Description

This invention relates to a prolonged release microcapsule of a water-soluble drug, and a method for producing the same.

A variety of dosage forms have been proposed for drugs which require a long-term of repeated administration. As one of such dosage forms, EP—A—52510 discloses a microcapsule prepared by the phase separation technique using a coacervating agent such as mineral oils and vegetable oils. However, microcapsules prepared by this and other analogous processes have the disadvantage that there tends to occur an inter-adhesion of particles in the course of production.

Reference is also made to FR—A—2 491 351 which relates to the preparation of microcapsules of lipophilic and water-insoluble agents.

Under the circumstances, the present inventors conducted studies to develop a prolonged release preparation of a water-soluble drug and found that a microcapsule having excellent properties can be produced with good efficiency by interposing a step of thickening or solidifying the inner aqueous layer of water in oil emulsion in the course of microencapsulation by an in water drying process. The above finding was followed by further studies, which have resulted in the present invention.

The prolonged release microcapsule of the present invention is made by preparing a water-in-oil emulsion comprising an inner aqueous layer containing said water-soluble drug and a drug retaining substance therefor and an oil layer containing a high polymer substance (microcapsule wall substance), then thickening or solidifying said inner aqueous layer to a viscosity of not lower than 5.0 Pas (5000 centipoises), and finally subjecting the resulting emulsion to an in water drying process.

The water-soluble drug employed in the practice of this invention is a drug which is highly hydrophilic and has a low oil/water distribution ratio. The term "low oil/water distribution" ratio means that the octanol/water distribution ratio, for instance, is not greater than 0.1.

There is no particular limitation on the kind and type of said water-soluble drug. Thus, for example, biologically active polypeptides and other antibiotics, antitumor agents, antipyretics, analgesics, antiinflammatory agents, antitussives and expectorants, sedatives, muscle relaxants, antiepileptics, antiulcer agents, antidepressants, antiallergic drugs, cardiotonics, antiarrhythmic agents, vasodilators, antihypertensive diuretics, antidiabetics, anticoagulants, haemostatics, antituberculotics, hormone drugs and antinarcotics, may be mentioned as the water-soluble drug.

The biologically active polypeptides which are employed in accordance with this invention are preferebly those consisting of two or more amino acid units and having a molecular weight between 200 and 80000.

Examples of such polypeptides include luteinizing hormone releasing hormone (LH—RH) and its ...atives having LH—RH like activity, i.e. the polypeptides of the formula (I):

$$(Pyr)Glu\text{-}R_1\text{-}Trp\text{-}Ser\text{-}R_2\text{-}R_3\text{-}R_4\text{-}Arg\text{-}Pro\text{-}R_5 \quad (I)$$

[wherein R_1 is His, Tyr, Trp or p-NH_2-Phe; R_2 is Tyr or Phe; R_3 is Gly or a D-amino acid residue; R_4 is Leu, Ile or Nle; R_5 is Gly-NH-R_6 (R_6 is H or a lower alkyl group which may optionally be substituted by OH) or NH—R_6 (R_6 is as defined above) or salts thereof] [see United States Patents No. 3,853,837, 4,008,209 and No. 3,972,859, British Patent No. 1,423,083, Proceedings of the National Academy of Sciences of the United States of America *78*, 6509—6512 (1981)].

Referring to the above formula (I), the D-amino acid residue designated by R_3 may be an α-D-amino acid residue of up to 9 carbon atoms (e.g. D-Leu, Ile, Nle, Val, Nval, Abu, Phe, Phg, Ser, Thr, Met, Ala, Trp, α-Aibu), and these may have suitable protective groups (e.g. t-butyl, t-butoxy, t-butoxycarbonyl, naphthyl). Of course, acid salts and metal complex compounds of peptides (I) can also be used in the same manner as the aforementioned peptides (I).

In this specification, when amino acids, peptides, protective groups, etc. are mentioned, in connection with polypeptides (I), by abbreviations, such abbreviations are those established by IUPAC—IUB Commission on Biochemical Nomenclature or those used commonly in the particular field of art and when there may exist optical isomers of such amino acids, L-forms are intended unless otherwise indicated.

It should be understood that the polypeptide of formula (I) wherein R_1 = His, R_2 = Tyr, R_3 = D-Leu, R_4 = Leu, and R_5 = $NHCH_2$—CH_3 is hereinafter referred to as TAP—144.

As examples of such polypeptides, LH—RH antagonists (United States Patents No. 4086219, No. 4124577, No. 4253977 and No. 4317815) may be mentioned.

As further examples of said polypeptides may be mentioned insulin, somatostatin, somatostatin derivatives (United States Patent No. 4087390, No. 4093574, No. 4100117 and No. 4253998), growth hormones, prolactin, adrenocorticotropic hormone (ACTH), melanocyte stimulating hormone (MSH), thyroid hormone releasing hormone (TRH), its salts, and derivatives thereof (U.S. Patent No. 3,957,247 and U.S. Patent No. 4,100,152), thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), vasopressin, vasopressin derivatives [Folia Endocrinologica Japonica *54*, No. 5, p. 676—691 (1978)]], oxytocin, calcitonin, parathyroid hormone, glucagon, gastrin, secretin, pancreozymin, cholecystokinin, angiotensin, human placental lactogen, human cholionic gonadotropin (HCG), enkephalin, enkephalin derivatives [United States Patent No. 4277394, European Patent Application

Publication No. 31567], endorphin, kyotorphin, interferons (α, β, γ), interleukins (I, II, and III), taftsin, thymopoietin, thymosin, thymostimulin, thymic humoral factor (TFH), serum thymic factor (FTS), and its derivatives (United States Patent No. 4229438) and other thymic factors [Medicine in Progress *125*, No. 10. p. 835—843 (1983)], tumor necrosis factor (TNF), colony stimulating factor (CSF), motilin, dinorphin, bombesin, neurotensin, cerulein, bradykinin, urokinase, asparaginase, kallikrein, substance P analogue and antagonist, nerve growth factor, blood coagulation factors VIII and IX, lysozyme chloride, polymixin B, colistin, gramicidin, protein synthesis stimulating peptides (British patent No. 8232082), gastric inhibitory polypeptide (GIP), vasoactive intestinal polypeptide (VIP), platelet-derived growth factor (PDGF), growth hormone releasing factor (GRF, somatocrinin), bone morphogenetic protein (BMP) and epidemale growth factor (EGF).

