that then cross-linking can be effected at the pre-determined temperatures.

It is only by way of example that from the broad class of suitable components for such redox systems the following may ne mentioned here: Peroxide compounds such as peracids, diacyl peroxides, hydroperoxides and the like, among which physiologically compatible acids, for example so-called edible acids, may be of particular importance as the peroxide-forming constitu-

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ent. From the broad class of the activators or reducing agents, compounds offering themselves are compounds such as ascorbic acids, sorbose, fructose, dextrose or other sugars, all of which throughout are physiologically acceptable components.

Metal compounds which are suitable for stimulating and/or activating the redox system are derived, more specifically, from iron which in a *per se* known manner may be added to the redox systems in the form of di- and/or trivalent iron. The successful formation of a homogeneous iron-containing mixture is especially safely effected, for example, by using the corresponding salts of glycolic acid and/or of lactic acid.

As has already been reported and will also be conspicuous, the variety of possible embodiments for the retard systems within the scope of the invention ensures an almost unlimited applicabilty of the carrier/cross-linker system to the broad range of interesting valuable materials of medicinal and generally biological activity. Not only the active substances themselves, but also the application forms thereof can be varied within wide limits. It is only by way of an example that this again may be illustrated by mixtures containing valuable materials which exhibit antibiotic action: The depot material designed to release pharmaceutical compositions, for example, may be placed into the tissue regions susceptible to become infected - for example laid thereinto - and then enclosed. However, on the other hand it is also possible to apply the depot material onto open wound areas, for example wounds caused by burns or the like, and then to leave it thereon and/or to remove it at least partially and to replace it by new pharmaceutical depot material in the course of a dressing change.

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The concentrations of the valuable materials in the pharmacological depot material may vary within wide limits. The dominant idea for the substance mixtures important in practice is the adjustment of the desired time-retarded release of the active substance. The valuable material will in general not amount to more than 40 to 45% by weight of the retard system in its entirety. For the important sector of medicinal valuables to be applied to the human and to the animal body, valuables concentrations of from about 20 to 25% by weight and preferably of from about 10 to 15% by weight will rarely be exceeded. Highly active valuables, such as the antibiotically active substances, cytostatics, hormones and the like will generally be used in amounts of from about 0.1 to 10% by weight, and especially in amounts of from about 1 to 8% by weight, in the pharmaceutic release materials.

The valuable materials in general will be charged in an intimate admixture with at least a portion of the carrier material employed, in order to achieve an optimum control of the release of the valuable material. Moreover, the considerations set forth above are applicable as relating to the possible inhomogeneous distribution of the active material in the particular unit of the retard system. The application forms of these retard systems within the teaching according to the invention range from a powdery nature to three-dimensional bodies shaped *ad libitum*. The amount of the retard systems applied which quantitatively is readily detectable and the predetermined amount of the valuable, relative to unit volume or weight of said retard system, allow the quantified administration of the valuable materials present in the depot material.

The utilization of the teaching according to the invention in connection with administration forms less critical than that of a direct implantation into the living tissue allows the con-

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comitant use of conventional galenic auxiliary materials and/or the formulation of the retard systems according to the invention into administration forms as common in practice. This may be illustrated again by way of an example as follows: Pharmaceutic depot materials produced according to the invention as finely divided particulates may have been formulated into tablets, suppositories, ointments and the like and, when in such form, may be introduced into the body or applied onto the body surface. Said galenic auxiliary materials in turn may contain non-retarded portions of pharmaceutics which will display immediate activity upon the introduction or application, which will subsequently be followed by the time-retarded period of action of the retarded release of the active substance.

In other cases, *per se* known auxiliary materials can be included in the use, thereby in a controlled manner to provide or enhance effects which are also characteristic of the substance properties concretely adjusted within the scope of the invention. This may be exemplified by way of preparations of bioadhesive valuable materials: The covalent bond from the surface of the multi-substance mixture within the scope of the teaching according to the invention to the surface of the mucosa and, hence, the effect of the bioadhesion, is directly caused by functional groups (carboxyl groups and/or hydroxyl groups) within the carrier material according to the invention. This effect may be further enhanced by concomitantly using known mucosa-adhesive materials as fillers in the multi-substance mixture. Suitable materials that have been well-proven in practice are, for example, in addition to carboxymethyl celluloses and (meth)acrylic acid polymers and/or copolymers, respectively, alginates, hydroxyalkylcelluloses, gelatin, pectins, polyvinylpyrrolidone, solid polyethyleneglycols and the like. In this respect, there may be referred, for example, to the following additional references from the

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literature: J.D. Smart *et al.*, "An in-vitro investigation of mucosa-adhesive materials for use in controlled drug delivery", J. Pharm. Pharmacol. 1984, **36**, 295-299; as well as Kinam Park *et al.*, "Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion", International Journal of Pharmaceutics **19** (1984), 102-127.

