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(73) Proprietor: **Takeda Chemical Industries, Ltd.**
1-1, Doshomachi 4-chome
Chuo-ku, OSAKA(JP)

Proprietor: **WAKO PURE CHEMICAL INDUSTRIES, LTD.**
10, Doshomachi-3-chome
Higashi-ku Osaka(JP)

(72) Inventor: **Yamamoto, Masaki**
23-1001, 13 Mikunihonmachi 2-chome
Yodogawa-ku Osaka 532(JP)
Inventor: **Okada, Hiroaki**
11-704, 44 Yamadaminami
Suita Osaka 565(JP)
Inventor: **Ogawa, Yasuaki**
32-503, 7 Nakahozumi 1-chome
Ibaraki, Osaka 567(JP)
Inventor: **Miyagawa, Tsutomu**
2090-21, Kasahata
Kawagoe Saitama 350(JP)

(74) Representative: **Laredo, Jack Joseph et al**
Elkington and Fife Prospect House 8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

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Description

This invention relates to a biodegradable (degradable in vivo) high molecular polymer useful as an excipient in producing pharmaceutical preparations and a method of producing the same.

Biodegradable high molecular polymers may be used, for example, as excipients for pharmaceutical preparations such as microcapsules. As examples of such biodegradable high molecular polymers, copolymers of lactic acid and glycolic acid are known to be obtainable by polycondensation of lactic acid and glycolic acid in the presence of a strongly acidic ion exchange resin (cf. U.S. Patent No. 4,273,920).

The present inventors also established that polymers or copolymers of lactic acid and/or glycolic acid may be obtained by polycondensation in the presence of a solid inorganic acid catalyst or by polycondensation without a catalyst followed by removal of water and then polycondensation (cf. EPC Patent Publication (laid open) No. 0171907).

When produced by the methods so far used, biodegradable high molecular polymers contain low molecular compounds such as an unreacted monomer or monomers and polymers of low polymerization degree, so that when they are used in producing microcapsules, incorporation rates into microcapsules of drugs to be microencapsulated are decreased or the so-called initial burst, namely extraordinarily initial drug release from microcapsules after administration, tends to increase.

Furthermore, biodegradable high molecular polymers are chemically unstable. When allowed to stand at room temperature for several weeks to several months, they undergo degradation, which results in a decrease in the polymerization degree.

In view of the above drawbacks, the present inventors treated said biodegradable high molecular polymers by a variety of methods and, as a result, it was found that the content of water-soluble low molecular compounds may be reduced by treating said polymers with water or a mixture of water and an organic solvent readily soluble in water. Further investigation based on this finding has now led to completion of the present invention.

Thus, the invention provides a biodegradable high molecular polymer with a weight average molecular weight of from 5,000 to 35,000, characterised in that said polymer consists of 50-100 mole percent of lactic acid residues and 50-0 mole percent of glycolic acid residues and a content of lactic acid or lactic acid and glycolic acid of less than 0.01 mole per 100 grams of said polymer.

Preferably the content of lactic acid or lactic acid and glycolic acid is 0.0055 mole per 100 grams of said polymer.

The invention also provides a method of producing the biodegradable high molecular polymer of the invention which method consists in preparing the polymer from lactic acid or lactic acid and glycolic acid under agueous reaction conditions, and thereafter reducing the content of lactic acid or lactic acid and glycolic acid in said polymer to a level of less than 0.01 mole per 100 grams of said polymer by extraction with water or a mixture of water and a water-soluble organic solvent, characterised in that said extraction step comprises dissolving said polymer containing not less than 0.01 mole percent of lactic acid or lactic acid and glycolic acid in a 3 to 20 times amount (w/v) of an organic solvent, and pouring the resulting solution into water with stirring at a temperature of from 20 °C to 70 °C.

The water-soluble organic solvent is preferably ethanol.

The invention additionally provides a microcapsule for injectable sustained release containing effective amount of an active ingredient and as an excipient, a biodegradable high molecular polymer as defined above and a method of producing the microcapsule which comprises preparing a water/oil (w/o) emulsion with a solution containing said active ingredient serving as an inner water phase and a solution containing said biodegradable polymer serving as an oil phase; dispersing said emulsion in a water (w) phase to yield a (w/o)/w emulsion; and subjecting the resulting emulsion to contact with a third aqueous phase to yield a (w/o)/w ternary phase emulsion, the solvent in the oil phase being desorbed.

The invention further provides the use of a biodegradable high molecular polymer as defined above as a matrix in a microcapsule for prolonged delivery of an active ingredient from said microcapsule.

The biodegradable high molecular polymer to serve as the starting material in performing the method of the invention may be produced by any method, for example by the method described in the above-cited U.S. Patent No. 4,273,920 and EPC Patent Publication (laid open) No. 0171907.

Said starting material contains lactic acid or lactic acid and glycolic acid in an amount of not less than 0.01 mole per 100 grams thereof.

The content of water-soluble monobasic acid may be determined by ordinary neutralization titration. Thus, for example, 300 mg of a starting high molecular compound is dissolved in 10 ml of dichloromethane, the solution is stirred and shaken with 20 ml of distilled water for 10 minutes, the mixture is separated into an aqueous phase and an oily phase using a centrifuge, and the aqueous phase is assayed for free acids

by neutralization titration using N/100 aqueous NaOH solution with phenolphthalein as an indicator. The number of moles of NaOH required for neutralization is converted to a free monobasic acid content.

The biodegradable high molecular polymer according to the present invention preferably has good biocompatibility and thus includes, among others, hydroxy acid polyesters (e.g. polylactic acid, polyglycolic acid, polyhydroxybutyric acid).

Said high molecular polymer may be a copolymer produced by using two or more different monomers as the monomers for forming said high molecular polymer. Said high molecular polymer may also be a block polymer or a graft polymer.