As examples of said antitumor agents, may be mentioned bleomycin hydrochloride, methotrexate, actinomycin D, mitomycin C, vinblastine sulfate, vincristine sulfate, daunorubicin hydrochloride, adriamycin, neocarcinostatin, cytosine arabinoside, fluorouracil, tetrahydrofuryl-5-fluorouracil, krestin, picibanil, lentinan, levamisole, bestatin, azimexon, glycyrrhizin, poly I:C, poly A:U and poly ICLC.

As examples of said antibiotics, may be mentioned gentamicin, dibekacin, kanendomycin, lividomycin, tobramycin, amikacin, fradiomycin, sisomicin, tetracycline hydrochloride, oxytetracycline hydrochloride, rolitetracycline, doxycycline hydrochloride, ampicillin, piperacillin, ticarcillin, cephalothin, cephaloridine, cefotiam, cefsulodin, cefmenoxime, cefmetazole, cefazolin, cefotaxime, cefoperazone, ceftizoxime, moxolactam, latamoxef, thienamycin, sulfazecin, and azthreonam.

The aforementioned antipyretic, analgesic and antiinflammatory drugs include sodium salicylate, sulpyrine, sodium flufenamate, sodium diclofenac, sodium indomethacin, morphine hydrochloride, pethidine hydrochloride, levorphanol tartrate and oxymorphone. As examples of said antitussives and expectorants may be mentioned ephedrine hydrochloride, methylephedrine hydrochloride, noscapine hydrochloride, codeine phosphate, dihydrocodeine phosphate, alloclamide hydrochloride, chlorphedianol hydrochloride, picoperidamine hydrochloride, cloperastine, protokylol hydrochloride, isoproterenol hydrochloride, salbutamol sulfate and terbutaline sulfate. Examples of said sedatives include chlorpromazine hydrochloride, prochlorperazine trifluoperazine, trifluoperazine, atropine sulfate and scopolamine methylbromide. The muscle relaxants include pridinol methanesulfonate, tubocurarine chloride and pancuronium bromide. The antiepileptics include sodium phenytoin, ethosuximide, sodium acetazolamide and chlordiazepoxide hydrochloride. Examples of said antiulceric drugs include metoclopramide and L-histidine monohydrochloride. Examples of said antidepressants include imipramine, clomipramine, noxiptiline and phenelzine sulfate. The antiallergic drugs include diphenhydramine hydrochloride, chlorpheniramine maleate, tripelenamine hydrochloride, methdilazine hydrochloride, clemizole hydrochloride, diphenylpyraline hydrochloride and methoxyphenamine hydrochloride. The cardiotonics include trans-π-oxocamphor, theophyllol, aminophylline and etilefrine hydrochloride. The antiarrythmic agents include propranolol hydrochloride, alprenolol hydrochloride, bufetolol hydrochloride and oxyprenolol hydrochloride. The vasodilators include oxyfedrine hydrochloride, diltiazem hydrochloride, tolazoline hydrochloride, hexobenzidine and bamethan sulfate. The antihypertensive diuretics include hexamethonium bromide, pentolinium, mecamylamine hydrochloride, ecarazine hydrochloride and clonidine hydrochloride. Examples of said antidiabetics include sodium glymidine, glypizide, phenformin hydrochloride, buformin hydrochloride and metformin. The anticoagulants include sodium heparin and sodium citrate. The haemostatic agents include thromboplastin, thrombin, menadione sodium bisulfite, acetomenaphthone, ε-amino-caproic acid, tranexamic acid, carbazochrome sodium sulfonate and adrenochrome monoaminoguanidine methanesulfonate. Among said antituberculotics are isoniazid, ethambutol and sodium p-aminosalicylate. The hormone drugs are exemplified by prednisolone succinate, prednisolone sodium phosphate, dexamethasone sodium sulfate, betamethasone sodium phosphate, hexestrol phosphate, hexestrol acetate and methimazole. The antinarcotic agents include levallorphan tartrate, nalorphine hydrochloride and naloxone hydrochloride.

The proportion of said water-soluble drug depends on the kind of drug, expected pharmacological effect and its duration etc. but its concentration in the inner aqueous layer is selected from the range of 0.001% to 90% (w/w) and preferably 0.01% to 80% (w/w).

The drug retaining substance employed in accordance with this invention is either a substance which is water-soluble, hardly soluble in the organic solvent contained in said oil layer and when dissolved in water assumes a viscous semi-solid consistency or a substance which gains considerably in viscosity to provide a semi-solid or solid matrix under the influence of an external factor such as temperature, pH, metal ions (e.g. Cu^{++}, Al^{+++} and Zn^{++}), organic acids (e.g. tartaric acid, citric acid and tannic acid), a salt thereof (e.g. calcium citrate) and chemical condensing agents (e.g. glutaraldehyde, acetoaldehyde).