The proportions of amounts of such concomitantly used auxiliary materials may vary within wide ranges and, in the concrete galenic embodiment, may also comprise a multiple of the substance mixtures within the scope of the definition according to the invention. Then, however, what always is essential for such preparations is that a non-insignificant section of the activity in practical use is governed by the substance combination defined according to the invention.

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E X A M P L E S

Example 1

1. Preparation and description of the resorbable waxes

a. Waxes, produced from glycolic acid/glycerol

General procedure for preparing the reaction products of glycolic acid with glycerol

A three-neck flask equipped with stirrer, Claisen head and condenser ("distillation bridge") is charged with glycolic acid and glycerol. The mixture is completely put under an inert nitrogen gas atmosphere and heated at 150 °C, and the reaction is continued for 3 to 5 hours until no further water of reaction is eliminated. Then the flask is cautiously evacuated at 150 °C to 10 torr. After two more hours at these reaction conditions, the mixture is cooled to 100 °C and brought to atmospheric pressure, is neutralized as described above, and the product is dispensed while hot.

The compositions of the batches and the properties of the oligomers are shown in Table 1.

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Table 1

Oligohydroxycarboxylic acids from glycolic acid and glycerol

Example	A	B
Starting materials:		
Glycolic acid (moles)	8	9
Glycerol (moles)	1	1
Yield: Water of reaction (%)	100	99,1
Consistency at room temperature	turbid, highly viscous	turbid, highly viscous
after neutralization	turbid, highly viscous	turbid, highly viscous
Viscosity at 100 °C MK-D at 20 rpm (mPa·s)	5,000	10,000
after neutralization	5,000	10,000
Degree of stringyness (cm to the break)	2	2
after neutralization	7	7

b. Waxes, produced from lactide and glycerol

General procedure for preparing the reaction products of lacitd with glycerol

Lactide {L(-)-lactide N from the company Böhringer, Ingelheim} and glycerol were heated with stirring at 195 °C in a conventional laboratory apparatus. The reaction was allowed to proceed at 195 °C for 3 hours, and after neutralization the product was dispensed while hot.

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A solution of Sn(II) chloride in ether had been added as a catalyst (7 ml of a solution of 2.5 g of $SnCl_2$ in 1,000 ml of ether in the reaction of 3 moles of lactide with 1 mole of glycerol).

The compositions and the properties of the oligomers are shown in Table 2.

Table 2

Oligohydroxycarboxylic acids from glycerol and lactide

Example	C	D
Starting materials:		
Glycerol (moles)	1	1
Lactide (moles)	5	6
Consistency at room temperature	clear, viscous	clear, viscous
after neutralization	turbid, highly viscous	turbid, highly viscous
Viscosity at 100 °C MK-D at 20 rpm (mPa·s)	8,000	10,000
after neutralization	10,000	10,000
Degree of stringyness (cm to the break)	about 60	about 50
after neutralization	30	30

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2. Preparation of the reactive cross-linker component

2.1 Preparation of the glycolic acid/ethylene glycol 4:1 oligomer

A 25 l test reactor was charged with 16.72 kg of glycolic acid and 3.41 kg of ethylene glycol. The crystal pulp was melted in an inert atmosphere under a nitrogen stream and then further heated to a maximum temperature of 145 °C to 150 °C (bottoms temperature). After the reaction had started with distillation of water, it was continued for 11 hours until no more reaction water was formed (drop in the vapor temperature to 70 °C to 73 °C at a conversion of 70%). The aqueous solution obtained upon distillation was analyzed for the quantity of distillate, the acid value (glycolic acid contents) and the water contents by the Karl Fischer method. In order to lead the reaction to completion, the mixture was carefully evacuated to 400 Torr, and the pressure was further reduced to 10 Torr within 2 hours and maintained at this level for 1 hour, in order to remove the residual water of reaction for accomplishing a quantitative conversion.

The additional amount of condensate was collected for quantification in a cold trap (cooled with dry ice and ethanol). After the total period of reaction, the mixture was cooled to 100 °C and re-pressurized to atmospheric pressure with nitrogen, and the product was dispensed while still hot. The product was directly used for the preparation of oligo-glycolic acid bis-methacrylate without further purification.

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2.2 Yield and mass balance

Amount of Distillate 4 222.8 g

Glycolic acid (from acid value = 46): 263.58 g - 263.6 g

Ethylene glycol determined by HPLC

Amount of water (by the Karl Fischer method)

91.6% in the distillate = 3 868.1 g

= 97.7% conversion.

