(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 August 2001 (23.08.2001)

PCT

(10) International Publication Number
WO 01/60425 A1

(51) International Patent Classification[7]: A61L 27/18, 27/58, 31/06, A61K 6/087

(21) International Application Number: PCT/FI01/00141

(22) International Filing Date: 14 February 2001 (14.02.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
20000317 15 February 2000 (15.02.2000) FI

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/60425 A1

(54) Title: BIODEGRADABLE MATERIAL

(57) Abstract: The invention focuses on essentially hydroxyacids based synthetic materials, which are biocompatible and possibly degradable at a controlled rate. The materials are polymers or copolymers of derivatives of organic hydroxy acids, such as lactides and lactones, having a melting temperature, in a range of 0-100 C, adjusted to be most preferably 2-20 C above the body, are melts, plastic masses or viscous fluids, and thus moldable by hand, injectable or processable by using some molding device of viscose masses, and that they are at normal body temperature solid plastic like materials, waxes or rubberlike materials, out of which active agents can be released with controlled rate, especially in connection to heat sensitive drugs or in the controlled release of other effective active agents so that the material is acting as the matrix in connection to implants or devices implanted into the body in connection to therapeutic treatments.

BIODEGRADABLE MATERIAL

During the last years in the biomedical applications synthetic implant materials have been taken into use to an ever-increasing degree. Biomaterial is defined to be a synthetic structural material whose aim is to interact with the biological system, and to replace, to treat, promote healing and renewal of and to join tissue, organs or some function of the body. Applications of these materials are reviewed in a publication edited by Höcker et al. (Klee, D., Severich, B., Höcker, H., Macromol. Symp. **103** , January 1996, pp. 19 - 29). Among the most important present and future applications are fixation materials of different types for bone fracture treatment which can be used for manufacturing screws, nails or rods for the above mentioned application, just to mention an example. These materials can be either non-biodegradable ones, e.g., metals or metal alloys, or polymeric materials degradable at a controlled rate in the body.

The most widely used biodegradable materials are high molecular weight lactide homopolymers, and lactide copolymers with, for example, glycolide. Useful parts or products are processed from these materials with processing methods for thermoplastics known in polymer technology, such as injection molding, hot pressing or extrusion.

Dentistry is well familiar with polymeric materials, too. Typical polymeric dental filling materials are chemically (for example, photochemically) curable plastics based on methyl methacrylate, dimethyl acrylate and their derivatives.

Fixation bone cements for orthopedic hip prostheses are also based on monomer combinations methacrylate type. In these applications the curing is based on redox initiated free radical polymerization, and on thus accomplished by means of cross-linking and network formation.

The methacrylate based implant materials are, however, neither biodegradable nor biocompatible to any particular extent, as Dr. Heikkilä reports in his dissertation (Heikkilä, J., Bioactive glass as a bone substitute in experimental and clinical bone defects, Publications of University of Turku Series D, Vol. **240,** 1996).

In the use of methacrylate based implant materials further problems are caused by the exposition of personnel to volatile compounds, and the heat released during the reaction which may lead to an excessive local temperature increase, and to tissue damages as a consequence .

Another application for synthetic implant materials is controlled release of drugs or other bioactive substances when the idea is that the potent agent is released at a controlled rate from the polymeric matrix. As an example of this kind of application one can mention Norplant, a product brand and a trade mark of Leiras Co., which is based on a non-degradable polymeric material. A definitely formed device is implanted into the body by a surgical operation, and it is removed therefrom in a similar manner after a defined time when the active component has been released and diffused to the body.

Specific needs for development in the present state of the art are connected to the following areas:

Biocompatibility

If the material is not biocompatible it may induce tissue inflammation, unwanted cell growth, or rejection. Biocompatibilities of the presently used bone cements based for the most part on poly(methyl methacrylate) are unsatisfactory. This causes a certain risk of loosening of the hip prosthesis even in the case that there exists connective tissue formation between the polymeric material and bone tissue. A better biocompatibility would be a significant benefit for these materials.

Bioactivity

A bioactive implant material makes possible an active interaction between the tissue and the implant. As an example can be taken a mechanism by which the tissue is enabled to reconstruct into the implanted material while the implanted material itself is gradually removed due to biodegradation. Heimke and Griss have characterized the concept of bioactivity and have been cited by Heikkilä in his publication (Fig. 1 from Heikkilä, J., Bioactive glass as a bone substitute in experimental and clinical bone defects, Publications of University of Turku Series D, Vol. **240**, 1996, p. 18) . As a scheme to clarify the matter , there is presented a non biocompatible material, a bioinert but at the interphase biocompatible material, and a bioactive material.

Bioactive materials have scarcely been reported in the literature. Especially in the case of bone cements bioactivity would be desirable and a significant benefit.

Controlled biodegradation

Depending on the application and purpose of implant materials, they are expected to have either long lasting durability or controlled degradability in the body at a predetermined rate to harmless degradation products. The wanted degradation rate is depending substantially on the renewal rate of the tissue. In the case of bone tissue, it may be case of several months, or even of a time span in the range of half an year to one year.

In the case of controlled drug delivery it is crucial what is the desired rate of release of the active ingredient from the biodegradable matrix. When the potent ingredient release is based on matrix degradation the rate of matrix degradation determines the release rate of the drug. When active agent is released from the matrix through diffusion, degradation of the matrix shall happen mainly only after the release of the active agent.

Industrial hygienic aspects

The materials in continuous clinical use have to be safe to the users in a sense of work safety and hygiene. This is a severe drawback with the present bone cements and dental filling materials which are based on methacrylates.

Controlled mechanical properties

The mechanical properties required from implant materials are depending on the application. With bone implants usually a compression strength of at least 50 Mpa is necessary, as well as bending strength and tensile strength values which are at the level of those of bone.

On the other hand, even in the bone applications , in case of bone grafting by filling of fractures and cavities, one can pretty well apply implant materials of lower strength if only the use properties, mouldability, biocompatibility, and possible biodegradability are at an optimum level.

In connection of soft tissue the requirement on the other hand is elasticity, flexibility and softness.

Plasticizability and hardening thereafter

The today used polymeric implant materials are either pieces of definite shape, i.e., processed before implanting to the final form using methods known in the plastics technology (as an example one can mention biodegradable bone nails based on polylactide, e.g., trade name Biofix), or bone cements based on methacrylate which typically have no biodergradability and lack bioactivity but as monomers, or as a blend of monomers, can be shaped in the target according to the needs, and can be hardened thereafter.

In surgery there would be plenty of applications for plasticizable, and afterwards to solid curable biodegradable polymeric materials. Then the idea is, that the material is plastic in connection to the surgical operation , and can be shaped according to the target's shapes or can be forced to penetrate even into small cavities, fractures and pores. Thereafter it again reversibly becomes solid, mechanically tough material which, however, has the property of controlled degradation. Thus plasticizable material can then be of the type of wax, plastic or rubber.

Better biocompatibility, bioactivity and wished mechanical properties as combined to the mouldability in the target and hardening occurring thereafter are typical properties for an implant material described in PCT-application WO 98/26814 .

Easiness in application (usability and transferability to the target)

The implant material is placed to the target in connection to a clinical situation, e.g., in connecton to an operation. Then the applicability and the mouldability of the material has to be easy: it must be possible to, for example, inject it, or to place it with a special press, to the target, and its hardening has to have a certain induction period during which the material can be shaped. On the other hand, one has to take into account that the possible drug present and/or the contact with tissue do not allow use of methods where the temperature even for a short period exceeds the typical upper limit of 55 °C. The publication WO 98/26814 brings a novel solution which significantly improves applicability of biodegradable implants, for example, in regenerating surgery and in long lasting drug therapy.

Applicability as a matrix for bioactive components

As bioactive effective agents in the implant materials can be mentioned different kinds of drugs, hormones, tissue regeneration promoting components (such as hydroxy apatite in connection to bone tissue), and building substances of tissue, such as proteins. The matrix material has to be such , that these components can easily be blended to form a

j´homogeneous blend. There are unevitably limitations for the highest processing temperature, due to the fact that many of the previously mentioned bioactive components do not resist elevated temperatures. but degrade, or their structure changes in a way, that the biological effects are reduced or lost. In the developments of the applications based on the controlled release of bioactive substances, one has to know firstly the degradation and transition temperatures of these organic molecules. Secondly one has to be able to produce mechanically acceptable, biodegradable and biocompatible polymeric matrix in the way that the above mentioned temperatures are not exceeded. As one example one can mention the melting temperature of poly-L-lactide of 160 °C , which essentially reduces the use of this polymer as the matrix of heat sensitive active agents.