As examples of such drug retaining substances may be mentioned natural or synthetic muciliages and high molecular waight compounds.

Among such natural mucilages are gum acacia, Irish moss, gum karaya, gum tragacanth, gum guaiac, gum xanthane and locust bean gum, while natural high molecular weight compounds include, among others, various proteins such as casein, gelatin, collagen, albumin (e.g. human serum albumin), globulin and fibrin, and various carbohydrates such as cellulose, dextrin, pectin, starch, agar and mannan. These substances may be used as they are or in chemically modified forms, e.g. esterified or etherified forms (e.g.

methylcellulose, ethylcellulose, carboxymethylcellulose and gelatin succinate), hydrolyzed forms (e.g. sodium alginate and sodium pectinate) or salts thereof.

As examples of said synthetic high molecular weight compounds may be mentioned polyvinyl compounds (e.g. polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl methyl ether and polyvinyl ether), polycarboxylic acids (e.g. polyacrylic acid, polymethacrylic acid and Carbopol [Goodrich & Co., U.S.A.]), polyethylene compounds (e.g. polyethylene glycol) and polysaccharides (e.g. polysucrose, polyglucose and polylactose) and salts thereof.

Also included are those compounds which undergo condensation or cross-linking under the influence of said external factors to give high molecular weight compounds.

Among the aforementioned compounds, gelatin, albumin, pectin and agar are particularly desirable.

These compounds may be used alone or in combination and while the proportion of such compounds depends on the kind of compound, it is selected from the range of 0.05% to 80% (w/w) in terms of concentration in the inner aqueous layer, preferably from the range of 0.1% to 50% (w/w) on the same basis. It should, however, be understood that such compounds must be used in sufficient amounts to ensure that the initial viscosity of the inner aqueous layer in the water-in-oil emulsion described hereinafter will be not lower than 5.0 Pas (5000 centipoises (cps)), preferably not lower than 10.0 Pas (10000 cps), or the inner aqueous layer may be increased in viscosity to not lower than 5.0 Pas (5000 cps), preferably not lower than 10.0 Pas (10000 cps), or be solidified by external factors.

The aforementioned polymer substances employed in the oil layer are polymers hardly soluble or insoluble in water and biocompatible. As examples of such polymer substances may be mentioned biodegradable aliphatic polymers (e.g., polylactic acid, polyglycolic acid, polycitric acid and polymalic acid), poly-133-cyanoacrylic acid esters, poly-β-hydroxybutyric acid, polyalkylene oxalate (e.g. polytrimethylene oxalate and polytetramethylene oxalate), poly(ortho-esters), poly(ortho-carbonate), other polycarbonate (e.g. polyethylene carbonate and polyethylene propylene carbonate) and polyamino acids (e.g. poly-γ-benzyl-L-glutamic acid, poly-L-alanine and poly-γ-methyl-L-glutamic acid). As further examples of biocompatible polymer substances may be mentioned, polystyrene, polyacrylic acid, polymethacrylic acid, copolymer of acrylic acid and methacrylic acid, nylon, tetron, polyamino acid, silicone polymer, dextran stearate, ethylcellulose, acetylcellulose, nitrocellulose, polyurethane, maleic anhydride copolymers, ethylene-vinyl acetate copolymer, polyvinyl acetate, polyvinyl alcohol and polyacrylamide. These polymer substances may be used alone or in the form of copolymers or mixtures of two or more species or of salts.

When used in injectable preparations, biodegradable polymers, among said polymers substances, are especially desirable, and as preferable examples of such polymer substances may be mentioned polylactic acid and a copolymer of lactic acid and glycolic acid and these mixtures. The average molecular weight of such a polymer substance as used in accordance with this invention preferably ranges from 2000 to 800000 and is more desirably selected from the range of 5000 to 200000.

When a lactic acid-glycolic acid copolymer is used as said polymer, its comonomer ratio is preferably in the range of 100/0 through 50/50.

The proportion of such a polymer substance depends on the strength of pharmacological activity of the water-soluble drug used and the rate and duration of release of the drug. By way of illustration, the proportion of this polymer substance may range from 1/5 to 1000 times and preferably 1 to 1000 times the weight of the water-soluble drug.

The concentration of said polymer substance in the oil layer is 0.5 to 90% (w/w) and preferably 2 to 60% (w/w).

The solution containing said polymer substance (oil layer) is a solution of the polymer substance in a solvent. The solvent for this purpose should be one which boils at a temperature up to 120°C and is immiscible with water and capable of dissolving the polymer substance and as such there may be mentioned halogenated alkanes (e.g. dichloromethane, chloroform, chloroethane, dichloroethane, trichloroethane, and carbon tetrachloride), ethyl acetate, ethyl ether, cyclohexane, benzene, n-hexane and toluene. These solvents may be used alone or in combination.

With regard to the microencapsulation procedure, the drug retaining substance in an amount sufficient to give the aforementioned concentration is first dissolved in water and, then, the water-soluble drug is added in an amount sufficient to give the aforementioned concentration, whereby an inner aqueous layer is provided.

As a pH-adjusting agent for maintaining the stability and solubility of the water-soluble drug, there may be imcorporated in this inner aqueous layer such an additive as carbonic acid, acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid or phosphoric acid, sodium or potassium salts thereof, hydrochloric acid or sodium hydroxide. Moreover, as a stabilizer for the water-soluble drug, there may also be added such an agent as albumin, gelatin, citric acid, ethylenediamine sodium tetraacetate, dextrin, and sodium hydrosulfite. The inner aqueous layer may also contain a preservative such as p-oxybenzoic acid esters (e.g. methylparaben, propylparaben, etc.), benzyl alcohol, chlorobutanol, and thimerosal.

