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Remarks:
The file contains technical information submitted after the application was filed and not included in this specification.
FIELD OF THE INVENTION

The present invention relates to a process for the production of a microcapsule preparation suitable for injection comprising microcapsule of a biodegradable polymer which contain a drug and are coated with a film of an agent for preventing aggregation of the microcapsule (hereinafter sometimes referred to as a microcapsule preparation).

BACKGROUND OF THE INVENTION

Various dosage forms have been proposed for drugs which require long-term repeated administration. For example, JP-A 57-118512 (U.S. Patent No. 4,675,189) discloses microencapsulation of a drug by phase separation process using a coacervation agent such as mineral oils, vegetable oils or the like. However, the microcapsules obtained by this technique have a disadvantage that they tend to readily to each other with low-shear in the course of production. Further, the large scale production thereof is difficult because a lot of solvent is used.

US patent no. 4,486,435 discloses encapsulated vitamin powders coated with a hydrophobic silica having improved free-flowing properties so that the vitamin powders are more suitable for direct tableting preparation. The traditional microencapsulation method which comprises formation of a three-phase emulsion containing a drug, followed by microencapsulation thereof by in-water drying process to obtain microcapsules is mentioned in JP-A 60-100516 (U.S. Patent No. 4,652,441). Although this technique improves the above disadvantage of adhesion, some points to be improved still remain. Namely, it is difficult to obtain microcapsules having a high drug content because, in the case of a water-soluble drug, the drug leaks out to the outer aqueous phase and the entrapping ratio thereof drops. In the case of both water-soluble and fat-soluble drugs, the in water drying process takes a long period of time, and a freeze-drying step is essential for pulverization. Further, in general, the microcapsules thus obtained have a large initial release rate of a drug. Furthermore, the microcapsules tend to be readily influenced by scaling up of the production and large scale treatment is difficult.

On the other hand, there are reports relating to microencapsulation by spray drying with one nozzle. However, in any of these reports, the initial release rate of a drug is large and the desired prolonged release over a long period of time is not achieved and there is a problem that a large amount of microcapsules often aggregate to each other and adhere to a spray dryer.

OBJECTS OF THE INVENTION

The main object of the present invention is to provide a process for the production of an improved prolonged release microcapsule preparation wherein the above problems in conventional prolonged release microcapsules such as aggregation of each other and adhesion to a spray dryer are minimized.

This object as well as other objects and advantages of the present invention will become apparent to those skilled in the art from the following description.

SUMMARY OF THE INVENTION

Under these circumstances, the present inventors have intensively studied to develop prolonged release preparations of water-soluble or fat-soluble drugs. As a result, it has been found that microcapsules having a high entrapping ratio of a drug, a small initial release rate of a drug and excellent properties can be obtained efficiently and continuously in a large amount in a short period of time by atomizing and spraying (1) a solution containing a drug and a polymer, (2) a water-in-oil (W/O) type emulsion whose internal phase is a solution containing a water-soluble drug and whose external phase is a solution containing a polymer or (3) a solid-in-oil (S/O) type suspension containing finely divided particles of a drug from one nozzle of a spray dryer (two-fluid nozzle, multi-fluid nozzle or pressure nozzle or rotary disc for two-liquid spraying) and by spraying a solution of an agent for preventing aggregation of microcapsules from the other nozzle. After further studies based on this finding, the present invention has been completed.

The present invention provides a process for the production of a microcapsule preparation suitable for injection comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and which are coated with a film of the water-soluble saccharides, water-soluble amino acids, water-soluble proteins and water-soluble cellulose which comprises spraying a solution of the poly fatty acid ester containing a drug and an aqueous solution of the water-soluble material separately from different nozzles and contacting them with each other in a spray dryer to produce microcapsules of the poly fatty acid ester which contain the drug and which are coated with a film of the water-
soluble material which prevents aggregation of the microcapsules.

[0010] According to the present invention, it is possible to produce a microcapsule preparation having a desired and strong structure with minimizing loss of a drug by spray-drying the solution, emulsion or suspension containing a drug and a polymer by using a spray dryer to volatilize water as well as an organic solvent in a moment. Further, it is possible to reduce the initial release rate of a drug to a smaller amount than that of the in-water drying process. Furthermore, it is possible to obtain powder particles having excellent fluidity in a short period of time without employing any freeze-drying step by spraying the solution of an agent for preventing aggregation of microcapsules (hereinafter referred to as "aggregation-preventing agent") from another nozzle at the same time to coat the surface of the microparticles with the aggregation-preventing agent, thereby preventing aggregation of the microcapsules to each other and adhesion of the microcapsules to a spray dryer.

DETAILED DESCRIPTION OF THE INVENTION

[0011] As the aggregation-preventing agent, in general, there can be used water-soluble materials which are applicable to human, solid at room temperature (about 15 to 25°C) and non-adhesive in their dried state. Examples thereof include water-soluble saccharides such as mannitol, sorbitol, lactose, glucose, sucrose, starch (e.g., corn starch, potato starch, etc.) and the like; amino acids (e.g., glycine, phenylalanine, etc.); proteins (e.g., gelatin, fibrin, collagen, albumin, etc.); water-soluble cellulose (e.g., crystalline cellulose, carboxymethyl cellulose and the like and salts thereof, etc.); and the like. These can be used alone or in combination thereof. Among them, water-soluble saccharides can be advantageously used. Among water-soluble saccharides, mannitol can be advantageously used.

[0012] The weight ratio of the aggregation-preventing agent to the polymer can be in the range wherein the desired aggregation-preventing effect is obtained, and is about 0.1 to about 100 times, preferably 0.1 to 50 times, more preferably 0.2 to 10 times the weight of the polymer.

[0013] The drug to be used in the present invention is not specifically limited. Examples thereof include peptides having biological activities, other antibiotics, antitumor agents, antipyretics, analgesics, antihypertensive agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antidepressants, antiallergic agents, inflammatory agents, other antibiotics, antitumor agents, anti-inflammatory agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations, narcotic antagonists, bone resorption inhibitors, angiogenesis-inhibiting substances and the like.

[0014] The peptides having biological activities to be used in the invention are those having two or more amino acids, preferably having molecular weight of about 200 to 80,000.