Among the high molecular polymers mentioned above, those degradable in vivo at relatively high degradation rates are preferred.

Preferred examples of the high molecular polymer according to the present invention are polylactic acid and copolymers of lactic acid and glycolic acid. As the copolymers of lactic acid and glycolic acid, mention may be made of those comprising about 100-50 mole percent of lactic acid with the balance being glycolic acid.

Furthermore, those copolymers of lactic acid and glycolic acid which have a weight average molecular weight of about 2,000-50,000 are preferred.

Further mention may be made of those copolymers of lactic acid and glycolic acid which are composed of about 90-50 mole percent of lactic acid and about 10-50 mole percent of glycolic acid and have a weight average molecular weight of about 5,000-35,000 and an inherent viscosity of about 0.05-0.5 dl/g as determined with a 0.5 weight percent chloroform solution thereof.

Examples of the organic solvent readily soluble in water which are suited for use in carrying out the method of the present invention are acetone, methanol, ethanol, tetrahydrofuran, acetonitrile and ethyl acetate. Among these, preferred from the safety viewpoint are acetone and ethanol, and ethanol is more preferred.

When a mixture of water and such readily water-soluble organic solvent is used, the water/organic solvent ratio (v/v) may be within the range of about 100/0 to 100/100, especially 100% water.

In carrying out the method of the invention, high molecular polymer as the raw material is preferably dissolved in a 3 to 20 timed amount (w/v) of an organic solvent [e.g. halogenated alkane (e.g. dichloromethane, chloroform, dichloroethane, trichloroethane), acetone, tetrahydrofuran, ethyl acetate, benzene] in advance, prior to treatment by said method since the use thereof in a solution form is advantageously more efficient, although it may be used also in solid form (e.g. powder). Thus, when brought into contact with water or a mixture of water and an organic solvent readily soluble in water, such a high molecular polymerization product dissolved in an organic solvent may acquire a markedly increased contact surface area upon application of stirring or some other appropriate means.

The method according to the invention is conducted generally at a temperature of about 0-90 °C, preferably about 20-70 °C.

In accordance with the present invention, the raw material biodegradable high molecular polymerization product is mixed with water or a mixture of water and an organic solvent readily soluble in water with stirring to thereby remove water-soluble low molecular compounds as a result of dissolution thereof in water or said mixture. Since the desired biodegradable high molecular polymer is insoluble in water or said mixture on that occasion, said low molecular compounds may be separated from the desired high molecular polymer.

Although the ratio in quantity between water or a mixture of water and an organic solvent readily soluble in water and the raw material high molecular polymerization product is not critical for the method according to the invention, it is desirable that water or the mixture should be used in a large excess. The treatment may also be carried out in a system equipped with an appropriate collecting means and suited for continuous rinsing with water.

The above-mentioned stirring of water or the mixture may be effected by means of any of the ordinary stirrers, shakers, blenders and the like. Means highly capable of causing sufficient mixing to remove unreacted material or materials and water-soluble low molecular compounds from said high molecular polymer to a satisfactory extent are desirable.

Since the desired high molecular polymer is not dissolved in water or said mixture but precipitates or separates, it may be recovered by separating the precipitate, liquid droplets or solids by, for example, filtration or the like, and then drying the same.

By carrying out the method according to the invention, water-soluble low molecular compounds may be eliminated from the raw material high molecular polymerization product with good efficiency.

In purifying high molecular polymerization products in general, the primary object is to remove catalysts, gaseous monomers, or highly toxic monomers (e.g. vinyl chloride). In some instances, removal of

low molecular compounds and/or unreacted materials is also intended, like the present invention. In such instances, the distillation method is mostly employed to thereby remove initial boiling fractions. However, removal of trace amounts of water-soluble substances is generally unnecessary and, as a general rule, such a method of removing trace amounts of water-soluble substances as provided by the present invention is thought unnecessary and is not in practice.

The biodegradable high molecular polymer thus obtained has the following features:

(1) The high molecular polymer obtained by the method of the present invention as it is as well as in pharmaceutical preparations produced by using said high molecular polymer shows good stability in aging.

(2) When microcapsules are produced by using the high molecular polymer obtained by the method of the present invention in w/o/w emulsion formation, followed by in-water drying, increased rates of drug incorporation in said microencapsulation are obtained.

(3) When microcapsules are produced by the method mentioned above in (2) using the high molecular polymer obtained by the method of the present invention, the initial burst (release by one day) of drugs from microcapsules is markedly reduced, so that the drugs are constantly released over a prolonged period of time.

The biodegradable high molecular polymer obtained by the method of the present invention may be used, for instance, as an excipient for microcapsules. Thus, for example, sustained release microcapsules containing a water-soluble ingredient, e.g. peptides such as those having luteinizing hormone releasing hormone-like activity and thyroid hormone releasing hormone-like activity may be produced by preparing a w/o emulsion with a solution containing a water-soluble ingredient serving as the inner water phase, with a drug-retaining substance (most preferably gelatin, albumin, pectin, agar, or the like) added to the inner water phase as desired, and a solution containing the biodegradable high molecular polymer obtained by the method of the invention serving as the oil phase, dispersing said emulsion in a water phase to give a w/o/w emulsion (preferably adjusting the viscosity of the w/o emulsion for preparing said w/o/w emulsion to about 150-10,000 cp), and subjecting the latter emulsion to a third aqueous layer to give a w/o/w ternary layer emulsion and then the solvent in the oil layer is desorbed. The thus-obtained microcapsules may be administered as a sustained release injection. The dose of such microcapsules may vary depending on the kind and content of the water-soluble active ingredient, the dosage form, the duration of drug release, the animal to be treated (e.g. warm-blooded mammal such as mouse, rat, horse, cattle or human) and the object of administration. In any case, a dose is sufficient if it corresponds to the effective amount of said active ingredient. For instance, the dose may be suitably selected within the range of about 0.02-200 mg/kg, preferably about 0.2-40 mg/kg, of microcapsules per administration. In the use in a suspension form for the above-mentioned administration as an injection, the dose may be suitably selected within the range of about 0.1-5 ml, preferably about 0.5-3 ml, of the suspension.