The inner aqueous layer thus prepared is poured into a solution of said polymer substance (oil layer) and the mixture is emulsified to give a water-in-oil emulsion.

The emulsification can be effected by the conventional dispersion techniques. For example, intermittent shaking, mixing by means of a propeller mixer, turbine mixer or the like, colloid mill operation,

mechanical homogenization and ultrasonication may be utilized.

When the viscosity of the inner aqueous layer in such a water-in-oil emulsion is more than 5.0 Pas (5000 centipoises) or preferably over 10.0 Pas (10000 centipoises) from the beginning, the emulsion is immediately subjected to a desorption procedure but, otherwise, resort is had to an external factor to thicken the inner aqueous layer to a viscosity over 5000 centipoises or preferably over 10000 centipoises or solidify the same.

Exemplary procedures for increasing the viscosity include a heat treatment, cooling to a low temperature, freezing, rendering the pH acidic or alkaline, or adding such an agent as metal ions (e.g. iron ions for gum acacia, copper ions for carboxymethylcellulose, or calcium or magnesium ions for sodium pectinate) or organic acids or salts thereof (e.g. calcium citrate for sodium alginate, or adipic acid or tartaric acid for polyvinyl alcohol). There may also be mentioned the technique of cross-linking and condensing the polymer substance in the inner aqueous layer using a chemical condensing agent (e.g. glutaraldehyde and acetaldehyde).

With regard to the heat treatment, the procedure must be carried out in a closed vessel so as to avoid evaporation of the solvent contained in the oil layer. The temperature is virtually optional provided it is higher than the gelation temperature. Taking proteins as an example, the temperature is generally 40 to 120°C and the time is 5 minutes to 8 hours. This treatment thickens or solidifies the inner aqueous layer.

The technique of cooling the emulsion to a low temperature comprises cooling it to −5°C to 35°C and maintaining the low temperature with stirring for 1 minute to 6 hours. In the case of agar whose gelation point is about 40°C, the emulsification is conducted under heating at 50 to 80°C and, then, caused to gel at the above-mentioned temperature. For all types of inner aqueous layer, it may be frozen by cooling at −60°C to 0°C but the temperature should not be below the solidification point of the oil layer.

As regards the procedure of adding a metal ion, an organic acid or a salt thereof, the amount thereof depends on the amount of the drug retaining substance in the inner aqueous layer and may range from about ½ to 20 molar equivalents and preferably from 1 to 10 molar equivalents. The time required for said thickening or solidification is preferably not more than 6 hours.

With regard to the technique of cross-linking and condensing the high molecular compound in the inner aqueous layer with a chemical condensing agent, such a condensing agent may for example be an aqueous solution of glutaraldehyde or acetaldehyde or a solution of the same in an organic solvent such as halogenated alkanes (e.g. chloroform and dichloromethane), toluene, etc. Particularly, a solution in the latter solvent which is miscible with the solvent used in the oil layer is desirable, because the particle size of the inner aqueous layer is not increased. The chemical condensing agent is added in a proportion of 2 to 5 molar equivalents based on the drug retaining substance in the inner aqueous layer and the mixture is reacted under stirring for 1 to 10 hours.

More specifically, taking gelatin as an example of said drug retaining substance, a water-in-oil emulsion of predetermined particle size is first prepared and then cooled to 0 to 10°C for 5 to 30 minutes with constant stirring, whereby the inner aqueous layer is caused to gel into semi-solid consistency. When agar is used as the drug retaining substance, the desired semi-solid consistency can be obtained by using a somewhat lower concentration than in the case of gelatin and the same procedure as that for gelatin. When albumin is employed, solidification is effected with a condensing agent such as glutaraldehyde. In this case, the water-soluble drug is dissolved in a 5 to 50% aqueous solution of human serum albumin and the resulting solution is added to the organic solvent solution of a high polymer to prepare a water-in-oil emulsion. Thereto is added a 1 to 50% solution of glutaraldehyde in an organic solvent miscible with the oil layer and the mixture is reacted under stirring for 1 to 10 hours so as to solidify the inner aqueous layer. In this procedure, albumin may be replaced with other substances that can be thickened or solifified by cross-linking and condensation, such as globulin, casein, collagen and other polyamino acids. After the reaction, a compound which is ready to react with the condensing agent, e.g. an amino compound such as ethanolamine and aminoacetic acid, may be added so as to inactivate the residual condensing agent.

When a substance capable of increasing in viscosity on alteration of pH, such as carboxyvinyl polymer (Carbopol, B. F, Goodrich, U.S.A.) is added to the inner aqueous layer, a 1 to 20% solution of sodium hydroxide in ethanol or methanol is separately prepared and a small quantity of the solution is added to the water-in-oil emulsion to increase the viscosity of the inner aqueous layer.

The water-in-oil emulsion thus prepared is subjected to in water drying. Thus, this water-in-oil emulsion is added to a third aqueous layer to give a W/O/W ternary layer emulsion and, finally, the solvent in the oil layer is desorbed to give microcapsules.

An emulsifying agent may be added to the third or outer aqueous layer. It may be virtually any emulsifier that forms a stable oil-in-water emulsion, and is thus exemplified by anionic surfactants (e.g. sodium oleate, sodium stearate, sodium laurylsulfate, etc.), nonionic surfactants (e.g. polyoxyethylene sorbitan fatty acid esters [Tween 80 and Tween 60, Atlas Powder, U.S.A.] (Tween is a Trade Mark), polyoxyethylene castor oil derivatives [HCO-60 and HCO-50, Nikko Chemicals, Japan], etc.), polyvinyl pyrrolidone, polyvinyl alcohol, carboxymethylcellulose, lecithin and gelatin. Such emulsifiers may be used either alone or in combination. The concentration of the emulsifier may be selected from the range of 0.01% to 20% and is preferably in the range of 0.05% to 10%.