[0015] Examples of the peptide having luteinizing hormone-releasing hormone (LH-RH), its derivatives having similar activity, i.e., a peptide of the formula (I):

\[
\text{(Pyr)Glu-R_1-Trp-Ser-R_2-R_3-R_4-Arg-Pro-R_5}
\]

wherein \(R_1\) is His, Tyr, Trp or p-NH₂-Phe; \(R_2\) is Tyr or Phe; \(R_3\) is Gly or D-amino acid residues; \(R_4\) is Lue, Ile or Nle; and \(R_5\) is Gly-NH₂-R₆ (wherein \(R₆\) is H or lower alkyl optionally substituted with a hydroxy group) or NH₂-R₆ (wherein \(R₆\) is as defined above), or salts thereof [see, U.S. Patent Nos. 3,853,837, 4,008,209 and 3,972,859; G.B. Patent No. 1,423,083; and Proc. Nat. Acad. Sci. U.S.A., vol. 78, pp. 6509-6512 (1981)].

[0016] As the D-amino acid residue represented by \(R_5\) in the above formula (I), there are, for example, \(\alpha\)-D-amino acids having up to 9 carbon atoms (e.g., Lue, Ile, Nle, Val, NVal, Abu, Phe, Phg, Ser, Tyr, Met, Ala, Trp, \(\alpha\)-Alb, etc.) and the like. These residues may have suitable protective groups (e.g., t-buty1, butoxy, t-butoxy, t-butoxycarbonyl, etc.). The acid addition salts and metal complexes of the peptide of the formula (I) [hereinafter referred to as the peptide (I)] can be used in the same manner as the peptide (I).

[0017] The abbreviations of amino acids, peptides, protective groups, etc. in the peptide (I) are those established by IUPAC-IUB Commission on Biochemical Nomenclature or those commonly used in the art. When optical isomers of amino acids are present, the amino acids are represented as L-isomers unless otherwise indicated.

[0018] In the present specification, the acetic acid salt of the peptide (I) wherein \(R_1\) is His, \(R_2\) is Tyr, \(R_3\) is D-Leu, \(R_4\) is Leu and \(R_5\) is NHCH₂-CH₃ is referred to as "TAP-144". The general name of the acetic acid salt of the peptide is leuprorelin. Other LH-RH analogues include nafarelin; (pyro)Glu-His-Trp-Ser-Tyr-(3-naphthyl)-D-Ala-Leu-Arg-Pro-GluNH₂, goserelin; (pyro)Glu-His-Trp-Ser-Tyr-O-tert-buty1-D-Ser-Leu-Arg-Pro-semicarbazide or salt thereof.


[0020] Further examples of the peptides having biological activities include oligopeptides such as insulin, somatostatin, somatostatin derivatives (see, U.S. Patent Nos. 4,087,390, 4,093,574, 4,100,117 and 4,253,998), growth hormone, prolactin, adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), thyrotropin-releasing hormone (TRH), their salts and derivatives (see, JP-A 50-121273, JP-A 52-116465), thyroid-stimulating hormone (TSH), luteinizing
hormone (LH), follicle-stimulating hormone (FSH), vasopressin, vasopressin derivatives [desmopressin [see. Folia Endocrinologica Japonica, vol. 54, no. 5, pp. 676-691 (1978)], oxytocin, calcitonin, parathyroid hormone, glucagon, gastrin, secretin, pancreaticpolypeptide, angiotensin, human plasma-activated cryptogam, human chorionic gonadotropin (HCG), enkephalin, enkephalin derivatives (see, U.S. Patent No. 4,277,394 and EP-A 31,567); and polypeptides such as endorphin, kyotorphin, interferon (α-type, β-type, γ-type), interleukin (I to XI), tufts, thyrophoepitin, thyromosin, thymosynthymin, thymic humoral factor (THF), serum thymic factor (FTS) and derivatives thereof (see, U.S. Patent No. 4,229,438) and other thymic factors [Medicine in Progress, vol. 125, no. 10, pp. 835-843 (1983)], tumor necrosis factor (TNF), colony stimulating factor (CSF), mitoin, deinosphrin, bombesin, neurontins, caerulein, bradykinin, urokinase, asparaginase, kallikrein, substance P, nerve growth factor, blood coagulation factor VIII and IX, lysozyme chloride, polyoxyxin B, colistin, gramicidin, bacitracin, protein synthesis-stimulating peptide (G.B. Patent No. 8,232,082), gastric inhibitory polypeptide (GIP), vasoactive intestinal polypeptide (VIP), platelet-derived growth factor (PDGF), growth hormone-releasing factor (GRF, somatocline), bone morphogenetic protein (BMP), epidermal growth hormone (EGF), erythropoietin (EPO) and the like.

Examples of the above antimicrobial include bleomycin hydrochloride, methotrexate, actinomycin D, mitomycin C, vinblastine sulfate, vincristine sulfate, daunorubicin hydrochloride, adriamycin, neocarzinostatin, cytosine arabinoside, fluorouracil, tetrahydrofurfuryl-5-fluorouracil, picibanil, lentinian, levarisolate, bestatin, azimexon, glycyrrhizin, poly I:C, poly A/U, poly ICLC, Cisplatin and the like.

Examples of the above antibiotics include gentamicin, dibekacin, kanamycin, lividomycin, amikacin, fradomycin, sisomycin, tetracycline, oxytetracycline, rolitetracycline, doxycycline, ampicillin, penicillin, ticarcillin, cefalotin, cefaloridine, cefotaxim, cefalosporins, cefazolin, cefapirin, cefepime, cephradine, moxolacactam, thienamycin, sulfamycin, azuslenon, salts thereof and the like.

Examples of the above antitumour include gentamicin, dibekacin, kanamycin, lividomycin, amikacin, fradomycin, sisomycin, tetracycline, oxytetracycline, rolitetracycline, doxycycline, ampicillin, penicillin, ticarcillin, cefalotin, cefaloridine, cefotaxim, cefalosporins, cefazolin, cefapirin, cefepime, cephradine, moxolacactam, thienamycin, sulfamycin, azuslenon, salts thereof and the like.

Examples of the above antipyretic, analgesic and anti-inflammatory agent include salicylic acid, sulfapenamide, salicylic acid, flufenamic acid, diclofenac, indometacin, morphine, levorphanol tartrate, oxymorphone and the like.