Analytical results of the oligomer

Designation		Immediately after the preparation	1 Month old	1 Year old
Batch size	kg	20	4.5	2
Consistency		pastous	pastous	pastous
Viscosity at room temperature (Epprecht Viscosimeter MK4)	mPa·s	12,500	13,000	12,800
Molecular weight				
M_n *		438	455	454
M_w		515	533	530
Free glycolic acid	%	2.1	1.4	1.9
Free ethylene glycol	%	0.2	0.2	0.2
Saponification value		765.4	754.4	754.0
Behavior in water				
pH after 2 minutes		3.8	3.8	3.8
pH after 60 minutes		3.4	3.4	3.4
Peroxide content		negative		
Analytical composition of the product glycolic acid/ethylene glycol		3.975:1	3.972:1	3.972:1

* Determination of the molecular weight as GPC analysis. Since the calibration was effected with polyethylene glycol as standard, the difference between M_n in theory and M_n as found is due to the calibration method.

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2.3 Oligoglycolic acid bis-methacrylate

Commercially available methacrylic acid (company Roehm) is newly inhibited with vitamin E according to the following procedure:

In a vacuum distillation apparatus, 15 moles (= 1,291.35 g) of methacrylic acid (b.p. 163 °C) are admixed with 3.87 g (= 3,000 ppm) of phenothiazine (as stabilizer); the methacrylic acid was distilled off under a strong stream of air in a water-jet vacuum. 100 ppm of vitamin E (Covitol F-1000-2, 67%, Henkel KGaA) (= 139 mg/l) are placed in the receiver, and the methacrylic acid is distilled with stirring. The distillation is stopped, once 932 g of the methacrylic acid have been collected after distillation.

2.4 Course of the reaction

A three-neck flask equipped with stirrer, Claisen head and condenser ("distillation bridge") was charged with 294 g of oligoglycolic acid, 206.4 g methacrylic acid and 17.5 g of p-toluenesulfonic acid; the mixture was inhibited with 0.86 g of vitamin E (α-tocopherol). Throughout the reaction, air was passed through the mixture at a rate of at least 40 l/h.

The esterification was effected at a maximum temperature of 105 °C by removal of the water formed, until the quantity of water removed was more than 35.78 g (more than 97% conversion).

The distillation receiver was cooled with a dry ice/ethanol mixture throughout the reaction. At a maximum bottoms temperature of 105 °C and a pressure of

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500 mbar the esterification time was between 12 and 14.5 hours at a total conversion of from 97 to 98.5%. The aqueous solution (as recovered from the receiver and cold trap) was sampled every 1.5 hours and was analyzed for the quantity of distillate, the acid value (methacrylic acid contents) and the water contents by the Karl Fischer method.

The water content and the amount of methacrylic acid as entrained in the distillation were calculated from the differences; after each determination, it was checked whether enough methacrylic acid was still available for the reaction. In most cases, additional 0.1 moles of methacrylic acid had to be replenished after about 7.5 or 8 hours.

Upon completion of the reaction (conversion in excess of 97%) the product was dispensed for purification.

2.5 Work-up of the reaction product

In the end of the reaction period, the product is not quite free from acid. Therefore, it was neutralized with $Ca(OH)_2$. Since in the determination of the acid value, due to the water required for the determination, the product underwent hydrolysis and a continuously increasing amount of acid was released by this reaction, it was not possible to determine the acid content by titration.

Therefore, the acid value had to be theoretically calculated.

The amount of $Ca(OH)_2$ calculated to be required for neutralization was introduced into the warm reaction

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product and the mixture was treated with stirring at 105 °C for 30 minutes, while 40 l/h of air under 500 mbar (gauge) were passed therethrough.

The neutralized product (highly viscous at 100 °C to 105 °C) is filtered by means of a pressurized nutsch filter and a Loeffler filter (80 NM012) at from 100 °C to 105 °C under 3 bar.

Then, the product - while still hot - was once more filtered under otherwise the same conditions through a round filter (NNG 16, medium filtering speed).

Example 2

Preparation of mixtures comprising resorbable waxes and reactive cross-linkers and the reaction thereof

The reactive cross-linker (monomer in accordance with Example 1.2) is mixed with alternatively either of the two waxes according to Example 1.1a based on glycolic acid or according to Example 1.1b based on lactic acid. The properties of the mixtures are set forth in the Tables 3 through 6. For the preparation of the polymerizates, the mixtures were exposed to the radiation from a UV light source (Dr. Hönle GmbH; UV ASpot 400/T; 400 W, 200/230 V) for 5 hours.