The aforesaid desorption of the solvent from the oil layer can be accomplished by the conventional technique. Thus, such desorption is effected by gradual decrease of pressure under agitation with a

propeller mixer or magnetic stirrer or by adjusting the degree of vacuum in a rotary evaporator. The higher the stirring speed, the smaller the diameter of the product microcapsule. The time required for such procedures can be shortened by warming the W/O/W emulsion by degrees so as to make the solvent desorption thorough, after the solidification of the polymer has progressed to some extent and the loss of the drug from the inner aqueous layer has decreased. When the thickening or solidification is effected by techniques other than temperature control, the desorption may be effected by allowing the W/O/W emulsion to stand under stirring, warming the emulsion or blasting it with nitrogen gas. The process of desorption of the solvent is an important process having an important bearing on the surface structure of microcapsules which governs the release of the drug. For example, when the desorption speed is increased, pits in the surface layer increase in number and size so that the release rate of the drug is increased.

The microcapsules obtained in the above manner are recovered by centrifugation or filtration, and the free water-soluble drug, emulsifying agents, etc. on the surface are removed by repeating washing with water, then, if necessary, the microcapsules are warmed under reduced pressure to achieve a complete removal of moisture and of the solvent from the microcapsule wall.

The above microcapsules are gently crushed and sieved, if necessary, to remove coarse microcapsules. The particle size of microcapsules depends on the desired degree of prolonged release. When the microcapsules are to be used as a suspension, the particle size may be within the range satisfying the required dispersibility and needle pass requirements. For example, the average diameter may range from 0.5 to 400 µm and preferably from 2 to 200 µm.

The method of this invention enables one to apply a high shear stress in the preparation of the W/O/W emulsion with a low breakdown of the inner aqueous layer and facilitates particle size control to thereby provide fine microcapsules with good efficiency. The additional commercial advantage of this invention is that the required quantity of organic solvent is small as compared with the drying-in-oil technique.

Moreover, the microcapsules produced by the method of this invention feature a reduced coalescence of individual microcapsules during production so that they are more truly spherical in configuration. In addition, desorption of the solvent from the oil layer can be easily controlled to adjust the surface structure (for example, the number and size of fine holes which serve as main routes of the drug release) of microcapsules.

The microcapsules according to this invention can be administered in clinical practice directly as fine granules or as a formulated preparation in a variety of preparations. Thus, they can be used as raw materials for the production of final pharmaceutical preparations.

Such preparations include, among others, injections, oral preparations (e.g. powders, granules, capsules and tablets), nasal preparations, and suppositories (e.g. rectal, vaginal).

When the microcapsules 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), carboxymethylcellulose and sodium alginate), preservative (e.g. methyl-paraben, propyl-paraben, benzyl alcohol and chlorobutanol), isotonizing agent (e.g. sodium chloride, glycerin, sorbitol and glucose), etc. The vehicle may also be a vegetable oil (e.g. olive oil, sesame oil, peanut oil, cottonseed oil and corn oil) or propylene glycol. In this manner, a prolonged release injection can be produced.

The prolonged release injection made from said microcapsules may be further supplemented with an excipient (e.g. mannitol, sorbitol, lactose and glucose), redispersed, and then be solidified by freeze-drying or spray-drying, and on extemporaneous addition of distilled water for injection or suitable vehicle for the reconstitution, such preparation gives a prolonged release injection with greater stability.

When the microcapsules according to this invention are to be processed into tablets, they are mixed with an excipient (e.g. lactose, sucrose and starch), disintegrating agent (e.g. starch and calcium carbonate), binder (e.g. starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone and hydroxypropylcellulose) or/and lubricant (e.g. talc, magnesium stearate and polyethylene glycol 6000), and the mixtures are compressed in molds.

To manufacture a nasal preparation from the microcapsules according to this invention, the microcapsules are provided in a 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 and microcrystalline cellulose) and/or thickener (e.g. natural mucilages, cellulose derivatives and polyacrylates 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 and sodium hydroxide) and a preservative (e.g. p-hydroxybenzoic acid esters, chlorobutanol and benzalkonium chloride).

A suppository of the microcapsules 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 provided it will not dissolve the microcapsules. Thus, for example, higher fatty acid glycerides [e.g. cacao butter, Witepsol (Dynamit-Vobel, West Germany)], intermedaite fatty acids [e.g. Miglyol (Dynamit-Novel)] and vegetable oils (e.g. sesame oil, soybean oil, cottonseed oil) 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 and polyacrylates.

The dosage of the prolonged release preparation according to this invention depends on the kind and amount of the active ingredient (i.e. water-soluble drug), dosage form, duration of drug release, recipient animal (e.g. warm-blooded animals such as mouse, rat, horse, cattle, man), and object of treatment. The dosage 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 1 mg to 10 g, preferably 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 0.1 to 5 ml, preferably 0.5 to 3 ml.

In this manner, there are provided pharmaceutical compositions made up of a water-soluble drug, a drug carrier substance and a biocompatible polymer which are capable of continuous and sustained release of the drug.

The prolonged release preparation according to this invention has the following and other advantages.

(1) The prolonged release of water-soluble drugs in various dosage forms can be ensured. Particularly when a long-term treatment with injections is required for the desired effect, the preparation helps achieve the desired pharmacological effects with an administration schedule of once a month or a week or even once a year, instead of giving injections every day. Moreover, compared with the conventional sustained release drugs, the prolonged release preparation according to this invention ensures longer sustained effects.