Examples of the above antitussive expectorant include ephedrine, methylenedrine, noscapine, codeine, dihydrocodeine, alloclamide, chlorphezianol, picoperidamine, cloperastine, protokylol, isoproterenol, salbutamol, terbutaline, salts thereof and the like.

Examples of the above antipyretic, analgesic and anti-inflammatory agent include salicylic acid, sulfapyridine, phenacetin, aspirin, diclofenac, indometacin, morphine, pethidine, levorphanol tartrate, oxymorphone and the like.

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Examples of the above antipyretic, analgesic and anti-inflammatory agent include salicylic acid, sulfapyridine, phenacetin, aspirin, diclofenac, indometacin, morphine, pethidine, levorphanol tartrate, oxymorphone and the like.
In the present invention, an n-octanol/water partition coefficient of the water-soluble drug is preferably not more than 1, more preferably not more than 0.1.

The oil/water partition coefficient can be determined by the method described in Robert E. Notari "Biopharmaceutics and Pharmacokinetics", Marcel Dekker Inc., 1975, New York, U.S.A. Thus, equal amount of n-octanol and a buffer solution (pH 5.5) are placed in a test tube to give a 1:1 mixture. The buffer solution is exemplified by Sorensen buffer [ Ergebniss der Physiologie 12, 393 (1912)], Clark-Lubs buffer [Journal of Bacteriology 2, (1), 109, 191 (1971)], MacIlvaine buffer [Journal Biological Chemistry 49, 183 (1921)], Michaelis buffer [Die Wasser-Stoffionenkonzentration, p. 186 (1914)], Kolthoff buffer [Biochemische Zeitschrift 79, 410 (1926)] and so on.

An adequate amount of the drug to be tested is added to the mixture, and the test tube is stopped, immersed in a constant-temperature bath (25°C) and shaken vigorously. When it appears that the drug has been dissolved in both the liquid layers and an equilibrium has been reached, the mixture is allowed to stand or is centrifuged, and aliquots of the upper and lower liquid layers are pipetted separately and analyzed for the concentration of the drug in each layer. The ratio of the concentration of the drug in the n-octanol layer to the concentration of the drug in the aqueous layer is the oil/water partition coefficient.

These drugs themself and their pharmaceutically acceptable salts can be used in the present invention.

Examples of the pharmaceutically acceptable salts of the drugs include a salt with an inorganic acid (e.g., hydrochloric acid, sulfuric acid, nitric acid, etc.), a salt with an organic acid (e.g., carbonic acid, citric acid, etc., when the drugs have a basic residue such as an amino group and so on. Examples of the pharmaceutically acceptable salts of the drugs include a salt with an inorganic base [e.g., alkaline metal such as sodium, potassium and so on, organic basic compound (e.g., triethylamine, etc.), basic amino acid (e.g., arginine, etc.) and so on], when the drugs have an acidic residue such as carboxyl group and so on.

The amount of the above drug to be used depends upon a particular kind of drug, desired pharmacological activity, duration of time and the like. In the case of a W/O emulsion, the concentration of the drug in an internal aqueous phase is about 0.001% to about 70% (w/w), preferably 0.01% to 50% (w/w).

"Slightly water-soluble" means that solubility of the polymer in water is not exceeding about 3% (w/w).

The polymer to be used depends upon a particular strength of the pharmacological activity of the drug, release rate and period of the drug and the like. For example, the polymer is used in an amount of 0.5 to 1,000 times the weight of the drug. Preferably, the polymer in an amount of about 1 to 100 times the weight of the drug is used.

The weight-average molecular weight of the polymer to be used may be selected from the range of about 3,000 to 30,000, preferably about 5,000 to 25,000, more preferably about 5,000 to 20,000.

The dispersity of the polymer to be used may be selected from the range of about 1.2 to 4.0, preferably about 1.5 to 2.5, more preferably about 1.5 to 2.5.

Examples of the polymer in the present invention include biodegradable polymers such as poly fatty acid esters [e.g., homopolymer (e.g., polyactic acid, etc.) of fatty acid or copolymer (e.g., copolymer of lactic acid/glycolic acid, copolymer of 2-hydroxybutyric acid/glycolic acid, etc.) of two or more fatty acids, a mixture of the homopolymer and/or copolymer (e.g., a mixture of polyactic acid and copolymer of 2-hydroxybutyric acid/glycolic acid, etc.), examples of the fatty acid include α-hydroxycarboxylic acid (e.g., glycolic acid, lactic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methyl butyric acid, 2-hydroxypropionic acid, 2-hydroxyisocaproic acid, 2-hydroxypropionic acid, etc.), cyclic dimers of α-hydroxycarboxylic acids (e.g., glycolide, lactide, etc.), hydroxydicarboxylic acid (e.g., malic acid, etc.), hydroxy tricarboxylic acid (e.g., citric acid, etc.), and so on, poly-α-cyanacrylate, polyalkylene oxalates (e.g., polytrimethylene oxalate, polytetramethylene oxide, etc.), poly ortho esters, poly ortho carbonates and other polycarbonates (e.g., polyethylene carbonate, polyethyleneoxide carbonate, etc.), polyamino acids (e.g., poly-γ-benzyl-L-glutamic acid, poly-L-alanine, poly-γ-methyl-L-glutamic acid, etc.) and the like. Further examples of the biocompatible polymers include polycrylic acid, polymethacrylic acid, copolymer of acrylic acid and methacrylic acid, polyamino acids, silicon polymer, dextran stearate, ethylcellulose, acetylcellulose, maleic anhydride copolymers, ethylene-vinylacetate copolymer, polyvinyl acetate, polyvinyl alcohol, polyacrylamide and the like. These polymers may be used alone or in combination thereof. They may be used in the form of a copolymer or a mixture of these two or more polymers. They may be in the form of salts thereof.

Among poly fatty acid esters, in particular, homopolymers of α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acid, copolymers of two or more α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acid and a mixture of the homopolymers and/or the copolymers are preferred. More preferred examples include homopolymers of α-hydroxycarboxylic acids, copolymers of two or more α-hydroxycarboxylic acids, and a mixture of the homopolymers and/or the copolymers. Most preferred examples include polyactic acid, copolymer of lactic acid and glycolic acid, copolymer of 2-hydroxybutyric acid and glycolic acid and a mixture thereof.