A very special task is to produce a polymeric matrix enabeling controlled release for peptide active agents. The denaturation temperatures of protein like peptide compounds consisting of amino acids , is typically in the range of 50 – 60°C. Theis means that the blending into the controlled release matrix or the production of the corresponding implant device, or processing or application of these has to take place at a temperature which is below the critical temperature. The present invention enables the production of well functioning controlled release systems for peptide active agents.

Special requirements for the matrix in the controlled release applications are not only in the previously mentioned processing and applicability aspects of the implant, also the need to control the active agent release rate according to the need of the end use application and therapeutic need. An important aspect affecting on the release rate and also a structural parameter for control of the same is the polarity of the polymer matrix. In the matrixes and method according to the present invention the polarity, and thus the release rates of active agents can be regulated through the selection of so called initiator compound. Then advantageous compounds are multifunctional alcohols, such as some glycols, glyuserol, pentaeritrythol or polyglycerol, just to mention a few, Also block copolymers of polyethylene oxide type can be used.

The description of the invention

The implant material described in the publication WO 98/26814 is based on as such known structural units used in synthesis of polymeric biomaterials , and also on structural units derived from capronic acid. Structural units derived from lactic acid can be, in addition to lactic acid itself, L- , D-, and DL-lactide units. Structural units derived from capronic acid can be, e.g., ε-caprolactone. In addition as structural units can be organic carbonates, like trimethylenecarbonate.

Lactones are cyclic esters based on hydroxyacids. Some of the most common lactones are L-lactide, DL-lactide, D-lactide and ε-caprolactone. With these to the same group of cyclic monomers can also be included cyclic carbonates, like trimethylenecarbonate.

The polymerization of lactones and cyclic carbonates can be carried out, as is well known, through catalytic ring opening polymerization. The catalyst used is typically some organometallic compound like tin(II)octoate (in other words stannous-2-ethylhexenoate), or trimethylaluminium.

The molecular weight control in this type of polymerization is based on the optimal selection of polymerization temperature and time, and it is possible also using so called initiator compounds, of which typical are multifunctional alcohols, e.g., glycerol. During the polymerization the polymer chains will start to grow from the -OH groups so that the molecular weight will be the lower the more initiator is present. By choosing the structure of the multifunctional alcohol the shape of the forming molecule can be affected. So, for example, glycerol forms a comb-like and pentaerythritol a star-shaped molecular structure, respectively.

The ring-opening polymerization of lactones is described, for example, in the following publication: Ylikangas , I., The polymerization of ε-caprolactone with stannous catalysts, Polyemer Technology Publication Series **No. 15**, Helsinki University of Technology, 1993, 1-23.

Thus it is as such known that by using the above mentioned structural units one can form a biodegradable polymeric material which has either plastic-like or rubbery properties but in the method according to the WO 98/26814 the structural units are used in a special way to achieve a biodegradable polymeric material which melts within a certain narrow temperature range and which, on the other hand, is either a mechanically tough plastic, a wax or a rubbery material below its melting temperature. In respect of implant application it is important that the material melts or plasticizes at a temperature which is somewhere 3 - 12 °C above the body temperature, and becomes again a solid material at a temperature still above the body temperature. The melting and plasticization temperature of the material must, of course, not to be too high in respect to the body temperature, taking into account the above described temperature resistance of tissue and of drug-like active agents. When melting or plasticizing the material according to the invention becomes a viscose mass or fluid which can be shaped, injected or otherwise used to fill hollows, fractures and cavities as well as to replace different kinds of tissue defects, as in bone grafting.

In the method according to the WO 98/26814 it has become possible to adjust the temperature at which the material becomes plastic to within the temperature range of 42 - 55 °C, or it can be adjusted to any temperature around this temperature range as well. The melting temperature of the material can be checked by means of measurements of entalphy changes, using differential scanning calorimetry (DSC) as the method. The control of the melting temperature of a polymeric material according to the invention is based on one hand on the specific monomer ratio selection in the starting materials, and, on the other hand, on the specific control of the molecular weight in the copolymerization. Both factors together namely affect the melting temperature of the copolymer, hence only certain combinations of them bring about the wished result. Figure 1 is a graphical presentation the combinations of monomer compositions and average molecular weights for the L-lactide/caprolactone copolymers which produce a suitable melting temperature for implant use, indicated by points falling within the shaded area between curves in the monomer molar ratio versus molecular weight coordination.

In several applications it is wanted that the implanted material is degradable in a controlled manner, or vice versa mechanically stable at least for a certain period of time. The first stage in bidegradation of the materials according to the present invention is hydrolysis which splits polymer chains to shorter segments until the molecular size is at a level where the own enzymatic functions of the body can convert the degradation products to compounds which are natural in the body.

The hydrophilic character of the polymer is an essential parameter affecting the degradation rate. Thus in copolymers of the present invention it is possible to control hydrolytic degradation rate through control of monomer composition, and so also hydrophilic character, which according to what has been presented above directly affects the degradation rate of the material in the body. One has to note, however, that the exact rate of the degradation in the body depends on the end use, and has to be always investigated case by case. Figure 2 indicates the dependence between the hydrolysis rate and monomer composition in the L-lactide / ε-caprolactone copolymers prepared in the examples.

An essential feature of the material according to the WO 98/26814 is that if the composition of the material comprises only or for the most part ε-caprolactone, the rest being L-lactide, DL-lactide, D-lactide or trimethyl carbonate, the polymer is almost stable in the body, or degrades very slowly, typically during several years. Through selection of the monomer composition keeping this in mind, and through adjusting the molecular

weight of the forming polymer by controlling the polymerization parameters, one can get benefit from the well-known biocompatibility and bioactivity of poly(hydroxy acid)s. On the other hand, a waxy version of the copolymers according to the invention can be made to degrade even really fast, just by controlling both average molecular weight and monomer composition as described above. In that case the degradation rate in the body is typically from some days to some weeks.

A material according to the invention is in a molten state, i.e., while being at a temperature exceeding 37 °C, preferably at the temperature range of 42 - 55 °C, and most preferably at the temperature range of 43 - 48 °C, a plastic mass or a viscous fluid. This makes it possible to shape the material by hand or by using specific tools to a desired shape to meet the needs of the target, or alternatively makes it possible that the material can, by different transportation methods, be used to fill different and variably shaped spaces, hollows, cavities and fractures numerously existing in surgery, dentistry and medicine.

Especially advantegous in the method according to the WO 98/26814 is an unexpected observation that the plasticizable material according to the invention can above its melting temperature be in such a state that it can be applied to the target using a specific press. Said press essentially consists of a heated cylinder , a die (which can be of different kinds according to the needs of the end uses), a piston , trigger , and a press mechanism . The temperature of the cylinder can be regulated at a desired level by a thermostat so that the implantable material is either in a molten state or in a plasticized state inside the cylinder in front of the piston , and thus it can be transferred using the press device through the die to the target area. Because the temperature of the molten or plasticized polymeric material is higher than the body temperature but in any case such that there is no danger of tissue damage, the implant material can be transferred directly to the target area where it solidifies when cooling down.

Advantages of the method according to the invention are the simplicity for the user (, e.g., for the surgeon), hygienicity because the implant material is all the time in a closed chamber, and the point that there are no volatile components utilized in the method (an advantage in respect of industrial hygiene and working safety), and further that there is no heat generation in connection with the solidification (as usually is the case in the solidification of bone cements) and the risk of tissue damages can thus be avoided. As an additional benefit one can mention that by using differently shaped longer dies it becomes possible to inject the mass to narrow, deep and variously shaped channels to their very end or to their deepest points, to fractures, to cavities and the like as target areas.

Another preferred embodiment of the implantation method according is the use of such a device which does not contain any specific piston, but the piston is replaced with a rod made up of polymeric material according to WO 98/26814 which penetrates through the unheated part of the cylinder to the heated part where it melts or plasticizes. The feeding mechanism pushes the rod into the cylinder, and correspondingly the molten or plasticized polymeric material is extruded out through the die.

Still one advantageous method to implantate is the one where the temperature of the cylinder is raised above one hundred degrees centigrade and is held there for the time required for completing heat sterilization. In this case any separate sterilization is not needed, and the sterilized material remains in its closed space sterile and ready for use. Naturally this form of implantation can be applied provided that there are no heat sensitive active agents, for example drugs, present as blend components. After the sterilization treatment the material is allowed to cool down to the temperature range of 37 - 55 °C so that it remains both sterile and in a molten or plasticized state for the implanting.

One specific way of implantation is the one where the polymer according to the invention is produced in a way that its melt viscosity is low enough to allow its injection to the target area with a suitable injection syringe. In this case the polymeric material when cooled down to its solid state at the body temperature is a waxy material.