Brief Description of the Drawing

Fig. 1 represents the changes with time in residual drug content in the microcapsules obtained in Reference Example 3.

Examples

The following reference examples and working examples illustrate the invention in further detail.

Reference Example 1

About 10 g of each of three lactic acid-glycolic acid copolymers (ratio 75/25; average molecular weight 12,500) synthesized by different methods [i.e. (1) strongly anionic ion exchange resin catalyst method, (2) solid acid (acid clay) catalyst method and (3) catalystless method, each being a polycondensation method described below] was dissolved in about 20 ml of dichloromethane and the solution was poured into 1,000 ml of hot water at about 60°C with stirring, whereby the dichloromethane was evaporated and the high molecular polymer came up to the surface. The latter was collected and dried under reduced pressure for drying and solvent removal to give the desired high molecular polymer. The polymer obtained was placed in a closed vessel and stored at room temperature. For stability evaluation, the thus stored sample was subjected to GPC (gel permeation chromatography) for average molecular weight determination. As shown by the results given in Table 1, marked improvement in stability was noted with the high molecular polymers obtained in accordance with the invention and having low free monomer acid contents.

Table 1

Method synthesis		Lot No.	Free acid content(*)	Average mol. wt.		Initial inherent viscosity dl/g
				Initial	After storage (months) at room temperature	
(1)	Control	1-1	0.02	12,000	(12) 4,400	0.14
	Invention	1-2	0.0033	11,900	(12) 11,600	0.14
(2)	Control	2-1	0.0132	12,500	(5) 4,100	0.15
	Invention	2-2	0.0033	12,500	(5) 11,500	0.15
(3)	Control	3-1	0.0165	12,500	(5) 5,800	0.15
	Invention	3-2	0.0055	12,500	(5) 12,000	0.15

(*) Method of free acid determination: 300 mg of a sample is dissolved in 10 ml of dichloromethane, the solution is extracted with 20 ml of distilled water and 10 ml of the aqueous layer is titrated to neutral with 0.01 N NaOH (phenolphthalein indicator).
The values of free acid content given in Table 1 indicates the number of moles of free acids dissolved in water per 100 grams of the high molecular polymer as calculated on the assumption that each of said free acids is a monobasic acid.

In preparing the lactic acid-glycolic acid copolymers used in the above, the following methods were used:

(1) Strongly anionic exchange resin catalyst method:

To 160 g of 85% aqueous lactic acid solution and 38 g of glycolic acid was added 6.8 g of Dowex 50W and the mixture was heated in a nitrogen atmosphere under reduced pressure for 6 hours in a manner such that the inside temperature and pressure were initially 105 °C and 350 mmHg, respectively, and finally 150 °C and 30 mmHg, respectively, while removing the water distilled. Then, 6.8 g of Dowex 50W was added and the reaction was further carried out at 175 °C and 3-5 mmHg for 40 hours. While hot, the reaction mixture was filtered to thereby remove the Dowex 50W. The filtrate was cooled to give a lactic acid-glycolic acid copolymer.

(2) Solid acid (acid clay) catalyst method:

To 160 g of 85% aqueous lactic acid solution and 38 g of glycolic acid was added 17.4 g of acid clay and the mixture was heated in a nitrogen atmosphere for 6 hours while increasing the temperature and degree of pressure reduction stepwise in a manner such that the inside temperature and pressure were initially 105 °C and 350 mmHg, respectively, and finally 150 °C and 30 mmHg, respectively and while removing the water distilled. Thereafter, the inside pressure was reduced to 3 mmHg and heating was conducted for 36 hours while maintaining the inside temperature at 175 °C. The reaction mixture was cooled to room temperature, 400 ml of methylene chloride was added, the resulting mixture was stirred for dissolution of the polymerization product, the acid clay was then filtered off, and the filtrate was concentrated to dryness to give a white lactic acid-glycolic acid copolymer.

(3) Catalystless method:

To 160 g of 85% aqueous lactic acid solution was added 38 g of glycolic acid and the mixture was heated in a nitrogen atmosphere under reduced pressure for 6 hours in a manner such that the inside temperature and pressure were initially 105 °C and 350 mmHg, respectively, and finally 150 °C and 30 mmHg, respectively, while removing the water distilled. Heating under reduced pressure was further conducted at 3-5 mmHg and 175 °C for 36 hours. Upon cooling to room temperature, there was obtained a colorless lactic acid-glycolic acid copolymer.

Reference Example 2

In 800 mg of distilled water were dissolved with warming 450 mg of leuprolide [the acetate of a polypeptide having the formula (Pyr)Glu-His-Trp-Ser-Tyr-D-Leu-Leu-Arg-Pro-NH-CH_2CH_3 and having luteinizing hormone releasing hormone (LH-RH)-like activity, wherein the abbreviations according to the IUPAC-IUB Commission on Bio-chemical Nomenclature are used, the amino acids, unless otherwise specified, being in the L form] and 40 mg of gelatin (internal water phase). Separately, 3.5 g of each of the lactic acid-glycolic

acid copolymers of Reference Example 1, Lot Nos. 2-1, 2-2, 3-1 and 3-3, was dissolved in 5 ml of methylene chloride (oil phase). The oil phase was added to the water phase with stirring using Polytron (Kinematica, Switzerland) to give a w/o emulsion. The viscosity at 15°C of the w/o emulsions derived from Lot No. 2-2 and No. 3-2 was 2,000. Separately, 200 ml of a 0.5% aqueous solution of polyvinyl alcohol was prepared. To this was added the w/o emulsion with stirring using an Autohomomixer (Tokushu Kika, Japan), whereby a (w/o)/w emulsion was produced.