When these α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acids, hydroxydicarboxylic acid.
hydroxytricarboxylic acids may be D-, L- or D,L-configured, the D-, L- and D,L-compounds can be used equally.

When a copolymer of lactic acid/glycolic acid is used as the above polymer, its composition (monomer) ratio is preferably about 100/0 to 50/50 (w/w). When a copolymer of 2-hydroxybutyric acid/glycolic acid is used as the above polymer, its composition (monomer) ratio is preferably about 100/0 to 25/75 (w/w).

The weight-average molecular weight of the copolymer of lactic acid/glycolic acid and the copolymer of 2-hydroxybutyric acid/glycolic acid is preferably about 3,000 to 30,000, more preferably about 5,000 to 20,000.

When a mixture of a polyactic acid (A) and a copolymer of 2-hydroxybutyric acid/glycolic acid (B) is used as one example of to above polymers, the mixture can be used in a blend ratio of about 10/90 to 90/10 (by weight), preferably about 25/75 to 75/25 (by weight).

The weight-average molecular weight of the polylactic acid (A) is preferably about 3,000 to 30,000, more preferably about 5,000 to 20,000.

The preferred proportion of glycolic acid in the copolymer (B) is in the range of about 40 to 70 mole%.

The weight-average molecular weight of the copolymer (B) is preferably about 5,000 to 25,000, more preferably about 5,000 to 20,000.

In the process of the present invention, when a drug is water-soluble, the drug is dissolved in water by adding it to water to prepare an aqueous solution for an internal aqueous phase. As a pH adjustor to maintain the stability or solubility of the water-soluble drug, for example, carbonic acid, acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid, phosphoric acid, sodium salt or potassium salt thereof, hydrochloric acid, sodium hydroxide or the like can be added to the aqueous solution. Further, as a stabilizer of the water-soluble drug, there can be added, for example, albumin, gelatin, citric acid, sodium ethylenediamine tetraacetate, dextrin, -sodium-hydrogensulfite or the like. Furthermore, as a preservative, there can be added, for example, paraxoxybenzoic acid esters (e.g., methylparaben, propylparaben, etc.), benzyl alcohol, chlorobutanol, thimerosal or the like.

The solution for the internal aqueous phase thus obtained is added to a solution (oil phase) containing the polymer, followed by emulsification to prepare a W/O type emulsion.

As the solution containing the above polymer, a solution of the polymer dissolved in an organic solvent is used.

As the organic solvent, there can be used any solvent whose boiling point is not more than about 120°C and which is slightly miscible with water and can dissolve the polymer. Examples thereof include halogenated alkanes (e.g., dichloromethane, chloroform, chloroethane, trichloroethane, carbon tetrachloride, etc.), fatty acid esters (e.g., ethyl acetate, butyl acetate, etc.), ethers (e.g., ethyl ether, isopropyl ether, etc.), hydrocarbons (e.g., cyclohexane, n-hexane, etc.), aromatic hydrocarbons (e.g., benzene, toluene, etc.) and the like. These solvents can be used alone or in combination thereof.

The emulsification can be carried out by conventional dispersion techniques. For example, intermittent shaking, mixing by means of a mixer such as a propeller agitator, turbine agitator or the like, colloid mill operation, mechanical homogenization, ultrasonication and the like.

Alternatively, the drug (which may be water-soluble or fat-soluble) and polymer are dissolved in an organic solvent or a mixture of a solvent miscible with water and water. When the drug is insoluble, the mixture is subjected to a suspending operation to prepare a S/O type suspension containing finely divided drug particles. As the organic solvent in this case, in addition to the aforementioned organic solvents, there can be used solvents readily miscible with water such as acetone, acetonitrile, tetrahydrofuran, dioxane, pyridine, alcohols (e.g., methanol, ethanol, etc.) or the like. These solvents can be used alone or in combination thereof. Further, there can be used a mixture having a suitable mixing ratio of water and the above organic solvent which can dissolve the drug and polymer homogeneously.

Then, the W/O type emulsion, S/O type suspension or solution thus obtained is sprayed into a drying chamber of a spray dryer through a nozzle, and the organic solvent and water in the atomized droplets are volatilized in an extremely short period of time to prepare a powdered microcapsule preparation. As the nozzle, a two-liquid type nozzles pressure type nozzle, rotary disc type nozzle or the like can be used. At the same time, in order to prevent aggregation of the microcapsules, an aqueous solution of an aggregation-preventing agent is sprayed from another nozzle. Namely, two nozzles are provided, and the W/O type emulsion, S/O type suspension or drug polymer solution is sprayed from one nozzle, while a suitable amount of an aqueous solution of an aggregation-preventing agent is sprayed from the other nozzle to form coating on the surface of the microcapsules. When a two-liquid nozzle or pressure nozzle is used as the nozzle, the two nozzles may be provided in the center of a spray dryer. Preferably, a nozzle having a structure for two-liquid spraying is used so that the drug-polymer solution and aqueous solution of the aggregation-preventing agent can be sprayed separately without mixing them in the nozzle.

The microcapsule preparation thus obtained is subjected to removal of water in the microparticle preparation and the solvent in the microcapsule preparation more completely under reduced pressure, if necessary, with warming. The particle size of the microcapsule preparation depends upon the desired degree of prolonged release. When the particles are used as a suspension, the particle size can be in the range which satisfies their dispersibility and needle pass requirements. For example, the average diameter is preferably in the range of about 0.5 to 400 μm, more preferably about 2 to 200 μm.
[0074] Thus, according to the process of the present invention, the uptake ratio of the drug into the microcapsule preparation can be increased up to about 100% without any loss of the active component which is apt to provide in the in-water drying process. Further, the amount of the organic solvent to be used is smaller than that of the in-oil drying process. Furthermore, although it takes an extremely long period of time to remove the solvent in the in-water drying process, this time can be extremely reduced: Thus, the process of the present invention is extremely useful in the industrial production.