The implant material according to WO 98/26814 can be applied in a way that the material forms a matrix in the controlled release of drugs, or it forms a matrix in blends containing bioactive inorganic materials where the bioactive component can be selected from the group including, for example, hydroxyapatite, a filler based on coral, bone allocrafts or its particles, titanium particles and carbon fibers, just to mention some. In this form of application the blend component can, of course, also be soluble to the polymeric matrix, as is the case in connection with the most drugs. On the other hand, the solid components in the mixtures may be platelets or fibrous particles so that the composition is comparable to the polymer composites, and in which case the blend component essentially improves mechanical properties. A special advantage is achieved in the aspect that the use of a biodegradable polymeric matrix yields adhesion between particles, plasticizability, ease of processing, and improved biocompatibility to this kind of materials containing solid particles.

In connection with drugs, hormones, or other corresponding active agents, the method according to the invention enables the controlled release and targeted location to the body, for example, in connection with an operation, or by injecting.

Both composite materials containing solid fillers and/or reinforcements and blends containing soluble components can be located according to the invention, for example, as is presented in WO 98/26814, easily and safely as a plastic mass or a viscous fluid directly to the end use target.

Furthermore it is characteristic for the method according to the invention that also other methods suitable for the dosing and transferring plastic masses and viscous fluids are suitable for use, and they are in accordance with the invention.

EXAMPLES 1 - 18

Polymerizations and product characterzation

The used chemicals

The copolymers were prepared from ε-caprolactone monomer (ε-CL), > 99% purity, Fluka Chemika , and D,L-lactide (D,L-LA), Purac. As catalyst was used tin(II)octoate (Stannous 2-ethylhexanoate; SnOct), 95 % purity , Sigma. As the initiator was used glycerol, 99,5% purity, Fluka BioChemika, and polyglycerol, having in average 8 -OH groups (Daicel PGL06).

The purification and storage of the used chemicals

In the used ε-caprolactone there was molecular sieves (adding date 15.02.1995), and the bottle was stored in a dark place at a temperature of 23 °C. The caprolactone was not distilled again .

D,L-lactide was purified with recrystallication from toluene (b.p. 110 °C) using a mass ratio of 1:2 toluene/lactide. The lactide dissolved to a hot toluene was poured from round bottom flask to a decanter. The lactide solubilized to the toluene was let to recrystallize overnight at 23 °C. After filtration the crystallized lactide was dried under reduced pressure for 4 days at +40 °C and 4 mbar. The same stages were repeated once. In the polymerizations was thus used twice recrystallized D,L-lactide which was stored in an exsiccator in a refrigerator at +4 °C.

The tin octoate and the glycerol were used as such. They were stored in a dark place at +23 °C.

Preparations for polymerization

At preceding night the used lactide has been placed into a vacuum chamber at +40 ¡C and 4 mbar. The two-piece polymerization reactor (volume about 0,7 liter) was assembled, and the condition of the Teflon gasket belonging to the reactor was checked. The proper closure of the upper part and the lower part of the reactor was ensured by a iron wire closing device.The male parts of the glass joints belonging to the reactor were wiped slightly with a vacuum grease.

Poly-D.L-lactide and poly-epsilon-caprolactone polymerizations were carried out batchwise in an agitated reactor of volume 2,5 liters, equipped with two intermeshing agitators, which create especially good agitation into the reaction mixture in every point of the conical reaction chamber.

Polymerization

The oil thermostat used for the reactor heating was regulated to 140°C. The oil temperature varies during a polymerization within 5°C above and below the set temperature. Lactide was weighed first about 10 g into a small decanter (accuracy 0,0001 g). On the lactide the tin octoate and the glycerol was weighed using a Pasteur pipet. After this the decanter was poured into the reactor, and the rest of the lactide was weighed with another balance (accuracy 0,01 g) . ε-Caprolactone was then either poured or pipeted on lactide.

The magnetic agitator has been added to the reactor before the reactor halves were closed. The reactor was placed into a thermostat, and the agitation was adjusted to the speed of 250 1/min. The reactor was flushed with Argon (AGA, grade S, 99,99%) for about 15 min. Argon was fed to the reactor through a glycerol trap. Finally the outside of the reactor was wrapped with a aluminum foil. When the forming copolymer started to become more viscous the agitation speed was adjusted again to the speed of 125 1/min.

In the D,L-lactide polymerizations the batch size was 500g D,L-lactide, catalyst concentration was 0,02mol-% corresponding 0,295g in the reaction mixture, and the initiator content when glycerol was used 0,25%, and when polyglycerol was used 3,0mol-%, the amounts correspondingly in the reaction mixture 0,81g and 48,8g. The batch size in the epsilon-caprolactone polymerization was 1000g, the catalyst concentration 0,01mol-%

corresponding 40,48g in the reaction mixture. The monomers were weighted with an accuracy of 1g, the catalyst and initiator with an accuracy of 0,001g.

After the addition of the raw materials the reactor was flushed first with nitrogen (Aga, grade 99,999%) for 5min and the reactor was closed. As the agitator speed 60 1/min was adjusted. The temperature of the reaction mixture was increased from room temperature (25°C) to the level of 140°C in 0,5h , whereafter the agitation was continued at this temperature for 3,5h.

The prepared copolymers and their analysis

Table 1 summarizes the copolymerizations and their results using ε-caprolactone and D,L-lactide (ε-CL/D,L-LA), homopolymerisations of epsilon-caprolactone and the analysis results of the products. In all the polymerizations except example 18 the temperature was 140 °C and the polymerization time was 24 h (except in Example nr. 3 where it was 29 h). In the homopolymerisation runs of D,L-lactide and epsilon –caprolactone the temperature reached was 140°C and the total polymerization time was 4h. In the example 18 the temperature was 160°C and polymerization time 4h.

Molecular weights determined by gel permeation chromatography (GPC) are presented in Table 1 in terms of number average molecular weight Mn, weight average molecular weight Mw, and the polydispersity PD calculated as the ratio of the previous ones Mw/Mn. In the same Table 1 there are also presented the transition temperatures of the polymerization products, i.e. melting temperature Tm and glass transition temperature Tg, determined using differential scanning calorimetry (DSC).

Table 1

Example	ε-CL	SnOct-	Glycerol	GPC results			DSC results	
	D,L-LA-	conc.	conc.					
	ratio							
		mol/ mol ·	mol/ mol ·	M_n	M_w	PD	T_m	T_g
		monomers	monomers					
	(M-%)			(g/mol)	(g/mol)		(¡C)	(¡C)
1	100/0	0.0001	0.005	-	-	-	56	-
2	80/20	0.0001	0.005	35000	50000	1.4	47	-
3	80/20	0.0001	0.005	40000	60000	1.5	42	-

4	80/20	0,0001	0,005	40000	60000	1,5	45	-
5	80/20	0,0001	0,0005	165000	272000	1,65	46	-53
6	80/20	0,0001	0,25	-	-	-	-	-
7	100/0	0,0001	0,25	4300	5200	1,2	35	-
8	100/0	0,0001	0,05	445	729	1,6	-	-
9	100/0	0,0001	0,05	-	-	-	-	-
10	100/0	0,0001	0,25	2000	2600	1,3	-	-
11	100/0	0,0001	0,0125	-	-	-	53	-
12	100/0	0,0001	0,023	10000	12000	1,2	-	-
13	100/0	0,0001	0,034	-	-	-	43	
14	80/20	0,0001	0,25	1100	1400	1,3	-	-
15	0/100	0,0002	0,0025	85900	106700	1,24	-	47
16	100/0	0,0001	0,01	17600	20900	1,18	46	-64
17	0/100	0,0002	0,03	5100	6100	1,20	-	28
18	95/5	0,0002	0,0025	79300	137200	1,73	-52	-58

GPC measurements

The GPC-samples for molecular weight measurements were prepared by dissolution of 15 mg of sample into 10 ml of chloroform. As columns were used columns of Polymer Laboratories Ltd with pore diameters of 100 - 10 000 Å. The used detector was RI-, i.e., refractive index detector, manufactured by Waters, and a 55 min run time with a flow rate of 1 ml/min were used. To determine the molecular weights of the samples were used polystyrene (PS) standards manufactured by Polymer Laboratories, and the calibration curve based on the same. Because there is no experimental Mark-Houwink constants a and K available, the molecular weights in the Table 1 are not absolute molecular weights for the samples but relative values in comparison with PS standards.