This emulsion was stirred with a propeller in a nitrogen stream for about 2 hours to thereby evaporate off the dichloromethane and to solidify the oil phase. The thus-formed microcapsules were collected by filtration, rinsed with water and dried. In 2 ml of dichloromethane and 7 ml of distilled water were dissolved 50 mg of the microcapsules obtained in the powder form, and the leuprolide concentration in the distilled water was determined by reversed-phase HPLC and the content of leuprolide incorporated into the microcapsules was calculated. Said content is given in Table 2 in terms of percentage to the theoretical content.

Table 2

	Lot	Leuprolide content (%)
Invention	2-2	95
Invention	3-2	97
Control	2-1	84
Control	3-1	64

As is evident from Table 2, the use of the high molecular polymers obtained by the method of the invention gave higher rates of leuprolide incorporation.

Reference Example 3

The microcapsules prepared in Reference Example 2 were weighed in 50-mg portions and each portion was dispersed in 10 ml of phosphate buffer (pH 7.0). The release of leuprolide from the microcapsules into the buffer was measured by stirring each dispersion at 25 rpm in a constant-temperature vessel maintained at 37°C.

With the leuprolide content as found in Reference Example 2 taken as the initial value, residual leuprolide percentages to the initial value were determined by subjecting the filtrates obtained after separation of microcapsules by filtration after storage at 37°C for 1, 7, 14, 21 and 28 days to HPLC for determination of residual leuprolide. The percentage values thus obtained are shown in Fig. 1.

The data shown in Fig. 1 clearly indicate that the use of the high molecular polymers according to the present invention reduced the initial burst (release by one day) and allowed leuprolide release of approximately zero order over 1-1.5 months.

In Fig. 1, □ is for the high molecular polymer of Lot No. 2-1, ■ for the high molecular polymer of Lot No. 2-2, o for the high molecular polymer of Lot No. 3-1 and ● for the high molelcular polymer of Lot No. 3-2.

Reference Example 4

A high molecular polymer was synthesized in the same manner as in Reference Example 1, method (3). The free acid content was found to be 0.021 mole per 100 g of the high molecular polymer obtained.

Reference Example 5

A high molecular polymer was produced by weighing 191 g of 85% aqueous lactic acid solution, 17.5 g of glycolic acid and 6.8 g of Dowex 50W and following the procedure of Reference Example 1, method (1). After removal of the water distilled, the reaction was performed at 3 mmHg and 175°C for 72 hours. In this case, the free acid content was 0.018 mole per 100 g of the high molecular polymer obtained.

Reference Example 6

By following the procedure of Reference Example 1, method (3), 150 g of 85% aqueous lactic acid solution was treated and the water distilled was removed. Thereafter, the reaction was further conducted at 3 mmHg and 175°C for 12 hours to give a high molecular polymer. In this case, the free acid content was 0.035 mole per 100 g of the high molecular polymer obtained.

Example 1

The polylactic acid-glycolic acid obtained in Reference Example 4 by the catalystless method and having a lactic acid/glycolic acid ratio of 75/25 and an average molecular weight of 13,000 was dissolved in dichloromethane, and the solution was poured into hot water at about 60°C with stirring, whereupon a high molecular polymer came up to the surface. This was collected and dried. The thus-obtained copolymer had a lactic acid/glycolic acid ratio of 75/25, a molecular weight of 13,000 and a free acid content of 0.005 mole per 100 g of the high molecular polymer. Its inherent viscosity was 0.15 as determined in chloroform at a concentration of 0.5%.

Example 2

The polylactic acid-glycolic acid synthesized in Reference Example 5 using Dowex 50W as a catalyst and having a lactic acid/glycolic acid ratio of 90/10 and an average molecular weight of 20,000 was dissolved in acetone, and the solution was poured into warm water at about 40°C, whereupon a high molecular polymer came up to the surface. The polymer was collected and dried. The copolymer thus obtained had a free acid content of 0.008 mole per 100 g of the high molecular polymer and an inherent viscosity of 0.48 as determined in chloroform at a concentration of 0.5%.

Example 3

The polylactic acid synthesized in Reference Example 6 without a catalyst and having an average molecular weight of 8,000 was finely pulverized and then treated in warm water at 50°C for 20 minutes with stirring, followed by filtration and drying. The thus-obtained high molecular compound had a free acid content of 0.009 mole per 100 g thereof and an inherent viscosity of 0.10 as determined in chloroform.

Example 4

The same high molecular polymer as used in Example 1 was rinsed in a 1:1 mixture of water and ethanol at 50°C and then treated in the same manner as in Example 1. The high molecular polymer obtained had a free acid content of 0.0028 mole per 100 g of the high molecular polymer.

Example 5

In dichloromethane (oil phase) 3 g of lactic acid-glycolic acid copolymer obtained in Reference Example 4 having a lactic acid/glycolic acid ratio of 75/25 and an average molecular weight of 13,000 was dissolved. 60 mg of thyroid hormone releasing hormone tartarate (TRH-T) was dissolved in 800 mg of water (inner water phase).

The oil phase was added to the inner water phase with stirring using Polytron to give a w/o emulsion. After cooling at 15°C, the w/o emulsiuon was added to 200 ml of 0.5% aqueous solution of polyvinyl alcohol, separately prepared and cooled at 15°C, with stirring using an Autohomomixer to give a (w/o)/w emulsion.

This emulsion was stirred with a propeller in a nitrogen stream for about 2 hours to thereby cause evaporation of the dichhoromethane and solidification of the oil phase. The thus formed microcapsules were collected by filtration, rinsed with water and dried to form a powder.