[0075] Further, the microcapsule preparations produced by the present invention have many advantages. For example, because the surface of the microcapsules is coated with the aggregation-preventing agent in the form of a film, aggregation of the microcapsule preparation with each other is little in the course of production, and even globular microcapsule preparations can be obtained. Further, it is easy to control the solvent removal step, and thereby the surface structure of the microcapsule preparation which affects the drug release rate (e.g., the number and size of pores which are the main release path of the drug, etc.) can be controlled.

[0076] The microcapsule preparation produced by the present invention can be administered as it is into the living bodies as implants, or by molding them in the form of various preparations. Further, the microcapsule preparation can be used as raw materials in the production of various preparations.

[0077] As the above preparation, for example, injectable preparations, oral preparations (e.g., powders, granules, capsules, tablets, etc.), nasal preparations, suppositories (e.g., rectal, vaginal), and so on can be mentioned.

[0078] The amount of drug to be included in the preparation depends on the kind of the drug, dosage form, object of treatment, and so on. However, the amount of drug per dosage from may usually be selected from the range of about 0.001 mg to about 5 g, preferably about 0.01 mg to about 2 g.

[0079] These preparations can be manufactured by using per se known method in the field of pharmaceutics.

[0080] When the microcapsule preparation produced according to this invention are to be processed into an injectable preparation, they are dispersed in an aqueous vehicle together with a dispersing agent (e.g., Tween 80, HCO-60 (Nikko Chemicals), carboxymethyl cellulose, sodium alginate, etc.), preservative (e.g., methyl-paraben, propyl-paraben, benzyl alcohol, chlorobutanol, etc.), isotonizing agent (e.g., sodium chloride, glycerin, sorbitol, glucose, etc.), etc. The vehicle may also be a vegetable oil (e.g., olive oil, sesame oil, peanut oil, cottonseed oil, corn oil, etc.), propylene glycol or the like. In this manner, a prolonged release injection can be produced.

[0081] When the microcapsule preparation produced according to this invention are to be processed into an oral preparation, by a per se known method, they are mixed with an excipient (e.g., lactose, sucrose, starch, etc.), disintegrating agent (e.g., starch, calcium carbonate, etc.), binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.) and/or lubricant (e.g., talc, magnesium stearate, polyethylene glycol 6000, etc.), and the mixtures are compressed in molds, and then if necessary, the preparations may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release property. Usable as coating agents are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, polyoxyethylene glycol, tween 80, Pluronic F68, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxyethylcellulose acetate succinate, Eudragit (Roehm, West Germany; methacrylic acid-acrylic acid copolymer) and pigments such as titanium oxide and ferric oxide.

[0082] To manufacture a nasal preparation from the microcapsule preparation produced according to this invention, they are provided solid, semi-solid or liquid state in the conventional manner. To manufacture the solid nasal preparation, for instance, the microcapsules either as they are or together with an excipient (e.g., glucose, mannitol, starch, microcrystalline cellulose, etc.) and/or thickener (e.g., natural mucilages, cellulose derivatives, polyacrylates, etc.) are processed into a powdery composition. To make a liquid composition, the microcapsules are processed into an oily or aqueous suspension in substantially the same manner as in the case of injections. The semi-solid preparation may be an aqueous or oily gel or ointment. In any case, there may be added a pH adjusting agent (e.g., carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), etc.

[0083] A suppository of the microcapsule preparation produced according to this invention, whether in oily or aqueous solid or semi-solid state or in liquid state, can be produced in the per se conventional manner. The kind of oleaginous base for such composition is optional only if it will not dissolve the microcapsules. Thus, for example, higher fatty acid glycerides (e.g., cacao butter, Witepsol (Dynamit-Novel, Germany), etc.), intermediate fatty acids [e.g., Miglyol (Dynamit-Novel), etc.] and vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.) may be mentioned. The aqueous base is exemplified by polyethylene glycol and propylene glycol, while the aqueous gel base may be selected from among natural mucilages, cellulose derivatives, vinyl polymers, polyacrylates, etc.

[0084] The dosage of the preparation produced according to this invention depends on the kind and amount of the active ingredient, dosage form, duration of drug release, recipient animal (e.g., warm-blooded animals such as mouse, rat, horse, cattle, man), and object of treatment. It is, however, sufficient to ensure that the effective dose of the active ingredient will be administered. For example, the amount per dose to humans may be selected from the range of about 1 mg to 10 g, preferably about 10 mg to 2 g, in terms of the weight of microcapsules.
When an injectable dosage form is employed, the volume of the suspension may be selected from the range of about 0.1 to 5 ml, preferably about 0.5 to 3 ml.

The polymer as a base for the microcapsule preparation in the present invention can be produced by a per se known method such as a method described in U.S. Patent Nos. 3,773,919, 4,273,920, 4,675,189, 4,767,628, 4,677,191, 4,849,228 or EP-A-481732.

The microcapsule preparation produced by the present invention have, for example, the following characteristics.

(1) The prolonged release of drugs in various dosage forms can be ensured. In particular, when a long-term treatment with injections is required for the desired effect, the preparation helps achieve the desired pharmacological activities stably with an administration schedule of once a week or a month or even once a year, instead of giving injections every day. Thus, compared with the conventional sustained release drugs, the prolonged release preparations of the present invention ensure longer sustained effects.

(2) When the injectable preparations are prepared by using the microcapsule preparation of the present invention, any surgical operation such as implantation is not required. The preparations can be administered subcutaneously or intramuscularly in quite the same manner as in the conventional injectable suspensions, and it is not required to remove them from the body.

Further, the injectable preparations can be administered directly to the tumor itself, the site of inflammation or the receptor region, so that systemic side effects can be controlled and the drug can be allowed to efficiently act on the target organ over a longer period of time, thus making for increased drug efficacy. Furthermore, the injectable preparations can be used in intra-arterial administration in the vascular embolic therapy proposed by Kato et al., of cancer of the kidney and of the lung [Lancet II, pp. 479-480 (1979)].

(3) The release of the active component is continuous and, in the case of hormone antagonists, receptor antagonists or the like, stronger pharmacological activities are obtained than by daily administration.

(4) A drug can be entrapped into the microcapsule preparation more efficiently than those obtained by the conventional in-water drying of the W/O/W type three-phase emulsion. Further, finely divided even globular microcapsule preparations can be obtained.

(5) The microcapsule preparations having a drug content of 10 to 50% which are hardly obtainable by the conventional in-water drying process can be obtained.