(2) When injections are prepared using biodegradable polymers, surgical procedures such as implantation are not required but the preparations can be administered subcutaneously or intramuscularly as easily as ordinary injectable suspensions, not entailing the need for removal from the body.

The preparation according to this invention can be directly administered to the tumor itself, the site of inflammation or the receptor region, so that systemic side effects can be controlled and the drug be allowed to act on the target organ for a longer time period with efficiency, thus making for increased drug efficacy, moreover, it can be used in intra-arterial administration in the vascular embolic therapy produced by Kato et al for cancer of the kidney and of the lung (Lancet II, 479—480, 1979).

(3) The release of the active ingredient is continuous, and in the case of antihormones, receptor antagonists, etc., greater pharmacological effects are obtained than by daily pulsatile administration.

(4) Since a drug retaining substance is employed, the water-soluble drug can be incorporated in the microcapsule more easily and efficiently than by the conventional drying-in-solvent technique. Moreover, the microcapsules are fine and more truly spherical in configuration.

(5) By varying the rate of desorption of the solvent from the polymer constituting the microcapsule wall, the number and size of fine holes in the surface layer of each microcapsule which are determinant of the rate of drug release can be freely controlled.

The following experimental and working examples are further illustrative of this invention.

Experimental Example 1

The repeated administration of TAP—144 to mature female rats in massive doses causes desensitization of the pituitary-gonad system to thereby halt the sexual cycle in the diestrous stage. It is known that this halt of the sexural cycle is promptly recovered as the administration of TAP—144 is discontinued. Therefore, using this halt of the sexual cycle of female rats as an indicator, the present inventors investigate the durations of action of 7 different microcapsules prepared using different polymers, which are among the 8 kinds of microcapsules according to Example 1, and of two other microcapsules (No. 039 and No. 0310) which are produced by using TAP—144 for the inner aqueous layer in amounts of ½ and 2.5 times, respectively, but in otherwise the same manner as Example 1. Thus, using SD female rats (aged 14 to 16 weeks) which are confirmed to show a normal 4-day cycle by the examination of vaginal smears during the preceding period of at least 1 week in groups of 5 individuals, each of the above-mentioned microcapsules is injected subcutaneously at the back of the neck in a dose of 3 mg/kg as TAP—144. Thereafter, the examination of vaginal smears is carried out every day to monitor changes in sexual cycle. The microcapsules are administered either in the form of oily suspensions in purified sesame oil or in the form of aqueous suspensions prepared using a dispersed vehicle constituted with 0.2% Tween® 80, 0.5% sodium carboxymethylcellulose, 0.14% methyl-paraben, 0.014% propyl-paraben and 8% D-sorbitol in distilled water for injection.

The results are presented in Table 1. It will be apparent from Table 1 that all of the microcapsules according to this invention have very satisfactory durations of action.

Table 1

Microcapsule No.	Formulation	Duration of action[a] (days)
031	Aqueous	≥105
033	Aqueous	19.0 ± 0.6
033	Oily	19.2 ± 0.5
034	Aqueous	≥123
035	Aqueous	59.0 ± 7.6
036	Aqueous	117.2 ± 1.8
037	Aqueous	39.8 ± 1.8
038	Aqueous	35.0 ± 1.3
039	Aqueous	60.0 ± 6.2
0310	Aqueous	19.6 ± 0.4

a) Mean ± standard error for 5 rats.

Experimental Example 2

The repeated administration of TAP—144 to male rats in massive doses causes an atrophy (decrease of organ weight) of the inner genital organs due to densitization of the putuitary-gonad system. Using this action, the duration of action of the TAP—144 microcapsules produced in Example 1 are investigated. Thus, No. 032 and No. 035 microcapsules according to Example 1 are injected subcutaneously at the back of the neck of SD male rats (aged 6 weeks) in the dose of 900 µg as TAP—144, after 1, 2 and 4 weeks the inner genital organs are removed and weighed. As the control, untreated rats of the same age are used and the percentages of organ weights relative to the control organ weights are calculated. The results are shown in Table 2. In the group of rats given No. 032 microcapsules, no marked difference is found between oily and aqueous formulations and a marked weight decrease persisting for 4 weeks is noted in the weight of testis. A marked weight decrease is also observed in the seminal vesicle, with a significant difference being noted even at 2 weeks. In the No. 035 microcapsule group, too, marked weight decreases of both the testis and seminal vesicle are found after 1 week. The above results indicate that the TAP—144 prolonged release injections according to this invention have satisfactory durations of action.

Table 2

Time	Organ	Microcapsule No. 032		Microcapsule No. 035
		Oily	Aqueous	Aqueous
1 Week	Testis	58.1 ± 8.3**	57.9 ± 7.4**	62.4 ± 5.3**a)
	Prostate	94.6 ± 4.7	92.9 ± 9.9	86.7 ± 7.9
	Seminal vesicle	67.6 ±10.6	62.7 ±10.7*,	66.4 ± 7.7*
2 Weeks	Testis	53.4 ± 6.5**	65.1 ±10.6*	
	Prostate	67.2 ± 6.3**	85.1 ± 7.3	
	Seminal vesicle	39.5 ± 6.3**	56.2 ± 7.8*	
3 Weeks	Testis	77.1 ± 5.7**	58.0 ± 5.7**	
	Prostate	97.4 ± 4.6	87.2 = 5.9	
	Seminal vesicle	89.3 ± 2.7	80.5 ± 6.4*	

a) Percentages relative to the organ weights of control rats (untreated, the same age)

** A highly significant difference ($P<0.01$) from control by t-test.

* A significant difference ($P<0.05$) from control by t-test.