DSC measurements

DSC-measurements were carried out for the copolymer samples by using Polymer Laboratories PL DSC-device, and for the poly-epsilon-caprolactone and CL/DL-LA 95/5 copolymer by using Mettler Toledo Star DSC 821-device. In the DSC measurements the 5 - 10 mg sample was heated with a rate of 10 °C/min in a calorimeter chamber. In order to get a similar thermic history for all the samples, the samples were heated above their

melting temperature to temperature of + 80 °C and cooled down to about -50 °C. The Tm and Tg values were determined from the curve recorded from the second heating, and they are presented in the Table 1. In Figure 1 is presented the DSC curve of the product prepared in Example 3, which is typical for all the polymers according to the invention. Figures 2 and 3 present the DSC-curves of correspondingly prepared poly-D,L-lactides .

The protein release experiments

The used chemicals

The used protein was albumin (BSA, molecular weight around 67 000 g/mol, Fluka) enrich from the serum of cows , lysozyme (molecular weight 14 600 g/mol, Fluka) and as a model substance ibuprofein (molecular weight 206,28 g/mol). The dissolution experiments were carried out at 37°C in a buffer solution with a pH of 7,0 (Reagecon)

The preparation of test specimens

The polymer used in the release experiments was polyD,L-lactide initiated with polyglycerol (PDLA-PGLE), the poly-D,L-lactide initiated by glycerol (PDLLA-G) and poly-epsilon-caprolactone and poly(epsilon-caprolactone-D,L-lactide) copolymer in which the monomer fed ratio was epsilon-CL/D,L-LA 95/5 both initiated by using glycerol. Polymers and proteins and caprolactone/lactide-copolymer and ibuprofein were homogeniously mixed in a DSM-midiextruder. The mixing time was 3min, and screw speed 50 1/min. The polymer was fed to the extruder as a premixed solid with a powdery active agent. The rectangular test specimens were cut from bars, having measures of 4,0 * 1,6 * 80mm, and which were injection molded by using DSM-mini injection molding device. The bars were cut into 4,0 mm pieces in legth.

The cylindrical test specimen were prepared by drawing the extrudate out of the DSM-midiextruder die, through an ice bath, so that the polymer was immediately solidified. The cooled polymer rope with a diameter of 1.4mm was cut into peaces of 5mm.

The preparation of film form specimen was done with a table press Fontijne TP 400 by using a 0,25mm sheet mold and force of 150kN. The cycle was as follows: preheating without compression 5min, compression with a force of 150 kN 5 min, cooling with a water cooled coled surface by using 150 kN force for 5min. Thus prepared sheets were cut to square specimen of 20mm or 5mm in their edges. The specimen were stored in refrigerator. Film samples were prepared as described by using glycerol initiated poly-D,L-

lactide and epsilon-CL/D,L-LA 95/5 copolymer and both of the proteins , and epsilon-CL/D,L-LA 95/5 copolymer and ibuprofein. The last was processed also into rectangular and cylindrical bars. The processing temperatures were adjusted for both of the mixtures based on GPC- and DSC-analysis, above the glass transition and melting temperatures.

The specimen based on polyglycerol initiated PDLLA were prepared by cutting from the midiexruder extrudate. The specimen were prepared in a way that they weighted as much as the film form specimen.

The properties of the polymers used in the dissolution experiments, and the specimen prepared thereof are presented in tables 2 and 3 in the way that table 2 includes the specimen used for the dissolution experiments and table 3 correspondingly the specimen used for the ibuprofein release experiments.

Table 2.

Polymer	PDLLA-PGLE	PDLLA-G	P(CL/D,L-LA)
Specimen	From extrudate	Film 0,25*20*20mm	Film 0,25*20*20mm
M_W (g/mol)	6100	106700	137200
T_g (°C)	27,6	46,7	-58
T_m(°C)	-	-	52,3

Table 3

Polymer	P(CL/D,L-LA)
Specimen	Rectangular bar, cylinder, film 0,25*5*5mm
M_w (g/mol)	137200
T_g (°C)	-58
T_m (°C)	52

Release experiments

The protein release experiments were carried out at 37°C in a thermostated shaker water bath. The specimen, which were 5 in parallel, were weighted into 50ml Erlenmeyer flasks. Into the flasks 30ml of buffer solution was added, and they were sealed with caps. The flasks were placed into water bath, and measurements were carried out in two weeks period daily, and from then on once a week (=7d) . to carry out the measurements each flask was removed from the bath, shaken thoroughly and 10ml of the solution was removed. The removed amount was replaced with an equal amount of clean buffer solution, and the flask was returned into the bath. The removed solution was analysed by using Unicam Helios Beta UV/VIS spectrometer , and the release curves were drawn based on the mean values of the parallel samples.

Figures 4 and 5 present the cumulative release rates for proteins BSA and lysozyme from all the matrix specimen materials. By comaring the figures , that the release rate of BSA from all the three polymers is the fastest. During a time period of one month (i.e. 30d) the cumulative release fraction of BSA from the glycerol initiated PDLLA is 42% and of lysozyme around 25%. From the polyglyserol initiated PDLLA releases BSA with the proportion of around 35% and lysozyme 15%.

The dissolution experiments of ibuprofein were carried out at a temperature of 37 C in a shaking air bath. The specimen, which were three parallel for each of the experimental point, were weighted into test tubes. Into the tubes was added 5-10 ml buffer solution depending on the specimen type, and they were sealed with caps. The test tubes were placed into the air bath, and measurements were carried out during the week daily by removing the tubes out of the bath, shaking them and the test specimen were removed. From the hydrolysis medium the released ibuprofein was analyzed by using Unicam Helios Beta UV/VIS spectrometer, and the release curves were drawn as mean values based on the parallel samples results.

Figure 6 presents the cumulative release rate of ibuprofein for different specimen calculated on surface area. The release rate from films is the fastest, since the ibuprofein is released already during 24 hours. The release rate calculated for surface area is the fastest from the rectangular bars, and the release from them continued at least for a week. From cylindrical samples all the ibuprofein was released in about four days time. The results indicate, that the release rate of the active agent can be controlled through the selection of the shape of the implanted specimen.

The release rate is for the BSA the greatest 0,06 mg/mm2*d and the smallest 0,0000014 mg/mm2*d. The release rate of lysozyme during a week is between 0,00000055 – 0,06mg/mm2*d. The release rate of ibuprofein during a month is in the range of 0,1 – 23 mg/mm2*d . The results indicate, that the the release rate of a protein type blended active agent out from a polymeric matrix material according to the invention, van be controlled through the selection of the initiator component selection in the polymer production. In general the control of the active agent release rate can be based on the matrix polymer properties as well as on the specimen shape, and it can be varied in very large range. The release total time can on the other hand be varied from a couple of hours to several months, even up to several years time spans. The figures 4 and 5 present cases , in which about half (figure 4) or about one third (figure 5) of certain protein type active agent releases in about a month. Figure 6 presents a case in which the small molecular active agent release rate is adjusted to occure in a weeks time after the implantation. These examples are however not presenting the outmost boundaries of the inventions application area, but only some typical cases , which is self evident for an expert in the field.

The controlled release of heat sensitive active agents like peptides without the reduction of their therapeutic effectiveness, is based in our invention on the fact that these agents are blended into the polymeric matrix material at a temperature which is above the melting temperature of the polymer melting temperature but at the same time below the decomposition or denaturation temperature of the active agent. The active agents can be in the mixture completely dissolved, or they can be dispersed and partially solubilized into the matrix polymer. The release itself occurs by diffusion mechanism, and it is of primary importance for the therapeutic methods , that the release rate is even at the desired level or that it is changing in a desired way with time, so that the release profile is desired. Too fast release rate , burst, or encapsulation of the active agent are not desirable , but unfortunately common cases in the present previous state of the art when matrix materials are used. By using materials according to the invention, it is possible to reach interesting, controlled release rates, even so that the release rate can be controlled by the raw material selection of the polymeric matrix material, as is described in the examples 15 – 17.

Another possibility is to control the active agent release from the polymeric matrix by adjusting the shape of the implantable specimen, due to the fact that the releasing surface area and the area/volume-ratio of the specimen are essentially important for the diffusional behavior. The material according to the invention can be processed with known processing methods be processed into bars, discs, cylindrical specimen, fibers , fabrics, tubes, spheres, microspheres and particles, just to mention some.

Claims

1. A biocompatible, and optionally at a controlled degradation rate biodegradable, polymeric material essentially being comprised of structural units derived from hydroxy acids which is at normal body temperatures a plastics-like, waxy or rubbery solid material, and being at a temperature in the range from 0 °C to 100 °C which preferably is 2-20 °C higher than body temperature molten, plasticizable mass or viscous fluid, and thus moldable by hand, inhjectable or processable by using any molding device for viscous masses, *characterized by the fact that* an active agent blended into it can be released at a controllable rate..