(6) Since, compared with the conventional in-water drying process, a solvent removal rate is higher, the hardening rate of the microcapsule preparation is higher and a microcapsule preparation having a stronger structure can be obtained. Therefore, the initial drug release rate after administration can be reduced.

(7) Aggregation and adhesion of the microcapsule preparation is remarkably diminished compared with spraying a solution containing only the drug and the polymer.

The following experiments and examples further illustrate the present invention in detail, but are not to be construed to limit the scope thereof. All the percents representing the concentration are weight/volume percents (w/v %) unless otherwise stated.

**Experiment 1**

Leuprolelin acetate (1 g) was dissolved in water (10 ml) at 60°C. To this solution was added a solution of lactic acid-glycolic acid copolymer (lactic acid/glycolic acid = 75/25, average molecular weight calculated in terms of polystyrene: 1,200) (9 g) dissolved in methylene chloride (25 ml).- The mixture was emulsified with a small-sized homogenizer (Polytron, manufactured by Kinematica, Switzerland) to obtain a W/O type emulsion.

(1) In-water drying process (the conventional method, hereinafter referred to as A process)

The above W/O type emulsion was converted into a (W/O)/W type emulsion in 0.5% PVA aqueous solution by using a homogenizer. Then, the emulsion was stirred slowly for 3 hours with a conventional propeller agitator.

As methylene chloride was volatilized, (W/O) type microcapsules were hardened and, then, the resulting microcapsules were collected by centrifugation. At the same time, the microcapsules were washed with purified water. The collected microcapsules were subjected to freeze drying for a whole day and night to obtain powder.

(2) Spray drying process (this invention, hereinafter referred to as B process)

The above W/O type emulsion was sprayed from one nozzle of a two fluid nozzle at a flow rate of 10 ml/min and, at the same time, 2% aqueous mannitol solution was sprayed from the other nozzle at a flow rate of 10 ml/min into...
a drying chamber of a spray dryer to obtain microcapsules as powder. The temperature at the entrance of the drying chamber was 100°C, the temperature at the outlet was 50°C and the air flow was 80 kg/hr.

[0092] Various properties of the microcapsules produced by A and B processes were compared. The results are shown in Table 1.
Table 1
Comparison of Properties of Microcapsules

<table>
<thead>
<tr>
<th>Process</th>
<th>Surface state</th>
<th>Drug 1) takeup (%)</th>
<th>Release rate for 1 day 2) (%)</th>
<th>Distribution of particle size 3) (μm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>many pores</td>
<td>5.3</td>
<td>78</td>
<td>5-200</td>
</tr>
<tr>
<td>B</td>
<td>few pores</td>
<td>99</td>
<td>24</td>
<td>5-40</td>
</tr>
</tbody>
</table>

1) Drug take up was determined as follows.
The leuprolide acetate in the microcapsules was determined by a high performance liquid chromatography (HPLC) procedure using Hitachi L-6300 equipment (Hitachi, Japan), microcapsules (50 mg) were dissolved in a mixture of 10 ml of dichloromethane and 20 ml of 1/30M phosphate buffer, pH 6.0, and leuprolide acetate extracted into the buffer was assayed by an HPLC procedure with an ultra violet (UV) detector under the following conditions; column, Lichrosorb RP-18 250 mm in length with 4 mm i.d.; column temperature, 30°C; mobile phase, a mixture of 100 ml of 0.25M acetonitrile and 150 ml of methyl alcohol; flow rate, 0.7 ml/min; wavelength, 280 nM.
Drug take up (%) was calculated from the following formula:

\[
\text{Drug take up (％)} = \left( \frac{\text{The leuprolide acetate in the microcapsule}}{\text{Initial amount of Leuprolide acetate added}} \right) \times 100
\]

2) Release rate for 1 day (%) was determined as follows.
The microcapsules (50 mg) were suspended in 10 ml of the release medium consisting of 1/30 M phosphate buffer, pH 7.0, containing 0.05% Tween-80 (Kao-Atlas, Tokyo) in a shaking bottle. This was shaken at 37°C for 1 day by using a shaker (Taiyo Scientific Industrial Co., Tokyo). The residual leuprolide acetate in the microcapsules was determined after filtering the microcapsules through a 0.8 μm Millipore filter by the analytical method mentioned 1).
Release rate for 1 day (%) was calculated from the following formula.

\[
\text{Release rate for 1 day (％)} = \left( 1 - \left( \frac{\text{The residual leuprolide acetate in the microcapsules}}{\text{The initial amount of leuprolide acetate in the microcapsules}} \right) \right) \times 100
\]

3) The distribution of particle size (μm) was determined as follows.
Micocapsules (10 mg) were suspended in Isoton II solution (Nikkaki Ltd., Japan). This suspension was subjected Multilizer (Coulter Inc. Co., U.S.A.) which was equipped with aperture tube of 100 μm or 280 μm to determine the distribution of particle size of the microcapsules.
As shown in Table 1, when the surface of the microcapsules was observed with a scanning electron microscope, many pores were observed on the surface of the microcapsules produced by A process, whereas pores were hardly observed on the surface of the microcapsules produced by B process and the surface was coated with mannitol homogeneously in the form of a film. The uptake of the drug, i.e., leuprolelin acetate was larger in B process than in A process. The amount of released drug for 1 day (initial release rate) in a release test of the microcapsules obtained by B process was larger than that obtained by A process.

The particle size distribution of the microcapsules obtained by B process was sharper than that obtained by A process. The time required for the production was about 24 hours in A process, while it was extremely short and about 10 minutes in B process. Thus, in view of the overall comparison, B process is an extremely useful production process of microcapsules compared with A process.

Experiment 2

Thyrotropin-releasing hormone (TRH) (1.0 g) and lactic acid-glycolic acid copolymer (lactic acid/glycolic acid = 75/25, average molecular weight: 16,000) (9.0 g) was dissolved homogeneously in a mixed solvent of acetone (30 ml) and water (3 ml). The solution was sprayed from one nozzle of 2 two-fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, 5% aqueous mannitol solution was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to obtain microcapsules as powder. The TRH content in the microcapsules was 9.8% (takeup: 98%), and the initial release rate in M/30 phosphate buffer (pH 7.0, 37°C) was 5%. The particle size distribution was 5 to 50 μm (average: 20 μm). The microcapsules were globular and had few pores on the surface.