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A biodegradable high molecular polymer with a weight average molecular weight of from 5,000 to 35,000, characterised in that said polymer consists of 50-100 mole percent of lactic acid residues and

50-0 mole percent of glycolic acid residues and a content of lactic acid or lactic acid and glycolic acid of less than 0.01 mole per 100 grams of said polymer.

2. A biodegradable high molecular polymer according to Claim 1, wherein said content of lactic acid or lactic acid and glycolic acid is 0.0055 mole or less per 100 grams of said polymer.

3. A method of producing the polymer of Claim 1, which method consists in preparing the polymer from lactic acid or lactic acid and glycolic acid under aqueous reaction conditions, and thereafter reducing the content of lactic acid or lactic acid and glycolic acid in said polymer to a level of less than 0.01 mole per 100 grams of said polymer by extraction with water or a mixture of water and a water-soluble organic solvent, characterised in that said extraction step comprises dissolving said polymer containing not less than 0.01 mole percent of lactic acid or lactic acid and glycolic acid in a 3 to 20 times amount (w/v) of an organic solvent, and pouring the resulting solution into water with stirring at a temperature of from 20 °C to 70 °C.

4. A method according to Claim 3, wherein said water-soluble organic solvent is ethanol.

5. A microcapsule for injectable sustained release containing an effective amount of an active ingredient and, as an excipient, a biodegradable high molecular polymer as claimed in Claim 1 or Claim 2.

6. A microcapsule as claimed in Claim 5, wherein said active ingredient is a water-soluble peptide.

7. A method of producing a microcapsule as claimed in Claim 5 or 6 which comprises preparing a water/oil (w/o) emulsion with a solution containing said active ingredient serving as an inner water phase and a solution containing said biodegradable polymer serving as an oil phase; dispersing said emulsion in a water (w) phase to yield a (w/o)/w emulsion; and subjecting the resulting emulsion to contact with a third aqueous phase to yield a (w/o)/w ternary phase emulsion, the solvent in the oil phase being desorbed.

8. The use of a biodegradable high molecular polymer according to Claim 1 as a matrix in a microcapsule for prolonged delivery of an active ingredient from said microcapsule.

Claims for the following Contracting State : AT

1. A method of producing a biodegradable high molecular polymer with a weight average molecular weight of from 5,000 to 35,000, and having 50-100 mole percent of lactic acid residues and 50-0 mole percent of glycolic acid residues, which method consists in preparing the polymer from lactic acid or lactic acid and glycolic acid under aqueous reaction conditions and thereafter reducing the content of lactic acid or lactic acid and glycolic acid in said polymer to a level of less than 0.01 mole per 100 grams of said polymer by extraction with water or a mixture of water and a water-soluble organic solvent, characterised in that said extraction step comprises dissolving said polymer containing not less than 0.01 mole percent of lactic acid and glycolic acid in a 3 to 20 times amount (w/v) of an organic solvent, and pouring the resulting solution into water with stirring at a temperature of from 20 °C to 70 °C.

2. A method according to Claim 1, wherein said content of lactic acid or lactic acid and glycolic acid is reduced to a level of 0.0055 mole or less per 100 grams of said polymer.

3. A method according to Claim 1 or Claim 2, wherein said water-soluble organic solvent is ethanol.

4. A method of producing a microcapsule for injectable sustained release which contains an effective amount of an active ingredient and, as an excipient, a biodegradable high molecular polymer as defined in Claim 1 having a content of lactic acid or lactic acid and glycolic acid of less than 0.01 mole per 100 grams of said polymer, or as defined in Claim 2 having a content of lactic acid or lactic acid and glycolic acid of 0.0055 mole or less per 100 grams of polymer, which method comprises preparing a water/oil (w/o) emulsion with a solution containing said active ingredient serving as an inner water phase and a solution containing said biodegradable polymer serving as an oil phase; dispersing said emulsion in a water (w) phase to yield a (w/o)/w emulsion; and subjecting the resulting emulsion to contact with a

third aqueous phase to yield a (w/o)/w ternary phase emulsion, the solvent in the oil phase being desorbed.

5. A method according to Claim 4, wherein said active ingredient is a water-soluble peptide.

6. The use of a biodegradable high molecular polymer as a matrix in a microcapsule for prolonged delivery of an active ingredient from said microcapsule, said polymer being as defined in Claim 1.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Biologisch abbaubares hochmolekulares Polymer mit einem Gewichtsmittel des Molekulargewichts von 5 000 bis 35 000, dadurch gekennzeichnet, daß das Polymer aus 50 bis 100 Mol-% Milchsäure-Resten und 50 bis 0 Mol-% Glycolsäure-Resten besteht und einen Gehalt an Milchsäure oder an Milchsäure und Glycolsäure von weniger als 0,01 mol auf 100 g des Polymers aufweist.

2. Biologisch abbaubares hochmolekulares Polymer nach Anspruch 1, worin der Gehalt der Milchsäure oder der Milchsäure und Glycolsäure 0,0055 mol oder weniger auf 100 g des Polymers beträgt.

3. Verfahren zur Herstellung des Polymers nach Anspruch 1, bestehend aus dem Herstellen des Polymers aus Milchsäure oder Milchsäure und Glycolsäure unter wäßrigen Reaktionsbedingungen und danach dem Reduzieren des Gehalts der Milchsäure oder der Milchsäure und Glycolsäure in dem Polymer auf einen Wert von weniger als 0,01 mol auf 100 g des Polymers durch Extraktion mit Wasser oder einem Gemisch aus Wasser und einem wasserlöslichen organischen Lösungsmittel, dadurch gekennzeichnet, daß dieser Schritt der Extraktion das Auflösen des nicht weniger als 0,01 Mol-% Milchsäure oder Milchsäure und Glycolsäure enthaltenden Polymers in der 3- bis 20-fachen Menge (Gew./Vol.) eines organischen Lösungsmittels und das Eingießen der resultierenden Lösung in Wasser unter Rühren bei einer Temperatur von 20 °C bis 70 °C umfaßt.