2. A material according to claim 1 *characterized by the fact that* the heat sensitive active agents blended into it, such as peptide drugs or peptide active agents, can be released into the body without reduction in the effectiveness of these agents at a controllable rate.

3. A material according to claim 1 *characterized by the fact that* its melting temperature, or the temperature at which the material is plasticized or is a viscous fluid, is below the degradation temperature of the active agent.

4. A material according to claim 1 *characterized by the fact* its melting temperature, or the temperature at which the material is plasticized or is a viscous fluid, is below the denaturation temperature of the blended peptide active agent.

5. A material according to claim 1 *characterized by the fact* the blended active agent releases in a time span of some hours to some years, advantageously from one day to one year, and that the said time span can be controlled through the selection of the raw substance composition.

6. A material according to claim 1 *characterized by the fact* the release of the active agent into the body occurs therapeutically or is in connection to treatment of a defect or a deficiency disease.

7. A material according to claim 1 *characterized by the fact that* the release of the active agent into the body occurs out of a specimen or device being in contact with the body.

8. A material according to claim 1 *characterized by the fact that* it can be processed by known melt processing methods into sheets, films, rods, particles, microparticles, fibers and products based on them like fabrics.

9. A material according to claim 1 *characterized by the fact that* specimen produced from it can be as heated close to their melting temperature molded by hand or by using a tool.

10. A material according to claim 1 *characterized by the fact that* the release rate of blended peptide or peptide type drug from the produced copolymer, in the units of milligrams peptide active agent per square millimeter and 24 hours, is controlled to be in the range of 0,0000001 – 0.01.

11. A method to produce biocompatible and possibly at a controlled rate biodegradable polymeric materials through ring opening polymerization of lactones essentially being comprised of structural units derived from hydroxy acids *characterized by the fact that* in the lactone ring opening polymerization the so called initiator compound is a compound having two or more functional hydroxyl groups, advantageously chosen from the group consisting of ethylene glycol, glycerol, pentaerytritol, polyvinyl alcohol, polysaccharides and hydroxyfunctional telechels, most preferably polyglyserol.

12. A method according to claim 11 *characterized by the fact that* the melting temperature, average molecular weight and time needed for the polymerization of the polymeric material can be controlled through selecting the initiator compound and its concentration in the raw material mixture.

13. A method according to claim 11 *characterized by the fact that* in the use of the polymeric material as a matrix for blended active agent, the release rate can be adjusted through the selection of the so called initiator compound and its concentration.

14. A method according to claim 11 *characterized by the fact that* a heat sensitive active agent such as peptide drug or peptide active agent blended into the polymeric matrix produced according to the invention is released at a rate, in the units of milligrams peptide active agent per square millimeter and 24 hours, in the range of 0,0000001 – 0.01.

15. Use of the polymeric material produced by the method according to claim 11 as a matrix in active agent release at a controlled rate.

16. Use of the polymeric material produced by the method according to claim 11 in the controlled release of heat sensitive active agents like peptide type drugs into the body without any essential reduction of effectiveness as incorporated in devices being in contact with body during therapeutic methods in surgery, medicine, dentistry or veterinary, or being set in contact with the body.

AMENDED CLAIMS

[received by the International Bureau on 18 July 2001 (18.07.01);
original claims 1-16 replaced by new claims 1-15 (3 pages)]

1. A method to produce such biocompatible and at a controlled rate biodegradable polymeric materials for implantation into the body during threrapeutic methods in surgery, medicine, dentistry or veterinary that at normal environmental temperatures are solid but by utilizing the temperature depenence of physical state at a temperature in the range from 36 °C to 100 °C, preferably at a temperature which is from 2 to 20 degrees C higher than body temperature, are made plastic and moldable and/or can be transferred to target area where they rapidly solidify to solid and tough plastics, waxes or rubbery materials through copolymerisation of as such known monomers being derived from hydroxy acids *characterized by the fact that*

   - the release of an active agent which may be temperature sensitive blended in the material can be controlled through methodological parameters of said polymerization by selecting to the so called initiator compound in the ring opening polymerisation of lactones an organic compound containing at least two but preferably three or more functional hydroxyl groups in its molecules one from the group including ethylene glycol, glycerol, pentaerytritol, polyglycerol, polyols, polyvinyl alcohol, polysaccharides and hydroxyfunctional telechels, most prefrerably polyglycerol, and
   - control of release of the active agent from the material is accomplished simultaneously with that the plastification temperature of the material is adjusted by selecting the combination of starting mixture and average molar mass of the product.

2. A method according to claim 1 *characterized by the fact that* the from hydroxy acid derived monomers for copolymerisation are lactide and ε-caprolactone.

3. A method according to claim 1 *characterized by the fact that* a heat sensitive active agent such as peptide drug or peptide active agent blended into the polymeric matrix produced according to the invention is released at a controlled rate which can be adjusted to be, in the units of milligrams peptide active agent per square millimeter and 24 hours, in the range of 0,0000001 – 0.01.

4. A method according to claim 1 *characterized by the fact that* the melting temperature of the produced copolymer, the rate of degradation in the body of an implant made of it and, in the use of the produced copolymer as a matrix for possibly temperature sensitive active agent, the release rate of that agent into the body all can simultaneously be adjusted through selection of the so called initiator compound and its concentration in the starting mixture of the copolymerization.

5. A method according to claim 1 *characterized by the fact that* the so called initiator compound is selected from a group of organic compounds which in their molecules contain at least two but preferably three or more functional hydroxyl groups thus including ethylene glycol, glycerol, pentaerytritol, polyglycerols, polyols, polyvinylalcohols, polysaccharides and hydroxyfunctional telechels, most preferably from the group of polyglycerols.

6. An implant material produced according to claims 1 – 5 *characterized by the fact that* the heat sensitive active agents blended into it, such as peptide drugs or peptide active agents, can be released into the body without reduction in the effectiveness of these agents at a controllable rate.

7. An implant material produced according to claims 1 – 5 *characterized by the fact that* its plasticizing temperature, or the lowest temperature at which the material becomes plastic or behaves as a viscous fluid, is below the degradation temperature of the active agent.

8. An implant material produced according to claims 1 – 5 *characterized by the fact that* its plasticizing temperature, or the lowest temperature at which the material becomes plastic or behaves as a viscous fluid, is below the denaturation temperature of the blended peptide active agent.

9. An implant material produced according to claims 1 – 5 *characterized by the fact that* the blended active agent releases in a time span of some hours to some years, advantageously from one day to one year, and that the said time span can be controlled through the selection of the raw material composition of the copolymerization.

10. An implant material produced according to claims 1 – 5 *characterized by the fact* the release of the active agent into the body occurs therapeutically or is in connection to treatment of a defect or a deficiency disease.

11. An implant material produced according to claims 1 – 5 *characterized by the fact that* the release of the active agent into the body occurs out of an implanted specimen of it, or from a device being in close contact with the body.

12. An implant material produced according to claims 1 – 5 *characterized by the fact that* it can be processed by known melt processing methods into sheets, films, rods, particles, microparticles, microspheres, fibers and products based on the latter like fabrics or mats.

13. An implant material produced according to claims 1 – 5 *characterized by the fact that* specimens produced from it when heated close to their melting temperature can be molded by hand or by using a tool.

14. An implant material produced according to claims 1 – 5 *characterized by the fact that* the release rate of a blended peptide or peptide type drug from the produced copolymer, in the units of milligrams peptide active agent per square millimeter and 24 hours, is controlled to be in the range of 0,0000001 – 0.01.

15. Use of an implant material according to claims 6 - 14 as matrix in the controlled release of heat sensitive active agents like peptide type drugs into the body without any significant reduction of effectiveness and at a suitable rate by incorporating them in devices being implanted into the body during therapeutic methods in surgery, medicine, dentistry or veterinary, or in devices being set in close contact with the body.