Example 1

α-interferon (500 mg) and gelatin (50 mg) were dissolved in water (300 mg) at 50°C. The solution was added to a solution of poly(lactic acid) (molecular weight: 21,000) (3,500 mg) dissolved in methylene chloride (4 ml). The resulting mixture was homogenized with Plytron for 20 seconds to obtain a W/O type emulsion. The W/O type emulsion was injected into and sprayed from one (internal) of the rotary disc type nozzles having a dual structure and, at the same time, 2% aqueous mannitol solution containing 0.5% polyvinyl alcohol (PVA) was injected into and sprayed from the other (external) nozzle. After spray drying, the desired microcapsules were obtained as powder.

Example 2

Methotrexate (1 g) and 2-hydroxybutyric acid-glycolic acid copolymer (2-hydroxybutyric acid/glycolic acid = 50/50, average molecular weight 10,000) (9 g) were dissolved in a mixed solution of water (5 ml) and acetonitrile (30 ml). The solution was sprayed from the most inner duct of the two fluid nozzle (three fluid nozzle) having a structure for two-liquid spraying. An aqueous solution of gelatin (1%) was passed through the middle duct and compressed air was passed through the most outer duct to atomize and spray the solution. Thus, the desired microcapsules were obtained.

Example 3

Cefotiam dihydrochloride (4 g) and sodium carboxymethyl cellulose (Na-CMC) (600 mg) were dissolved in water (2 ml) at 60°C. The solution was mixed with a solution of poly(lactic acid) (molecular weight: 30,000) (10 g) dissolved in chloroform (40 ml). The mixture was stirred to obtain a W/O type emulsion. The W/O type emulsion was sprayed from one of the two-fluid nozzles and, at the same time, 5% aqueous lactose solution was sprayed from the other nozzle to obtain the desired microcapsules.

Example 4

A fat-soluble drug, DN-2327 (0.5 g) and lactic acid-glycolic acid copolymer (lactic acid/glycolic acid = 75/25, average molecular weight: 10,000) (4.5 g) were dissolved in acetonitrile (15 ml). The solution was sprayed from one of the two-fluid nozzles and, at the same time, 5% aqueous mannitol solution was sprayed from the other nozzle to obtain the desired microcapsules.

As described hereinabove, the microcapsule preparation produced by the present invention is a superior preparation having a high drug content, a reduced initial release rate of a drug and a sharp particle size distribution.
Claims

1. A process for the production of a microcapsule preparation suitable for injection comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and which are coated with a film of an agent for preventing aggregation of the microcapsules, wherein said agent which is applicable to humans, is solid at room temperature and non-adhesive in its dried state and is selected from a water-soluble material selected from the group consisting of water-soluble saccharides, water-soluble amino acids, water-soluble proteins and water-soluble cellulose which is applicable to humans, is solid at room temperature and non-adhesive in its dried state and is selected from a water-soluble material selected from the group consisting of water-soluble saccharides, water-soluble amino acids, water-soluble proteins and water-soluble cellulose which comprises spraying a solution of the poly fatty acid ester containing a drug and an aqueous solution of the water-soluble material separately from different nozzles and contacting them with each other in a spray dryer to produce microcapsules of the poly fatty acid ester which contain the drug and which are coated with a film of the water-soluble material which prevents aggregation of the microcapsules.

2. A process according to claim 1, wherein the poly fatty acid ester solution containing the drug is a homogeneous solution.

3. A process according to claim 1, wherein the poly fatty acid ester solution containing the drug is a W/O type emulsion whose internal phase is an aqueous solution containing the drug and whose external phase is a solution containing the poly fatty acid ester.

4. A process according to claim 1, wherein the poly fatty acid ester solution containing the drug is an S/O type suspension containing drug particles.

5. A process according to claim 1, wherein the poly fatty acid ester is a slightly water-soluble or water-insoluble poly fatty acid ester having a weight-average molecular weight of about 1,000 to 800,000.

6. A process according to claim 5, wherein the poly fatty acid ester is selected from the group consisting of polylactic acid, copolymer of lactic acid and glycolic acid, copolymer of 2-hydroxybutyric acid and glycolic acid and a mixture thereof.

7. A process according to claim 3, wherein the internal aqueous phase contains about 0.001% to about 70% (w/w) of the drug.

8. A process according to claim 1, wherein the drug is a member selected from the group consisting of biologically active peptides, antibiotics, antitumor agents, antipyretics, analgesics, antiinflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations and narcotic antagonists.

9. A process according to claim 1, wherein the amount of the agent for preventing aggregation is about 0.1 to about 100 times the weight of the poly fatty acid ester.

10. A process according to claim 1, wherein the particle size is about 0.5 to 400 μm.

11. A process according to claim 1, wherein the microcapsule preparation is a prolonged release microcapsule preparation.

Patentansprüche

1. Verfahren zur Herstellung eines Mikrokapselpräparats, das zur Injektion geeignet ist, umfassend Mikrokapseln aus einem biologisch abbaubaren Polyfettsäureester, die einen Wirkstoff enthalten und die mit einer Schicht aus einem Mittel überzogen sind, um die Aggregation der Mikrokapseln zu verhindern, wobei das Mittel, das man dem Menschen verabreichen kann, bei Raumtemperatur fest und in getrocknem Zustand nicht klebrig ist und aus einem wasserlöslichen Material ausgewählt ist, das aus der Gruppe ausgewählt ist, die aus wasserlöslichen Sacchariden, wasserlöslichen Aminosäuren, wasserlöslichen Proteinen und wasserlöslicher Cellulose besteht, umfassend das ge-
trennte Sprühen einer Lösung des Polyfettsäureesters, der einen Wirkstoff enthält, und einer wässrigen Lösung des
wasserlöslichen Materials aus verschiedenen Düsen und das Miteinander-Bringen derselben in einem
Sprührohrkranz unter Bildung von Mikrokapseln aus dem Polyfettsäureester, die den Wirkstoff enthalten und die mit
einer Schicht aus dem wasserlöslichen Material überzogen sind, das die Aggregation der Mikrokapseln verhindert.