In the following Tables, "GS" refers to glycolic acid, and "EG" refers to ethyleneglycol. The substance mixtures set forth in Tables 3 and 4 were reacted under UV light without addition of a stabilizer. In contrast thereto, the substance mixtures set forth in Tables 5 and 6 were reacted with the addition of a UV sensitizer (cf. the indications in the headline of Table 5).

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Table 3

Properties of mixtures comprising wax (glycolic acid/glycerol 9:1) and cross-linker {oligoester (GS/EG 4:1) bis-methacrylate} before and after reaction. Curing under UV light without sensitizer.

No.	Mixing ratio		Properties of the uncured mixture	Properties of the mixture after the reaction
	Wax %	Cross-linker %		
2.1	98	2	white waxy mass, slightly tacky	waxy deformable white elastic material, slightly tacky
2.2	97	3	white waxy mass, slightly tacky	waxy deformable white elastic material, slightly tacky
2.3	95	5	white waxy mass, almost tack-free	waxy deformable white elastic material, almost tack-free
2.4	90	10	light-beige waxy mass, almost tack-free	waxy deformable light beige elastic material, almost tack-free
2.5	80	20	miscible	white waxy material, tack-free
2.6	60	40	miscible	white hard brittle material, tack-free
2.7	40	60	miscible	glassy hard material, slightly turbid
2.8	20	80	miscible	glassy hard material, slightly turbid

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Table 4

Properties of mixtures comprising wax (lactide/glycerol 6:1) and cross-linker {oligoester (GS/EG 4:1) bis-methacrylate} before and after reaction. Curing under UV light without sensitizer.

No.	Mixing ratio		Properties of the uncured mixture	Properties of the mixture after the reaction
	Wax %	Cross-linker %		
2.9	98	2	tacky tough highly stringy glass-clear mass	elastic, somewhat tacky glass-clear product
2.10	97	3	tacky tough highly stringy glass-clear mass	elastic, virtually tack-free glass-clear product
2.11	95	5	tacky tough highly stringy light-beige clear mass	slightly brittle elastic slightly turbid colorless material
2.12	94	6	tacky tough highly stringy light-beige clear mass	somewhat brittle elastic slightly turbid colorless material
2.13	90	10	tacky tough highly stringy light-yellow clear mass	hard brittle tack-free light-beige turbid material
2.14	80	20	tacky highly stringy light-yellow slightly turbid mass	hard brittle tack-free beige turbid material
2.15	60	40	slightly tacky readily fluid slightly stringy gold-colored turbid mass	hard brittle tack-free beige turbid material
2.16	40	60	miscible, liquid	hard brittle tack-free light-brown turbid material
2.17	20	80	miscible, liquid	hard brittle tack-free light-brown turbid material

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Table 5

Properties of mixtures comprising wax (lactide/glycerol 6:1) and cross-linker {oligoester (GS/EG 4:1) bis-methacrylate} before and after reaction. Curing under UV light with sensitizer - 4-(2-acryloyloxyethoxy)phenyl-(2-hydroxy-2-propyl)ketone (Company Merck) (4%, relative to the total composition).

No.	Mixing ratio		Properties of the uncured mixture	Irradiation time, properties of the mixture after the reaction (UV curing)
	Wax %	Cross-linker %		
2.18	98	2	tacky tough highly stringy glass-clear mass	5 minutes; somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	15 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	1 hour; readily deformable almost tackfree yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	5 hours; elastic somewhat brittle tackfree golden-yellow clear material
2.19	97	3	tacky tough highly stringy glass-clear mass	5 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	15 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	1 hour; readily deformable almost tackfree yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	5 hours; somewhat elastic brittle tackfree golden-yellow clear material

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Table 6

Properties of mixtures comprising wax (lactide/glycerol 6:1) and cross-linker {oligoester (GS/EG 4:1) bis-methacrylate} before and after reaction. Curing under UV light with sensitizer - (same as in Table 5).

No.	Mixing ratio		Properties of the uncured mixture	Irradiation time, properties of the mixture after the reaction (UV curing)
	Wax %	Cross-linker %		
2.20	96	4	tacky tough highly stringy glass-clear mass	5 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	15 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	1 hour; readily deformable almost tackfree yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	5 hours; slightly elastic brittle tackfree golden-yellow clear material
2.21	95	5	tacky tough highly stringy glass-clear mass	5 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	15 minutes; deformable somewhat tacky light-yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	1 hour; slightly deformable almost tackfree yellow clear material
	"	"	tacky tough highly stringy glass-clear mass	5 hours; slightly elastic brittle tackfree golden-yellow clear material

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Example 3

Samples of depot material according to the invention loaded with valuable material(s) according to the indications set forth hereinbelow are prepared, which samples are used for the determination of the release of the valuable material in an experimental model in series experiments.