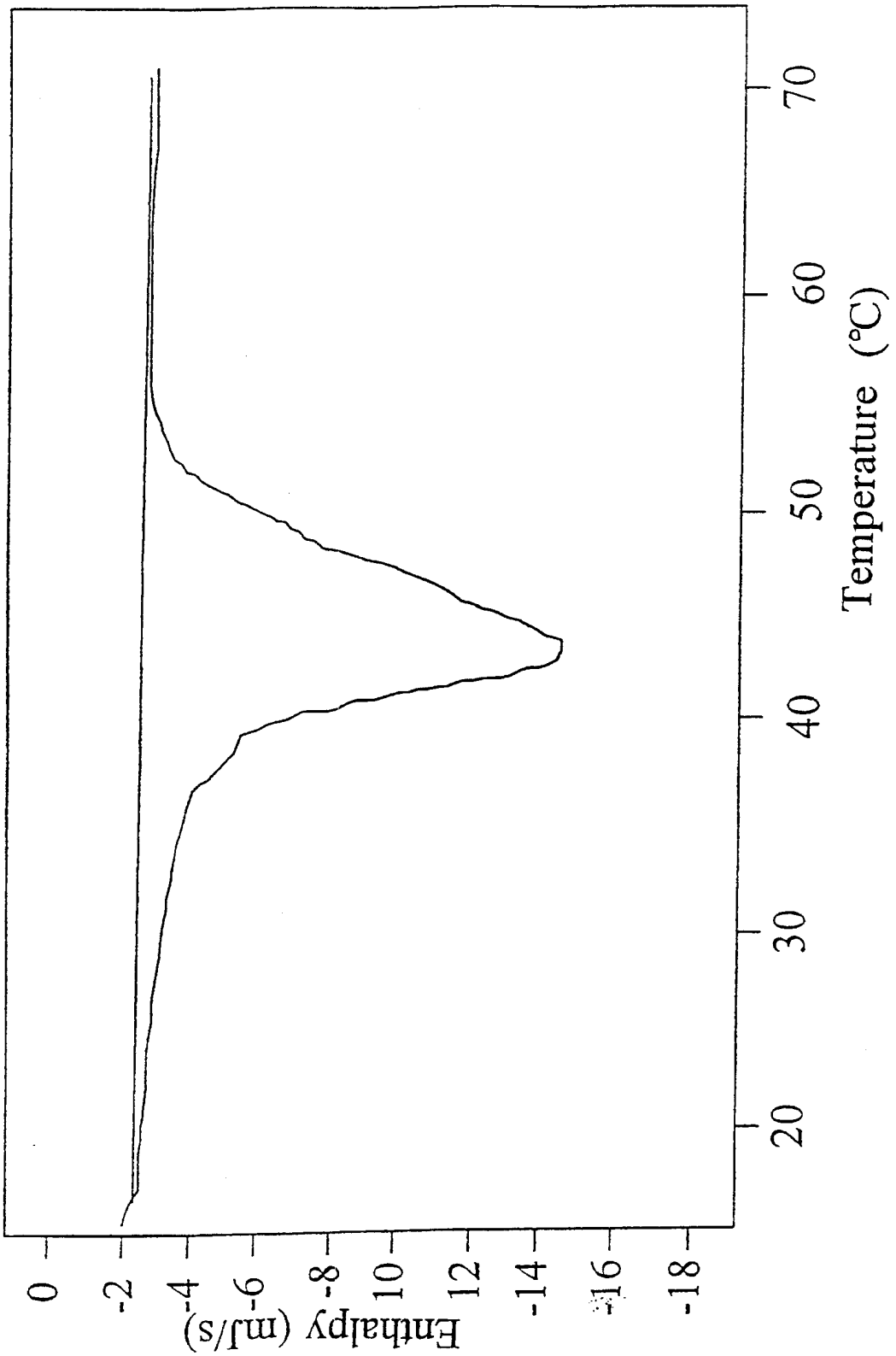
Enthalpy (mJ/s)
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
20
30
40
50
60
70
Temperature (°C)

Fig. 1

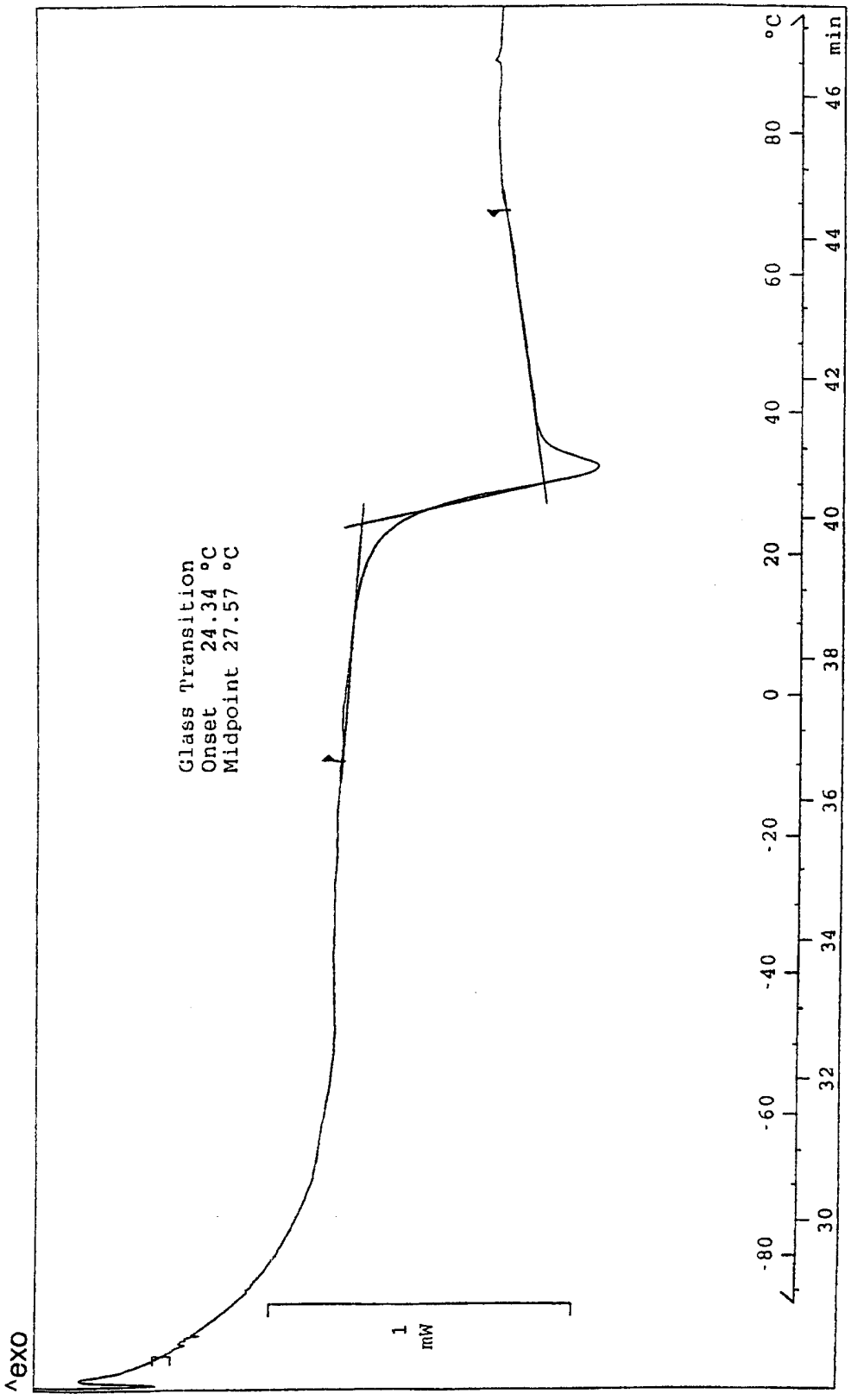
Glass Transition
Onset 24.34 °C
Midpoint 27.57 °C
^exo
1 mW
°C
min
-80
-60
-40
-20
0
20
40
60
80
30
32
34
36
38
40
42
44
46