2. Verfahren gemäß Anspruch 1, wobei die den Wirkstoff enthaltende Polyfettsäureesterlösung eine homogene Lösung
ist.

3. Verfahren gemäß Anspruch 1, wobei die den Wirkstoff enthaltende Polyfettsäureesterlösung eine Emulsion des
W/O-Typs ist, deren interne Phase eine wässrige Lösung ist, die den Wirkstoff enthält, und deren externe Phase
eine Lösung ist, die den Polyfettsäureester enthält.

4. Verfahren gemäß Anspruch 1, wobei die den Wirkstoff enthaltende Polyfettsäureesterlösung eine Suspension des
S/O-Typs ist, die Wirkstoffteilchen enthält.

5. Verfahren gemäß Anspruch 1, wobei der Polyfettsäureester ein in Wasser schwerlöslicher oder in Wasser
löslicher Polyfettsäureester mit einem Gewichtsmittel des Molekulargewichts von etwa 1000 bis 800 000 ist.

6. Verfahren gemäß Anspruch 5, wobei der Polyfettsäureester aus der Gruppe ausgewählt ist, die aus Polymilchsäure,
einem Copolymer von Milchsäure und Glycolsäure, einem Copolymer von 2-Hydroxybuttersäure und Glycolsäure
sowie einem Gemisch davon besteht.

7. Verfahren gemäß Anspruch 3, wobei die interne wässrige Phase etwa 0,001% bis etwa 70% (w/w) des Wirkstoffs
enthält.

8. Verfahren gemäß Anspruch 1, wobei der Wirkstoff aus der Gruppe ausgewählt ist, die aus biologisch aktiven Pep-
tiden, Antibiotika, Antitumormiten, Antipyretika, Analgetika, entzündungshemmenden Mitteln, antitusiven Expek-
torantien, Sedativa, Muskelrelaxantien, Antiepileptika, Antiulcusmitteln, Antidepressiva, Antiallergika, Cardiotonika,
Antihypertensiva, Vasodilatoren, hypotensiven Diuretika, Antikoagulantien, Hämostatika, Antituberkulosemitteln,
Hormonpräparaten und Antagonisten von Narkotika besteht.

9. Verfahren gemäß Anspruch 1, wobei die Menge des Mittels zur Verhinderung der Aggregation dem etwa 0,1- bis
etwa 100fachen des Gewichts des Polyfettsäureesters entspricht.

10. Verfahren gemäß Anspruch 1, wobei die Teilchengröße etwa 0,5 bis 400 μm beträgt.

11. Verfahren gemäß Anspruch 1, wobei das Mikrokapselpräparat ein Mikrokapselpräparat mit verzögert Freisetzung
ist.

Revendications

1. Procédé de production d’une préparation injectable à microcapsules, comprenant des microcapsules d’un poly(ester
d’acide gras) biodégradable qui contiennent un principe actif et qui portent un enrobage homogène constitué d’un
film d’un agent destiné à empêcher l’agrégation des microcapsules, lequel agent est une substance hydrosoluble
qui peut être administrée à l’homme, qui est solide à température ambiante et non adhésive à l’état sec, et qui est
choisi dans l’ensemble formé par les saccharides hydrosolubles, les acides aminés hydrosolubles, les protéines
hydrosolubles et la cellulose hydrosoluble, lequel procédé comporte le fait de pulvériser séparément, à partir de
buses différentes, une solution du poly-(ester d’acide gras) contenant un principe actif et une solution aqueuse de
la substance hydrosoluble, le fait de les mettre en contact l’une avec l’autre dans un dispositif de séchage par
pulvérisation de manière à produire des microcapsules du poly(ester d’acide gras) qui contiennent le principe actif
et qui sont enrobées d’un film de la substance hydrosoluble qui empêche l’agrégation des microcapsules.

2. Procédé conforme la revendication 1, dans lequel la solution de poly(ester d’acide gras) contenant le principe actif
est une solution homogène.

3. Procédé conforme à la revendication 1, dans lequel la solution de poly(ester d’acide gras) contenant le principe
actif est une émulsion de type eau/huile dont la phase dispersée est une solution aqueuse contenant le principe
actif et dont la phase continue est une solution contenant le poly(ester d’acide gras).

4. Procédé conforme à la revendication 1, dans lequel la solution de poly(ester d’acide gras) contenant le principe actif est une suspension de type solide/huile contenant des particules de principe actif.

5. Procédé conforme à la revendication 1, dans lequel le poly-(ester d'acide gras) est un poly(ester d’acide gras) peu soluble ou insoluble dans l'eau, qui présente une masse molaire moyenne en poids d'à peu près 1000 à 800 000.

6. Procédé conforme à la revendication 5, dans lequel le poly-(ester d’acide gras) est choisi dans l'ensemble formé par le poly(acide lactique), un copolymère d’acide lactique et d’acide glycolique, un copolymère d’acide 2-hydroxy-butyrilque et d’acide glycolique, et un mélange de ceux-ci.

7. Procédé conforme à la revendication 3, dans lequel la phase aqueuse dispersée contient d'environ 0,001 à environ 70 % (poids/poids) de principe actif.

8. Procédé conforme à la revendication 1, dans lequel le principe actif est un élément de l'ensemble formé par les peptides à activité biologique, les antibiotiques, les agents anti-tumoraux, les antipyrétiques, les analgésiques, les agents anti-inflammatoires, les expectorants anti-tussifs, les sédatifs, les agents myorclaxants, les agents antépi- leptiques, les agents anti-ulcéreux, les antidépresseurs, les agents antiallergéniques, les cardiotoniques, les anti-arythmiques, les vasodilatateurs, les diurétiques hypotenseurs, les agents antidiabétiques, les anticoagulants, les hémostatiques, les agents anti-tuberculeux, les préparations d'hormones et les antagonistes de narcotiques.

9. Procédé conforme à la revendication 1, dans lequel la quantité d'agent destiné à empêcher l'agrégation représente d'environ 0,1 à environ 100 fois le poids du poly(ester d’acide gras).

10. Procédé conforme à la revendication 1, dans lequel la taille des particules vaut à peu près de 0,5 à 400 μm.

11. Procédé conforme à la revendication 1, dans lequel la préparation à microcapsules est une préparation à micro-capsules à libération prolongée.
REFERENCES CITED IN THE DESCRIPTION

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