4. Verfahren nach Anspruch 3, worin das wasserlösliche organische Lösungsmittel Ethanol ist.

5. Mikrokapsel zur verlängerten Abgabe eines injizierbaren Stoffes, enthaltend eine wirksame Menge eines aktiven Inhaltsstoffs und als Exzipienten ein biologisch abbaubares hochmolekulares Polymer, wie es in Anspruch 1 oder Anspruch 2 beansprucht ist.

6. Mikrokapsel nach Anspruch 5, worin der aktive Inhaltsstoff ein wasserlösliches Peptid ist.

7. Verfahren zur Herstellung einer Mikrokapsel nach Anspruch 5 oder Anspruch 6, umfassend das Herstellen einer Wasser/Öl(W/O)-Emulsion mit einer den aktiven Inhaltsstoff enthaltenden wäßrigen Lösung, die als innere Wasser-Phase dient, und einer das biologisch abbaubare Polymer enthaltenden Lösung, die als Öl-Phase dient, das Dispergieren der Emulsion in einer Wasser(W)-Phase zur Bildung einer (W/O)/W-Emulsion und das In-Berührung-Bringen der resultierenden Emulsion mit einer dritten wäßrigen Phase zur Bildung einer (W/O)/W-Ternär-Phasen-Emulsion, wobei das Lösungsmittel in der Öl-Phase desorbiert wird.

8. Verwendung eines biologisch abbaubaren hochmolekularen Polymers nach Anspruch 1 als Matrix in einer Mikrokapsel für die verlängerte Abgabe eines aktiven Inhaltsstoffs aus dieser Mikrokapsel.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Herstellung eines biologisch abbaubaren hochmolekularen Polymers mit einem Gewichtsmittel des Molekulargewichts von 5 000 bis 35 000 und mit 50 bis 100 Mol-% Milchsäure-Resten und 50 bis 0 Mol-% Glycolsäure-Resten, bestehend aus dem Herstellen des Polymers aus Milchsäure oder Milchsäure und Glycolsäure unter wäßrigen Reaktionsbedingungen und danach dem Reduzieren des Gehalts der Milchsäure oder der Milchsäure und Glycolsäure in dem Polymer auf einen Wert von weniger als 0,01 mol auf 100 g des Polymers durch Extraktion mit Wasser oder einem Gemisch aus Wasser und einem wasserlöslichen organischen Lösungsmittel, dadurch gekennzeichnet, daß dieser Schritt der Extraktion das Auflösen des nicht weniger als 0,01 Mol-% Milchsäure oder Milchsäure und

Glycolsäure enthaltenden Polymers in der 3-bis 20-fachen Menge (Gew./Vol.) eines organischen Lösungsmittels und das Eingießen der resultierenden Lösung in Wasser unter Rühren bei einer Temperatur von 20 °C bis 70 °C umfaßt.

2. Verfahren nach Anspruch 1, worin der Gehalt der Milchsäure oder der Milchsäure und Glycolsäure auf einen Wert von 0,0055 mol oder weniger auf 100 g des Polymers reduziert wird.

3. Verfahren nach Anspruch 1 oder Anspruch 2, worin das wasserlösliche organische Lösungsmittel Ethanol ist.

4. Verfahren zur Herstellung einer Mikrokapsel zur verlängerten Abgabe eines injizierbaren Stoffes, enthaltend eine wirksame Menge eines aktiven Inhaltsstoffs und als Exzipienten ein biologisch abbaubares hochmolekulares Polymer, wie es in Anspruch 1 definiert ist, mit einem Gehalt an Milchsäure oder an Milchsäure und Glycolsäure von weniger als 0,01 mol auf 100 g des Polymers oder, wie es in Anspruch 2 definiert ist, mit einem Gehalt an Milchsäure oder an Milchsäure und Glycolsäure von weniger als 0,0055 mol auf 100 g des Polymers, umfassend das Herstellen einer Wasser/Öl(W/O)-Emulsion mit einer den aktiven Inhaltsstoff enthaltenden wäßrigen Lösung, die als innere Wasser-Phase dient, und einer das biologisch abbaubare Polymer enthaltenden Lösung, die als Öl-Phase dient, das Dispergieren der Emulsion in einer Wasser(W)-Phase zur Bildung einer (W/O)/W-Emulsion und das In-Berührung-Bringen der resultierenden Emulsion mit einer dritten wäßrigen Phase zur Bildung einer (W/O)/W-Ternär-Phasen-Emulsion, wobei das Lösungsmittel in der Öl-Phase desorbiert wird.

5. Verfahren nach Anspruch 4, worin der aktive Inhaltsstoff ein wasserlösliches Peptid ist.

6. Verwendung eines biologisch abbaubaren hochmolekularen Polymers als Matrix in einer Mikrokapsel für die verlängerte Abgabe eines aktiven Inhaltsstoffs aus dieser Mikrokapsel, wobei das Polymer eines ist, wie es in Anspruch 1 definiert ist.

Revendications

Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Polymère biodégradable de poids moléculaire élevé, dont le poids moléculaire moyen est de 5 000 à 35 000, caractérisé en ce que ledit polymère consiste à raison de 50 à 100 moles pourcent en radicaux d'acide lactique et à raison de 50 à 0 moles pourcent en radicaux d'acide glycolique et qu'il a une teneur en acide lactique ou acide lactique et acide glycolique inférieure à 0,01 mole par 100 grammes dudit polymère.