Example 1

In 2.5 ml of a 20% aqueous gelatin solution prepared by warming (at 60 to 70°C) is dissolved 200 mg of TAP—144 and the whole solution is added to 10 ml of a 20% dichloromethane solution of one of the 7 different lactic acid or lactic acid-glycolic acid polymers (2 runs for polylactic acid with a molecular weight of 50000). The mixture is ultrasonicated (20 KHz, 100 W, for a few minutes, the ultrasonicator manufactured by Ohtake Seisakusho Inc., Japan) to give a microfine W/O emulsion. This emulsion is immediately cooled with ice to cause gelation of the gelatin layer. This is then added to 100 ml of 0.5% polyvinyl alcohol (Gosenol EG—40, the Nippon Synthetic Chemical Industry Co., Ltd., Japan)-1/30 M phosphate buffer (pH 6.0) and dispersed using a homogenizer (T. K. Homomixer, Tokushu Kika Kogyo Inc., Japan, 30 V) (3,000 r.p.m.) for 15 seconds to give a W/O/W emulsion. This emulsion is quickly transferred to a rotary evaporator in which the dichloromethane is desorbed under ice-cooling. After foaming has subsided, the emulsion is warmed to 30 to 40°C in a constant-temperature water bath for complete desorption of the organic solvent. The hardened microcapsules are then filtered through a glass filter and washed 5 times with 10 ml portions of distilled water. They are then spread on a glass dish and allowed to dry under reduced pressure for 1 to 3 days. The product is sieved through a 100-mesh screen (Sieve opening: 147 µm) to give TAP—144 microcapsules.

In 10 ml of dichloromethane is dissolved 10 mg of the above microcapsules and TAP—144 in the solution is extracted with 10 ml of distilled water under shaking for 10 minutes. The TAP—144 content of the aqueous layer is assayed by high performance liquid chromatography (HPLC) and the percentage of TAP—144 taken up into the microcapsules relative to the initial amount of TAP—144 added is calculated. The results are shown in Table 3.

Table 3

Microcapsule No.		High polymer: Lactic acid/glycolic acid	High polymer: Mol. weight	Takeup (%)
Control	021	100/0	50000	6.7
	022	100/0	50000	5.5
	023	100/0	50000	1.9

Microcapsule No.		High polymer: Lactic acid/glycolic acid	High polymer: Mol. weight	Takeup (%)
This invention	031	100/0	73000	70.4
	032	100/0	50000	70.7
	033	100/0	50000	71.5
	034	100/0	15000	54.8
	035	100/0	6800	55.8
	036	88.7/11.3	19000	44.0
	037	78.1/21.9	10000	58.3
	038	54.5/45.4	20000	53.1

It will be apparent from Table 3 that when the drying-in-water technique under the same conditions is carried out without gelation of the first aqueous layer (control), the takeup ratios are as low as 1.9 to 6.7% whereas the takeup ratios for the microcapsules according to this invention are as high as 44.0 to 71.5%. In the repeated experiments by the same production procedure using polylactic acid with a molecular weight of 50000, the take up ratios are almost comparable.

Example 2

In a 20% aqueous gelatin solution prepared by warming (60 to 70°C) is dissolved 200 mg of TAP—144. This solution is added when hot to a 20% dichloromethane solution of polylactic acid (average mol. wt. 50000) and the mixture is ultrasonicated in the same manner as Example 1 to give a fine W/O emulsion. Separately, 5 ml of a 25% aqueous solution of glutaraldehyde is extracted with 5 ml of dichloromethane (using the aforementioned ultrasonicator, 50 W, 2 min.) and the organic layer is added to the emulsion prepared above. Using a four-blade rotary mixer, the mixture is reacted at room temperature under agitation for 6 hours. Thereafter, 4 ml of ethanolamine is added and the reaction is further conducted for 1 hour. After ice-cooling, the reaction mixture is poured into 100 ml of ice-cooled 0.5% polyvinyl alcohol-1/30 M phosphate buffer (pH 6.0).

Then, as in Example 1, a W/O/W emulsion is prepared and the organic solvent is desorbed to give TAP—144 microcapsules (Microcapsule No. 0311). In addition, a 30% aqueous solution of human serum albumin in lieu of said 20% gelatin is treated with glutaraldehyde in the same manner as above to prepare TAP—144 microcapsules (Microcapsule No. 0312).

These microcapsules are dispersed in purified sesame oil and the dispersions are subcutaneously injected into mature female rats at a dose of 12 mg/kg as TAP—144 in the same manner as Experimental Example 1 to assess the durations of action of the respective prolonged release preparations.

The results are presented in Table 4. It will be seen that their actions last for about 4 months, indicating that these microcapsules are satisfactory prolonged release preparations.

Table 4

Microcapsule No.	Drug retaining substance	Duration of action[a] (days)
0311	20% gelatin	≥147
0312	30% human serum albumin	114.8 ± 5.9

a) Mean ± standard error for 5 rats

Example 3

In 10 ml of dichloromethane is dissolved 3 g of lactic acid-glycolic acid copolymer (monomer ratio: 88.7/11.3, average mol. wt. 19000) followed by addition of 3 ml of a 30% aqueous solution of gelatin (dissolved at 60°C). Then a soltion of 200 mg of LH-RH antagonist (N-Ac-[D-P-Cl-Phe^{1,2}, D-Trp^{3}, D-Arg^{6}, D-Ala^{10}]-LH-RH) (EP—A—81,877) is added and the mixture is ultrasonicated in the same manner as Example 1 to give a W/O emulsion. This emulsion is immediately cooled with ice and dispersed in a water-cooled 0.5% aqueous solution of polyvinyl alcohol. Then, the dichloromethane is desorbed and LH-RH antagonist microcapsules recovered in the same manner as Example 1.