As the valuable materials there are employed various commercially available antibiotics which are first incorporated in the carrier to form a homogeneous mixture. Then the cross-linker is added into the mixture, and the multi-component mixture as a material layer of about 1 to 2 mm in thickness applied onto a Teflon film is exposed to UV light for several hours.

Under the working conditions employed (no sensitizer added; cooled UV lamp 500 W, irradiation time 10 hours, temperature of the multi-component mixture 28 °C) there is obtained a material the surface of which is not yet tack-free. If so desired, the mass is after-cured with an uncooled UV lamp until tack-free (15 hours; temperature 80 °C).

The following details are applicable:

Carrier material: Condensation product of lactide/glycerol in a molar ratio of 6/1

Cross-linker: Oligo(glycolic acid/ethyleneglycol 4:1) bis-methacrylate

Valuable materials: The antibiotic active substances available under the following tradenames Gentamycinsulfat®, Chloramphenicol® and Tetracyclin®.

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Mixing ratios of valuables/carrier:
5% by weight and 0.1% by weight

Amount of cross-linker, relative to the valuables/carrier mixture: 3% by weight

The depot materials containing the valuable materials are prepared as follows: The oligolactic acid-based carrier material is intimately mixed with the finely divided antibiotic in the respective predetermined amounts, optionally with slightly warming the carrier material. At a temperature of 50 °C, the cross-linker component is introduced so that a homogeneous mixture is formed. The composition is spread over a Teflon film to form a layer of from 1 to 2 mm in thickness and then subjected to UV curing.

Determination of the retard effect

Glass plates coated with nutrient agar were inoculated over a large area and uniformly with the test bacteria employed. The material samples to be tested were brought into contact with the substrate. After two days of incubation, the inhibitory zones formed around the respective material sample to be tested were measured by determining the distance between the sample substance containing the antibiotic and the outer borderline of the inhibitory zone. Then the antibiotic-containing material samples are subjected to stepwise leaching in running tap water. After completion of each washing stage the inhibitory zones still to be formed are determined on freshly inoculated nutrient agar plates. This operation is repeated in a number of steps until no inhibitory zones are detectable any more around the tested material samples.

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Staphylococcus aureus (ATCC 6538) and *Escherichia coli* (ATCC 11229) were used as the test bacteria.

The operation of leaching with water is carried out as follows: The material to be leached is placed between to synthetic sponges. Then, using a hand shower, a uniform water flow is formed through the sponge. If required, the material samples are wrapped in a permeable thin fabric in order to exclude any material losses due to possible breakage in the course of the leaching operation.

For a better evaluation of the retard effect of the depot materials providing a sustained release of the active substance according to the invention the leaching behavior of a commercially available retard antibiotic preparation used in clinical practice is tested, in a parallel procedure under identical working conditions. The material employed here is sold by the Company Merck, Darmstadt, under the tradename of "Septopal®"-10er-Minikette. Said material of prior art is a methyl methacrylate-methyl acrylate copolymer which has been admixed with 5% by weight of gentamycin sulfate. This polymer carrier is not body-resorbable. After a surgical implantation, said material will have to be completely removed - usually after 5 to 7 days - or even after a period of from about 1 to 3 month(s), if necessary by surgery.

3.1 Test germ employed: *Staphylococcus aureus*

In a test series including 6 steps a retard material having the composition as set forth in the beginning of Example 3 and containing 5% by weight of gentamycin is subjected to leaching for altogether 19 days. The inhibitory zones to be formed around the respective tested material sample are determined in the beginning of the test and

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between the individual leaching steps in the above-described manner.

The long-term behavior of the "Septopal®" element is tested in parallel and under absolutely identical conditions.

Leaching is carried out in the following sequential steps interrupted by the determination of the inhibitory zones:

1st step	4 days
2nd step	4 days
3rd step	3 days
4th step	2 days
5th step	3 days
6th step	3 days

The size of the observed inhibitory zones (in mm) is summarized in the following Table 7:

Table 7

	Depot material of Example 3	"Septopal®"
Inhibitory zone (mm)	12 - 15	12 - 15
1st step	8	8 - 10
2nd step	5 - 7	5 - 10
3rd step	6 - 8	7 - 9
4th step	5	7
5th step	6 - 8	6 - 8
6th step	4	2 - 3

In a comparable investigation the depot material of the above-described composition according to the invention is

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admixed with gentamycin sulfate in a concentration of 1% by weight and is then subjected to stepwise leaching in the same manner. The inhibitory zones determined with the fresh material and after the respective steps are as follows:

Fresh material		7 - 10 mm
	Days of water leaching	
1st step	4	5 mm
2nd step	4	1 - 2 mm
3rd step	3	3 - 5 mm
4th step	2	0 mm

3.2

Comparable investigations are carried out with depot materials according to the invention which contained the following valuable materials, each in a concentration of 0.1% by weight of the antibiotic: Gentamycin sulfate, erythromycin, tetracyclin and chloramphenicol.