2. Polymère biodégradable de poids moléculaire élevé selon la revendication 1, dans lequel ladite teneur en acide lactique ou acide lactique et acide glycolique est de 0,0055 mole ou moins par 100 grammes dudit polymère.

3. Procédé de préparation du polymère selon la revendication 1, lequel procédé consiste à préparer le polymère à partir d'acide lactique ou d'acide lactique et d'acide glycolique en des conditions réactionnelles aqueuses, puis à réduire la teneur en acide lactique ou acide lactique et acide glycolique dans ledit polymère jusqu'à un niveau inférieur à 0,01 mole par 100 grammes dudit polymère par extraction à l'eau ou au moyen d'un mélange d'eau et d'un solvant organique soluble dans l'eau, caractérisé en ce que, pour ladite étape d'extraction, on dissout ledit polymère qui ne contient pas moins de 0,01 mole pourcent d'acide lactique ou d'acide lactique et d'acide glycolique dans une quantité (poids/volume) de 3 à 20 fois plus grande d'un solvant organique et on verse la solution obtenue dans l'eau, en agitant, à une température de 20 °C à 70 °C.

4. Procédé selon la revendication 3, dans lequel ledit solvant organique soluble dans l'eau est l'éthanol.

5. Microcapsule pour libération prolongée par injection, contenant une quantité efficace d'une substance active et, comme excipient, un polymère biodégradable de poids moléculaire élevé selon la revendication 1 ou la revendication 2.

6. Microcapsule selon la revendication 5, dans laquelle ladite substance active est un peptide soluble dans l'eau.

7. Procédé de préparation d'une microcapsule selon la revendication 5 ou 6, selon lequel on prépare une émulsion d'eau dans l'huile (eau/huile) à partir d'une solution contenant ladite substance active, servant de phase aqueuse interne, et d'une solution contenant ledit polymère biodégradable, servant de phase huileuse, on disperse ladite émulsion dans une phase aqueuse (eau) pour obtenir une émulsion (eau/huile)/eau, et on met en contact l'émulsion obtenue avec une troisième phase aqueuse, pour obtenir une émulsion en phase ternaire (eau/huile)/eau avec désorption du solvant dans la phase aqueuse.

8. Utilisation d'un polymère biodégradable de poids moléculaire élevé selon la revendication 1 comme matrice dans une microcapsule pour la libération prolongée d'une substance active à partir de ladite microcapsule.

Revendications pour l'Etat contractant suivant : AT

1. Procédé de préparation d'un polymère biodégradable de poids moléculaire élevé, dont le poids moléculaire moyen est de 5 000 à 35 000 et qui consiste à raison de 50 à 100 modes pourcent en radicaux d'acide lactique et à raison de 50 à 0 moles pourcent en radicaux d'acide glycolique, procédé consistant à prépaparer le polymère à partir d'acide lactique ou d'acide lactique et d'acide glycolique en des conditions réactionnelles aqueuses, puis à réduire la teneur en acide lactique ou acide lactique et acide glycolique dans ledit polymère jusqu'à un niveau inférieur à 0,01 mole par 100 grammes dudit polymère par extraction à l'eau ou au moyen d'un mélange d'eau et d'un solvant organique soluble dans l'eau, caractérisé en ce que, pour ladite étape d'extraction, on dissout ledit polymère qui ne contient pas moins de 0,01 mole pourcent d'acide lactique ou d'acide lactique et d'acide glycolique dans une quantité (poids/volume) de 3 à 20 fois plus grande d'un solvant organique et on verse la solution obtenue dans l'eau, en agitant, à une température de 20 °C à 70 °C.

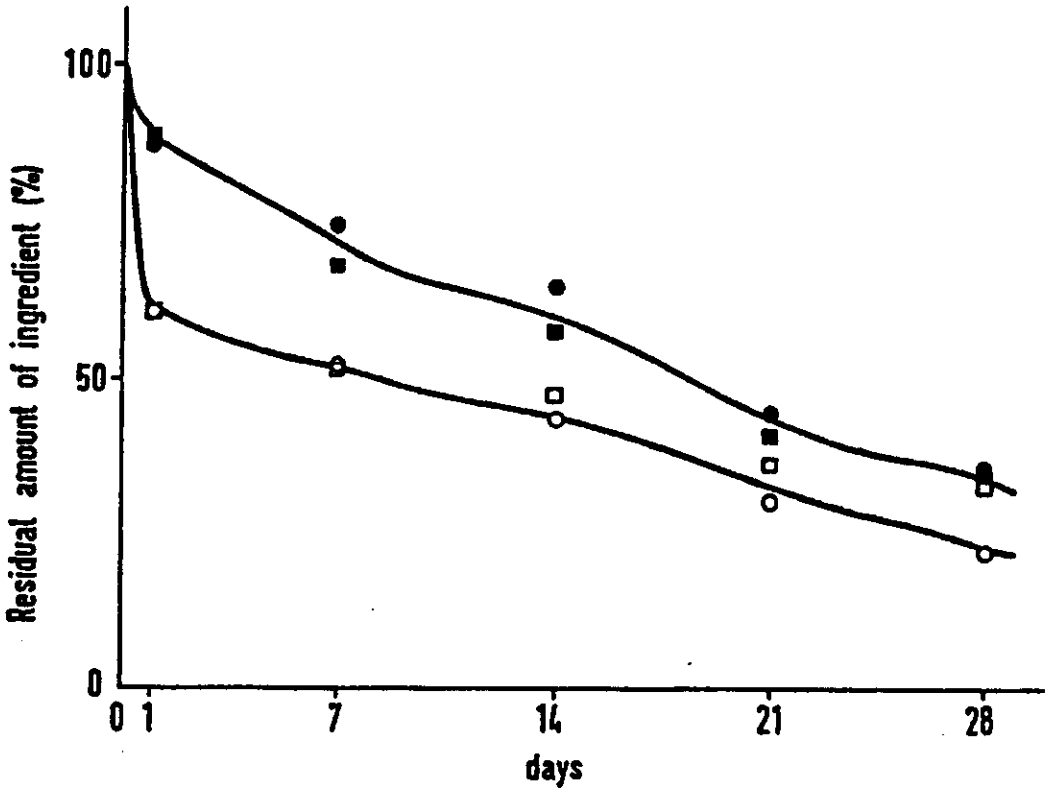
2. Procédé selon la revendication 1, dans lequel ladite teneur en acide lactique ou acide lactique et acide glycolique est réduite à un niveau de 0,0055 mole ou moins par 100 grammes dudit polymère.