Fig. 3

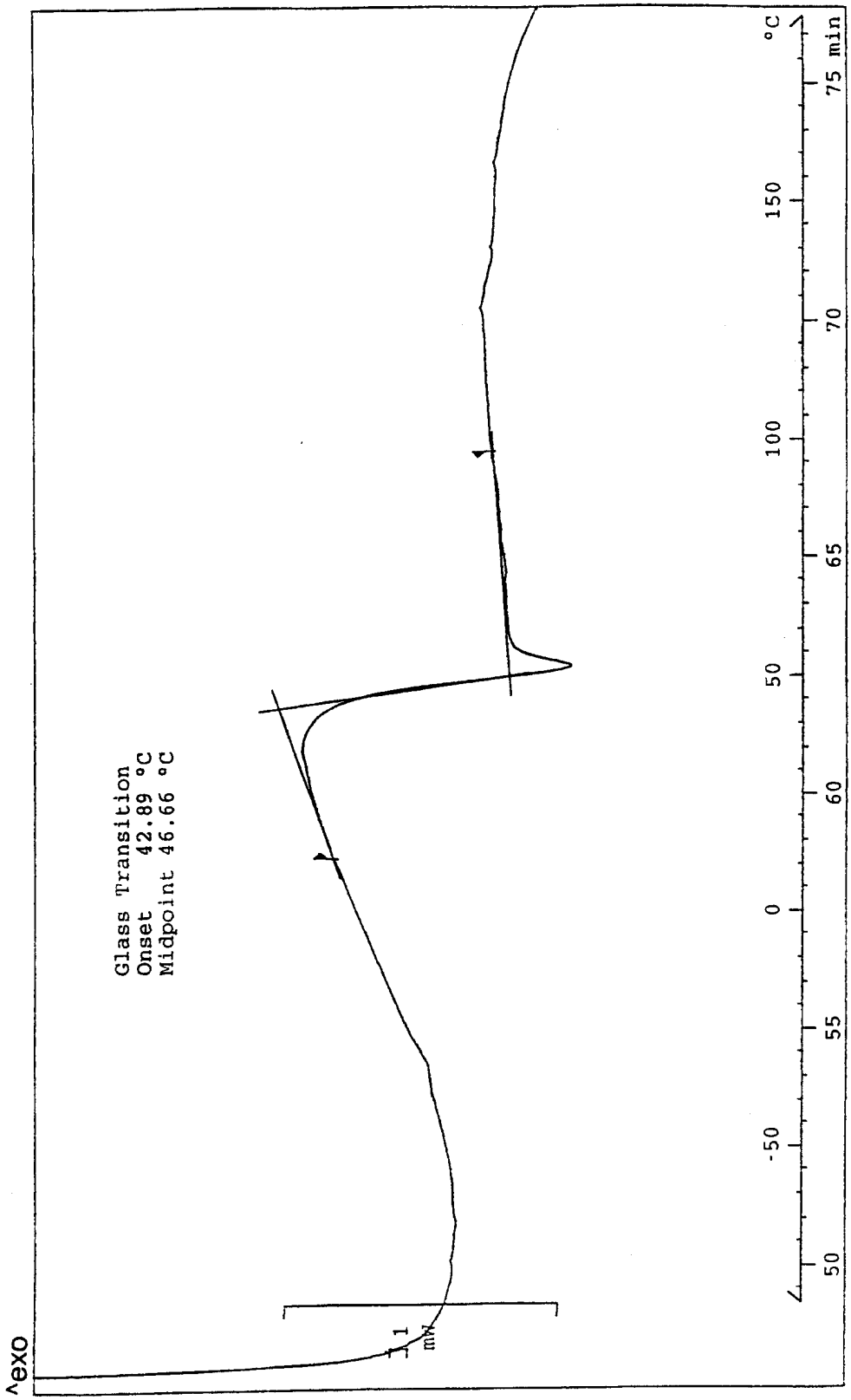
Glass Transition
Onset 42.89 °C
Midpoint 46.66 °C
^exo
1 mW
°C
75 min
150
100
50
0
-50
70
65
60
55
50

Fig. 2

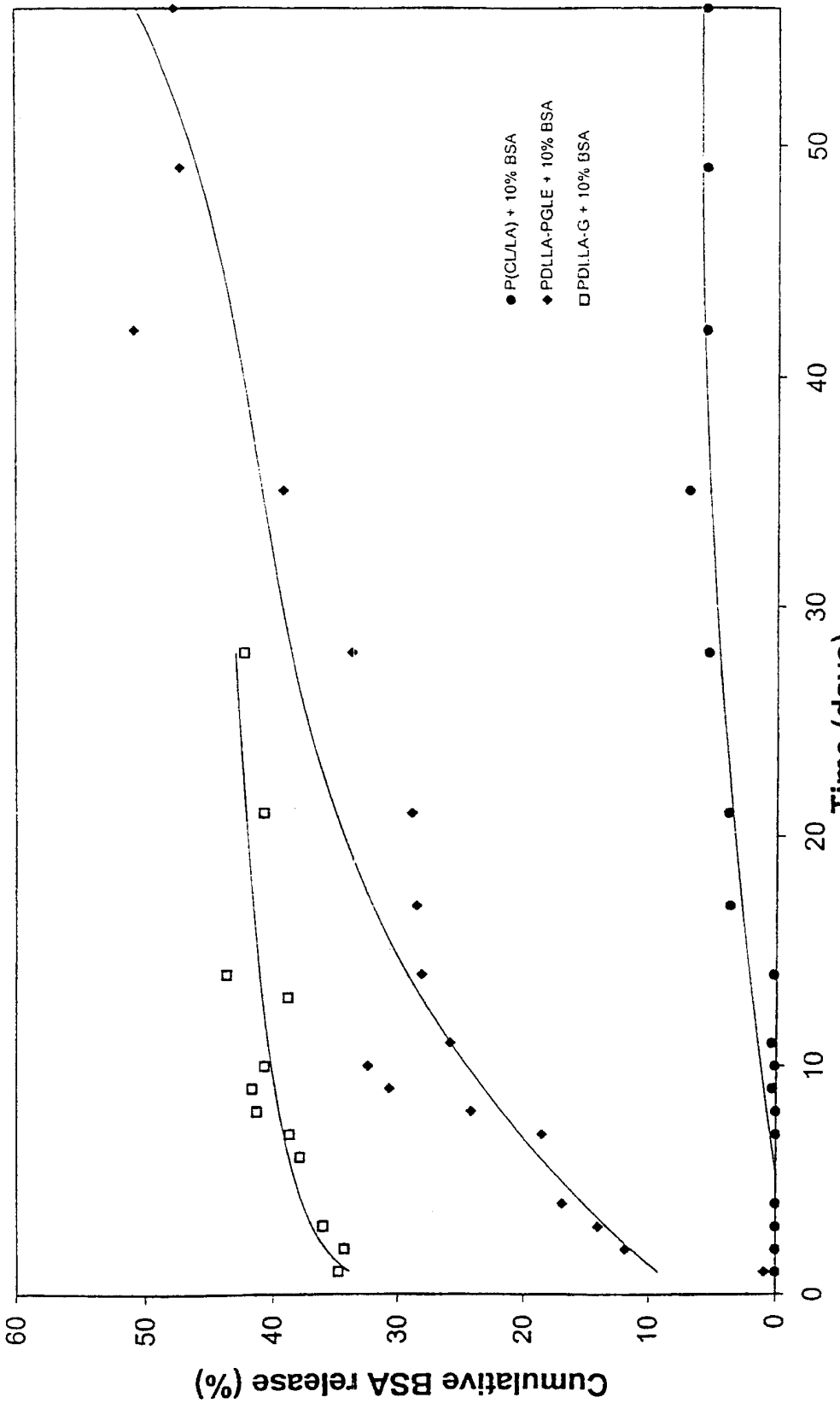
Cumulative BSA release (%)
Time (days)
P(CL/LA) + 10% BSA
PDLLA-PGLE + 10% BSA
PDLLA-G + 10% BSA
0
10
20
30
40
50
60