The leaching steps were carried out in periods of one day each, between which the size of the inhibitory zone as still observable is determined.

The blank value for the inhibitory zone (test germ: *Staph. aureus*) is about 5 to 6 mm for all of the material samples employed. The activity of the gentamycin sulfate depot material remains virtually unchanged until the third day of water leaching; then an approximately linear decrease of the size of the inhibitory zone is observed, reaching zero in the end of the 7th day of leaching. Approximately comparable is the course of the plot of the inhibitory zone size over the time for the retard material containing erythro-

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mycin. Here, however, the zero value is reached only after the end of the 8th day of leaching. Within the periods of leaching steps 5 to 7 the inhibitory zone values are improved over those of the preparation containing gentamycin sulfate.

The retard preparation containing tetracyclin shows hardly any reduction in activity after the first leaching step; then, however, a rapid activity loss occurs. The preparation containing chloramphenicol shows an activity loss to less than 50% of the initial value already in the end of the 1st day of water leaching.

If, however, now the concentration of the active ingredient is increased to 5% by weight and an oligomer based on glycerol/glycolic acid/lactic acid in a molar ratio of 1/2/10 is employed, then the blank value of the inhibitory zone produced by the tetracyclin-containing preparation (42 mm) is just comparably insignificantly decreased by about 10 units (31 mm) within a period of 8 days of water leaching. Somewhat higher within said period is the activity loss of the material samples containing, on the one hand, gentamycin sulfate and, on the other hand, erythromycin as the antibiotic. Nevertheless, also here an antibiotic activity of more than 50% of the blank value is retained.

Corresponding investigations carried out on nutrient substrates with *E. coli* as the test germ confirm the retard effect in the release of the antibiotic substances within the meaning of the teaching according to the invention.

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The claims defining the invention are as follows:

1. A composition for preparing a sustained release formulation, which composition comprises a pharmaceutically or biologically active substance, a carrier material of at least one oligomer and/or polymer of a lower hydroxycarboxylic acid and cross-linker components prepared from olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

2. A composition according to claim 1, wherein the cross-linker components are at least partly polyfunctional.

3. A composition according to claim 2 wherein the cross-linker components are di- to tetrafunctional hydroxycarboxylic acid derivatives.

4. A composition according to any one of claims 1 to 3 wherein the carrier material oligomer and/or polymer compounds of hydroxycarboxylic acids have from 2 to 6 carbon atoms.

5. A composition according to claim 4 wherein the hydroxycarboxylic acids have from 2 to 4 carbon atoms.

6. A composition according to claim 5 wherein the hydroxycarboxylic acids are lactic acid and/or glycolic acid.

7. A composition according to claim 1 or claim 2 wherein the cross-linker components are reactive derivatives of hydroxycarboxylic acids having 2 to 6 carbon atoms.

8. A composition according to claim 7 wherein the cross-linker components are derived from lactic acid and/or glycolic acid.

9. A composition according to any one of claims 1 to 8 suitable for use in and/or on a human and/or animal.

10. A composition according to claim 9 for implantation and/or for topical administration to the human or animal.

11. A composition according to claim 1 or claim 2 wherein the cross-linker components are at least partly esters and/or oligoesters of lower polyfunctional alcohols or carboxylic acids with lactic acid and/or glycolic acid and have terminal olefinically unsaturated groups.

12. A composition according to claim 11 wherein the cross-linker components are derived from lower di- to tetrahydric alcohols and have been olefinically substituted with (meth)acrylic acid moieties.

13. A composition according to claim 12 wherein the cross-linker components are derived from ethyleneglycol and/or glycerol.

14. A composition according to claim 1 or claim 2 wherein the cross-linker components are reaction products of glycerol esters of lactic acid and/or its oligomers

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and (meth)acrylic acid and/or reactive derivatives thereof which, as a random average, comprise from 2 to 3 olefinic terminal groups per one mole of glycerol.

15. A composition according to any one of claims 1 to 3 wherein the carrier material oligomers and/or polymers of the lower hydroxycarboxylic acids have a tough-viscous to solid nature at room temperature.

16. A composition according to claim 15 for implantation into a living organism wherein the oligomers are esters of lower functional alcohols.

17. A composition according to claim 16 wherein the oligomers are ethylene glycol and/or glycerol.

18. A composition according to any one of claims 1 to 8 for topical administration wherein oligomer compounds having terminal carboxyl groups can also be employed at least partly in the carrier material.