3. Procédé selon la revendication 1 ou la revendication 2, dans lequel ledit solvant organique soluble dans l'eau est l'éthanol.

4. Procédé de préparation d'une microcapsule pour la libération prolongée par injection, qui contient une quantité efficace d'une substance active et, comme excipient, un polymère biodégradable de poids moléculaire élevé selon la revendication 1, ayant une teneur en acide lactique ou acide lactique et acide glycolique inférieure à 0,01 mole par 100 grammes dudit polymère, ou selon la revendication 2, ayant une teneur en acide lactique ou acide lactique et acide glycolique de 0,0055 mole ou moins par 100 grammes de polymère, procédé selon lequel on prépare une émulsion d'eau dans l'huile (eau/huile) à partir d'une solution contenant ladite substance active, servant de phase aqueuse interne, et d'une solution contenant ledit polymère biodégradable, servant de phase huileuse, on disperse ladite émulsion dans une phase aqueuse (eau) pour obtenir une émulsion (eau/huile)/eau, et on met en contact l'émulsion obtenue avec une troisième phase aqueuse, pour obtenir une émulsion en phase ternaire (eau/huile)/eau avec désorption du solvant dans la phase aqueuse.

5. Procédé selon la revendication 4, dans lequel ladite substance active est un peptide soluble dans l'eau.

6. Utilisation d'un polymère biodégradable de poids moléculaire élevé comme matrice dans une microcapsule pour la libération prolongée d'une substance active à partir de ladite microcapsule, ledit polymère étant tel que défini à la revendication 1.


100
50
0
Residual amount of ingredient (%)
0 1
7
14
21
28
days

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Applicants/Proprietors
TAKEDA CHEMICAL INDUSTRIES, LTD., 27, Doshomachi 2-chome Higashi-ku, Osaka-shi Osaka, 541, Japan [ADP No. 50635234001]

WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]

Inventors
MASAKI YAMAMOTO, 23-1001, 13 Mikunihonmachi 2-chome, Yodogawa-ku Osaka 532, Japan [ADP No. 54437207001]

HIROAKI OKADA, 11-704, 44 Yamadaminami, Suita Osaka 565, Japan [ADP No. 54437215001]

YASUAKI OGAWA, 32-503, 7 Nakahozumi 1-chome, Ibaraki, Osaka 567, Japan [ADP No. 54437223001]

TSUTOMU MIYAGAWA, 2090-21, Kasahata, Kawagoe Saitama 350, Japan [ADP No. 54437231001]

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Address for Service
ELKINGTON AND FIFE, Prospect House, 8 Pembroke Road, SEVENOAKS, Kent, TN13 1XR, United Kingdom [ADP No. 00000067004]

EPO Representative
JACK JOSEPH LAREDO, Elkington and Fife High Holborn House 52/54 High Holborn, London, WC1V 6SH, United Kingdom [ADP No. 50448315001]

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TAKEDA CHEMICAL INDUSTRIES, LTD., 27, Doshomachi 2-chome Higashi-ku, Osaka-shi Osaka, 541, Japan [ADP No. 50635234001]

WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]
to
TAKEDA CHEMICAL INDUSTRIES, LTD., 3-6, Doshomachi 2-chome Chuo-ku, Osaka, Japan [ADP No. 56769722001]

WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]
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from
TAKEDA CHEMICAL INDUSTRIES, LTD., 3-6, Doshomachi 2-chome Chuo-ku, Osaka, Japan [ADP No. 56769722001]
to
WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]

TAKEDA CHEMICAL INDUSTRIES, LTD., 1-1, Doshomachi 4-chome, Chuo-ku, OSAKA, Japan [ADP No. 56769722001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

28.08.1992 Notification from EPO of change of Applicant/Proprietor details
from
WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]

TAKEDA CHEMICAL INDUSTRIES, LTD., 1-1, Doshomachi 4-chome, Chuo-ku, OSAKA, Japan [ADP No. 56769722001]
to
TAKEDA CHEMICAL INDUSTRIES, LTD., 1-1, Doshomachi 4-chome, Chuo-ku, OSAKA, Japan [ADP No. 06430813001]

WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan [ADP No. 50608025001]
Entry Type 25.14 Staff ID. RD06 Auth ID. EPT

04.03.1993 ELKINGTON AND FIFE, Prospect House, 8 Pembroke Road, SEVENOAKS, Kent, TN13 1XR, United Kingdom [ADP No. 00000067004]
registered as address for service
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JACK JOSEPH LAREDO, Elkington and Fife High Holborn House 52/54 High Holborn, London, WC1V 6SH, United Kingdom [ADP No. 50448315001]
to
JACK JOSEPH LAREDO, Elkington and Fife Prospect House 8 Pembroke Road, Sevenoaks, Kent TN13 1XR, United Kingdom [ADP No. 50448315001]
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PROPRIETOR(S)

Takeda Chemical Industries, Ltd., 1-1, Doshomachi 4-chome, Chuo-ku, OSAKA, Japan

WAKO PURE CHEMICAL INDUSTRIES, LTD., 10, Doshomachi-3-chome, Higashi-ku Osaka, Japan

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