Fig. 4

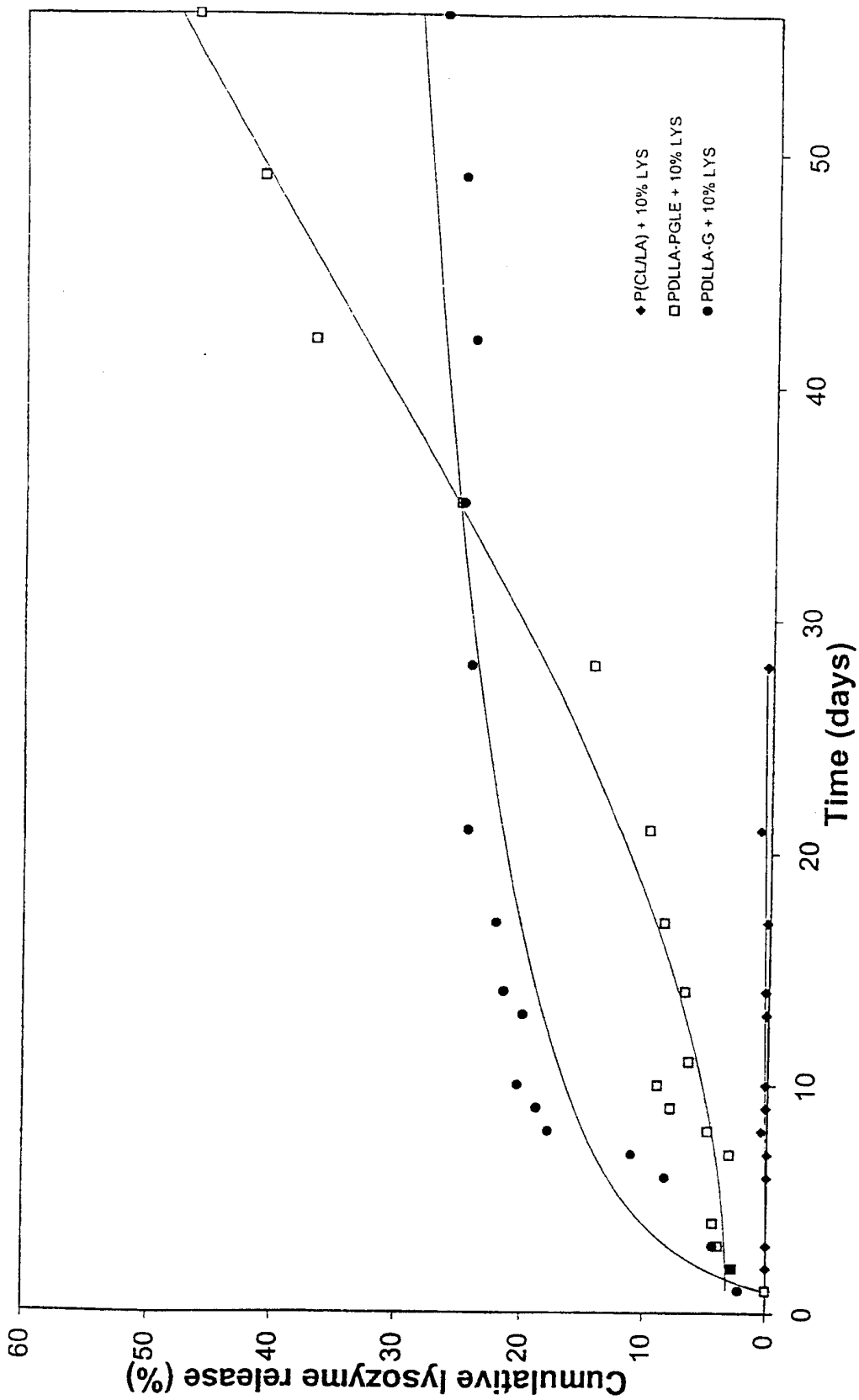
Cumulative lysozyme release (%)
Time (days)
P(CL/LA) + 10% LYS
PDLLA-PGLE + 10% LYS
PDLLA-G + 10% LYS
0
10
20
30
40
50
60

Fig. 5

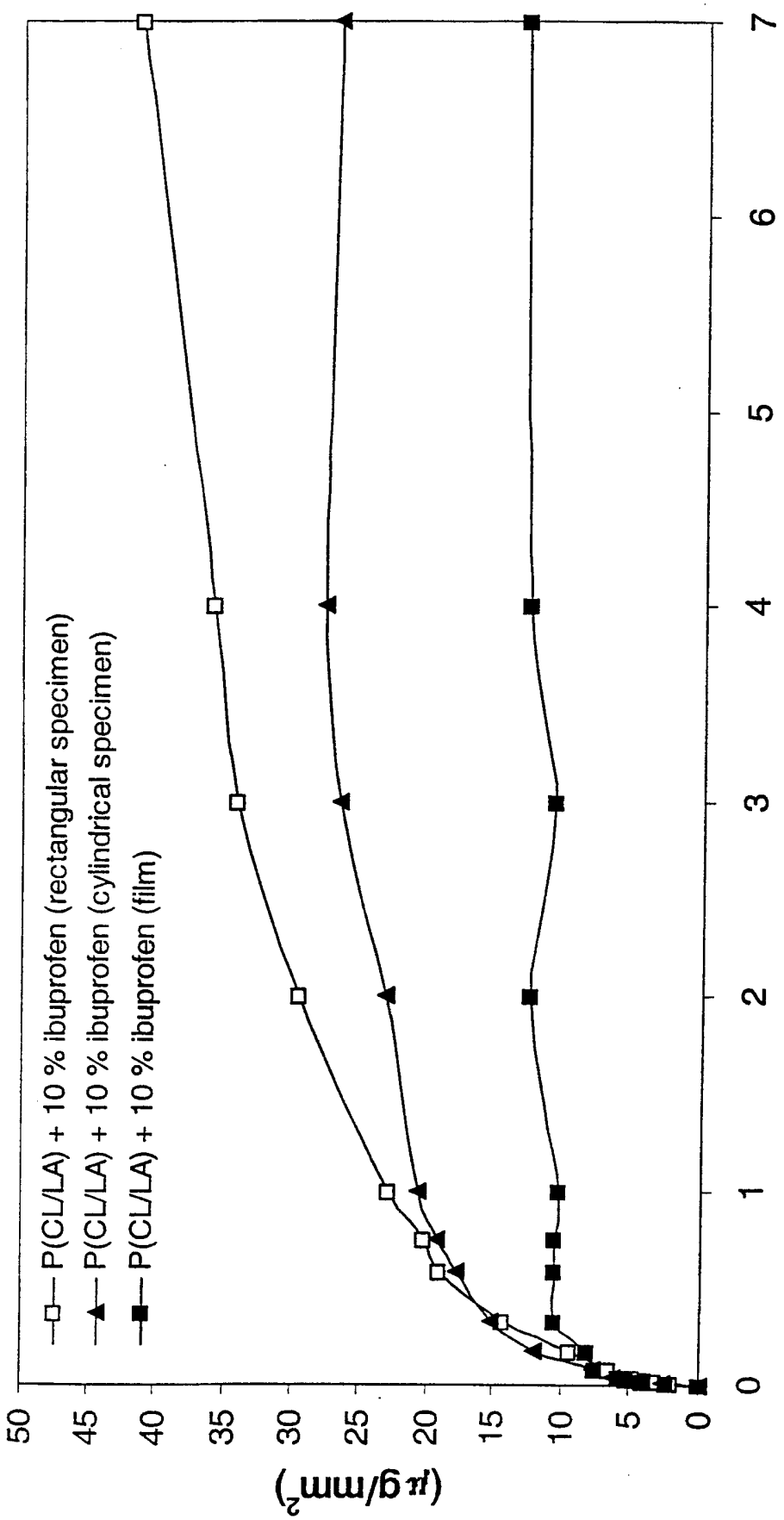
Cumulative ibuprofen release
(µg/mm²)
Time (days)
P(CL/LA) + 10 % ibuprofen (rectangular specimen)
P(CL/LA) + 10 % ibuprofen (cylindrical specimen)
P(CL/LA) + 10 % ibuprofen (film)
0
5
10
15
20
25
30
35
40
45
50
0
1
2
3
4
5
6
7

Fig. 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FI 01/00141

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: A61L 27/18, A61L 27/58, A61L 31/06, A61K 6/087
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: A61K, A61L, A61M

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

SE,DK,FI,NO classes as above

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5733950 A (DUNN ET AL), 31 March 1998 (31.03.98), abstract, claims ---	1-16
X	WO 9826814 A1 (JVS-POLYMERS OY), 25 June 1998 (25.06.98), page 6, line 21 - line 29; page 7, line 17 - line 19, abstract, claims ---	1-16
X	EP 0747072 A2 (UNITED STATES SURGICAL CORPORATION NORWALK), 11 December 1996 (11.12.96), column 3, line 42 - column 4, line 10; column 6, line 14 - line 23, abstract --- --------	1,5-11,15-16

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"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
2 July 2001	04 -07- 2001
Name and mailing address of the ISA Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Helena Danielsson/BS Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.
PCT/FI 01/00141

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5733950 A	31/03/98	US 5990194 A	23/11/99
		US 5739176 A	14/04/98
		US 5340849 A	23/08/94
		US 5632727 A	27/05/97
		US 5725491 A	10/03/98
		US 5278201 A	11/01/94
		US 5278202 A	11/01/94
		AT 151257 T	15/04/97
		AU 644581 B	16/12/93
		AU 666050 B	25/01/96
		AU 4501789 A	01/05/90
		AU 5067793 A	17/02/94
		BR 8907686 A	30/07/91
		DE 68927956 D,T	17/07/97
		DK 57291 A	03/06/91
		EP 0436667 A,B	17/07/91
		SE 0436667 T3	
		EP 0773034 A	14/05/97
		HK 1005012 A	00/00/00
		IL 91850 A	30/03/95
		IL 107393 A	29/06/95
		JP 2992046 B	20/12/99
		JP 4503163 T	11/06/92
		KR 158669 B	15/12/98
		KR 158670 B	15/12/98
		NO 304413 B	14/12/98
		NO 911277 D	00/00/00
		US 4938763 A,B	03/07/90
		WO 9003768 A	19/04/90
		ZA 8907511 A	26/06/91
WO 9826814 A1	25/06/98	EP 0946223 A	06/10/99
		FI 965067 D	00/00/00
EP 0747072 A2	11/12/96	CA 2175285 A	08/12/96
		US 5641502 A	24/06/97