19. A composition according to any one of claims 1 to 18 wherein the carrier material comprises oligomers have average molecular weights within the range of from 200 to 5,000.

20. A composition according to claim 19 wherein the oligomers have an average molecular weight in the range of from 300 to 2,000.

21. A composition according to claim 19 wherein the oligomers are glycerol/oligo-lactic acid esters having average molecular weights within the range of from 200 to 1,500.

22. A composition according to claim 21 wherein the oligomers have a molecular weight within the range of from 300 to 1,000.

23. A composition according to any one of claims 1 to 22 wherein the cross-linker components are at least partially reacted and are present in minor amounts relative to the weight of the carrier material.

24. A composition according to claim 23 wherein the cross-linker components are present in an amount of 0.5 to 40% by weight, relative to the sum of carrier material and cross-linker components.

25. A composition according to claim 24 wherein the content of cross-linker components is less than 10% by weight.

26. A composition according to claim 24 wherein the cross-linker components are present in an amount of from 1 to 20%.

27. A composition according to any one of claims 1 to 26 wherein the carrier material and polymeric cross-linker components are either in a largely homogeneous mixture with the active substance and/or, in a layered arrangement such that regions which are at least largely free from crosslinker components are enclosed by regions having reacted cross-linker components.

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28. A composition according to any one of claims 1 to 27 wherein the carrier material has at least a bimodal structure nature, combining oligo- and/or polyesters having a comparably high decay rate under the conditions of use, with oligo- and/or polyesters having a slower decay rate.

29. A composition according to claim 28 wherein the oligo- and/or polyesters of high decay rate are derived from glycolic acid, and the oligo- and/or polyesters of slower decay rate are derived from lactic acid.

30. A composition according to any one of claims 1 to 3 which comprises as carrier material at least largely homogeneous admixtures of oligomers and/or polymers derived from lactic acid and from glycolic acid, and optionally multiphase admixtures of discrete regions of individual components of the carrier material.

31. A composition according to claim 30 wherein in the multiphase admixtures the cross-linker components are optionally also present depending on configuration, kind and/or amount.

32. A composition according to any one of claims 1 to 8 comprising medicaments or substances used for crop protection and/or plant growth promotion as said biological valuable materials.

33. A composition according to claim 32 wherein said medicaments are antibiotics, cytostatics, cortisone and/or hormones.

34. A composition according to claim 33 wherein said medicaments have been designed for implantation into a living organism.

35. A sustained release formulation prepared from the composition of any one of claims 1 to 34.

36. A method of preparing a composition used in a sustained release formulation, which method comprises reacting cross-linker components which are reactive via free radicals, said components based on olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

37. A method according to claim 36 wherein said composition is used to prepare a sustained release formulation which contains pharmaceutically and/or biologically active substances in admixture with a carrier material.

38. A method according to claim 36 or claim 37 wherein the cross-linker components are present as polymer compounds and are arranged in a largely homogeneous or non-uniform distribution.

39. A method according to claim 38 wherein the polymers forming the cross-linker components have been prepared in situ from the free radical-reactive cross-linker components in admixture with at least a proportion of the depot material.

40. A method according to any one of claims 36 to 39 wherein polyfunctional cross-linker components are employed which have been derived from lactic acid and/or

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glycolic acid esters, said components containing at least 2 to 4 olefinic groups in the molecule.

41. A method according to claim 40 wherein the components contain at least 2 and/or 3 olefinic groups in the molecule.

42. A method according to any one of claims 36 to 39 wherein polyfunctional (meth)acrylic acid esters of hydroxy-terminated reaction products from the reaction of lower polyfunctional alcohols with lactic acid and/or acid or glycolic acid are used as the cross-linker components.

43. A method according to claim 42 wherein the lower polyfunctional alcohols are ethyleneglycol and/or glycerol.

44. A method according to claim 37 wherein either the cross-linker components are admixed with the admixture of carrier material and pharmaceutically and/or biologically active substance and allowed to react, and/or the admixture of carrier material with pharmaceutically and/or biologically active substance is enclosed by a layer containing reacted cross-linker components.

45. A method according to any one of claims 36 to 44 wherein body-compatible oligomers and/or polymers of lower hydroxycarboxylic acids are present as carrier material.

46. A method according to claim 45 wherein the body-compatible oligomers are based on lactic acid and/or glycolic acid.

47. A method according to claim 45 or 46 wherein the oligomers and/or polymers have average molecular weights within the range of from 200 to 5,000.

48. A method according to claim 47 wherein the oligomers have average molecular weight of from 300 to 2,000.

49. A composition for preparing a sustained release formulation substantially as herein described with reference to Example 2.

50. A method of preparing a composition used in a sustained release formulation, which method is substantially as herein described with reference to Example 2.

Dated 4 May, 1995
Henkel Kommanditgesellschaft auf Aktien
Patent Attorneys for the Applicant/Nominated Person
SPRUSON & FERGUSON

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IMPROVED RETARD SYSTEMS FOR THE SUSTAINED RELEASE OF MEDICINAL AND/OR BIOLOGICAL VALUABLE MATERIALS FROM A DEPOT CARRIER MATERIAL

Abstract of the Disclosure

The invention, in a first embodiment, relates to the use of free radical-reactive cross-linker components based on olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof for modifying depot materials, and especially retard systems, which contain medicinal and/or biological valuable materials in admixture with a carrier material in a sustained release of the active substance(s) in practical application. The cross-linkers are present as polymer compounds in the application form of the retard system and may be provided in the retard system or depot material to be applied in a largely homogeneous as well as in a non-uniform distribution.

The invention further relates to retard systems which contain medicinal and/or biological valuable materials and have been based on oligomer and/or polymer compounds of lower hydroxycarboxylic acids as carrier materials providing a sustained release of the active substance, the invention being characterized in that said retard systems and/or depot materials have been modified with polymer compounds prepared from olefinically unsaturated esters of lower hydroxycarboxylic acids and/or oligomers thereof.

AUSTRALIA PATENT OFFICE MTB

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 92/00825

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl.^{5} A 61 K 9/20
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)

Int. Cl.^{5} A 61 K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO, A, 9107999 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 13 June 1991 (cited in the application) see page 1, paragraph 1, see page 25 - page 29; examples 2	1-5,7,14
Y	PATENT ABSTRACTS OF JAPAN, vol. 13, No. 427, 22 September 1989 & JP, A, 1163135 (TAKI CHEM CO LTD) 27 June 1989, see abstract	1-5,7,14
A	EP, A, 0290983 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 17 November 1988, (cited in the application), see the whole document	1-21
A	EP, A, 0086401 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 24 August 1983, (cited in the application) see the whole document	1-21
A	EP, A, 0352588 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 31 January 1990 (cited in the application) see the whole document	1-21

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

* Special categories of cited documents:
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 June 1992 (15.06.92)	22 June 1992 (22.06.92)
Name and mailing address of the ISA/ European Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200825 SA 58277

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9107999	13-06-91	DE-A- 3939161	29-05-91
		AU-A- 6718590	26-06-91
EP-A-0290983	17-11-88	DE-A- 3716302	24-11-88
		JP-A- 63302858	09-12-88
EP-A-0086401	24-08-83	DE-A- 3204504	18-08-83
		EP-A,B 0085944	17-08-83
		JP-A- 58147421	02-09-83
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		US-A- 4731425	15-03-88
		US-A- 4626310	02-12-86
		US-A- 4675433	23-06-87
EP-A-0352588	31-01-90	DE-A- 3825211	01-02-90
		JP-A- 2080054	20-03-90

INTERNATIONALER RECHERCHENBERICHT

PCT/EP 92/00825

Internationales Aktenzeichen

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Kl. 5 A61K9/20

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff [7]

Klassifikationssytem	Klassifikationssymbole
Int.Kl. 5	A61K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen [8]

III. EINSCHLAGIGE VEROFFENTLICHUNGEN [9]

Art.°	Kennzeichnung der Veröffentlichung [11], soweit erforderlich unter Angabe der maßgeblichen Teile [12]	Betr. Anspruch Nr.[13]
P,Y	WO,A,9 107 999 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 13. Juni 1991 in der Anmeldung erwähnt siehe Seite 1, Absatz 1 siehe Seite 25 - Seite 29; Beispiel 2 ---	1-5,7,14
Y	PATENT ABSTRACTS OF JAPAN vol. 13, no. 427 22. September 1989 & JP,A,1 163 135 (TAKI CHEM CO LTD) 27. Juni 1989 siehe Zusammenfassung ---	1-5,7,14
A	EP,A,0 290 983 (HENKEL KOMMANDITGESELLSCHAFT AUF AKTIEN) 17. November 1988 in der Anmeldung erwähnt siehe das ganze Dokument ---	1-21
	-/--	

° Besondere Kategorien von angegebenen Veröffentlichungen [10]:

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

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IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
15.JUNI 1992	22. 06. 92
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
EUROPAISCHES PATENTAMT	BOULOIS D. Boulois

III. EINSCHLAGIGE VEROFFENTLICHUNGEN (Fortsetzung von Blatt 2)

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ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

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In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 15/06/92
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

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