Example 4

In 2.5 ml of a 20% aqueous solution of gelatin (prepared at 60°C) is dissolved 500 mg of an enkephalin derivative (H-Tyr-D-Met(O)-Gly-EtPhe-NH-NHCOCH$_3$·AcOH) (United Patent No. 4277394, TAI—1399) and the solution is added to 10 ml of a 20% solution of polylactic acid (average mol. wt. 50000) in dichloromethane. The mixture is further worked up in the same manner as Example 1 to give a W/O emulsion. Under ice-cooling, this emulsion is further worked up in 0.5% polyvinyl alcohol-1/30 M phosphate buffer (pH 6.0) to give a W/O/W emulsion. The organic solvent is then desorbed under reduced pressure in a rotary evaporator and the mixture is warmed from ice-cooling to 35°C and when foaming has subsided, it is sieved through a 100-mesh screen and filtered through a glass filter to give TAI—1399 microcapsules.

The microcapsules thus produced are washed 4 times with 10 ml portions of distilled water and dispersed in a mixed aqueous solution of 0.2% Tween® 80, 0.5% sodium carboxymethylcellulose and 10% mannitol, followed by freeze-drying to give a prolonged release preparation of TAI—1399 which is of a reconstituted suspension type and the action of which lasts *in vivo* for more than 2 weeks.

Example 5

In a 20% aqueous solution of gelatin (prepared at 60°C) is dissolved 2.2 billion units of γ-interferon and the solution is added to 10 ml of a 20% dichloromethane solution of polylactic acid (average mol. wt. 73000). Then, the same procedure as Example 1 is followed to give a W/O/W emulsion under ice-cooling, remove the solvent in a roatary evaporator and recover solid microcapsules by filtration to give γ-interferon microcapsules.

The above microcapsules are washed 4 times with 10 ml portions of distilled water and dispered in 50 ml of a mixed aqueous solution of 0.2% Tween® 80, 0.5% sodium carboxymethylcellulose and 8% D-sorbitol, and 1 ml portions of the dispersion are distributed into glass vials and freeze-dried. The contents of each vial are extemporaneously redispersed in 1 ml of distilled water for injection containing 0.4% methyl-paraben and 0.04% propylparaben to give a prolonged release injection containing about 25,000,000 units of γ-interferon per dose.

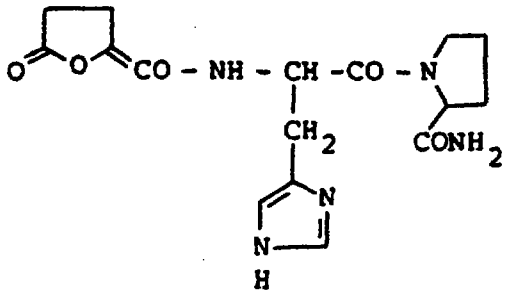
Example 6

In 2.5 ml of distilled water are dissolved 300 mg of synthetic serum thymic factor (FTS: H-Glu-Ala-Lys-Ser-Gln-Ala-gly-Ser-Asn-OH) and 750 mg of human serum albumin, and the whole solution is added to 10 ml of a dichloromethane solution containing 3 g of lactic acid-glycolic acid copolymer (monomer ratio: 78.1/21.9, average mol. wt. 10000). Thereafter, the same procedure as Example 1 is followed to prepare a W/O emulsion. To this emulsion is added 3 ml of a dichloromethane extract of 25% aqueous glutaraldehyde (3 ml) and the reaction is carried out under stirring for 5 hours. Then, 3 ml of ethanolamine is added and the mixture is further stirred for 1 hour. This W/O emulsion is poured into 100 ml of a 0.5% aqueous solution of polyvinyl alcohol and the solution is worked up in the same manner as Example 1 to give a W/O/W emulsion. Finally, the solvent is removed in a rotary evaporator and the product microcapsules are recovered.

The microcapsules thus obtained are dispersed in 20 ml of the same dispersing medium as the one used in Eample 5 and 2 ml portions of the dispersion are distributed into glass vials and freeze-dried to give a prolonged release injection containing about 15 mg of FTS per dose.

Example 7

In 2.5 ml of a 2% aqueous solution of agar (liquefied by warming at 60°C) is dissolved a citrate of a thyroid hormone derivative (DN—1417) of the following formula:



This solution is added to 10 ml of a 20% solution of polylactic acid (average mol. wt. 50000) in dichloromethane. The mixture is worked up in the same manner as Example 1 to give a W/O emulsion which is further processed into a W/O/W emulsion under ice cooling. Finally, the organic solvent is removed to give DN—1417 microcapsules.

These microcapsules are recovered by filtration, dried in vacuo at 40°C for 24 hours and sieved through a 100-mesh screen. Vials are filled with 500 mg portions of the product to give a prolonged release injection containing about 75 mg of DN81417 which is used by a reconstituted suspension.

Example 8

In 10 ml of dichloromethane is dissolved 2 g of lactic acid-glycolic acid copolymer (monomer ratio: 54.5/45.5, average mol. wt. 20000). To this solution is added 3 ml of a 20% aqueous gelatin solution containing 400 mg of mitomycin C (liquified by warming at about 60°C) and the mixture is worked up in the same manner as Example 1 to give mitomycin C microcapsules.

The microcapsules are dried in vacuo and sieved through a 100-mesh screen. 200 mg of the product is taken as a prolonged release injection containing about 20 mg of mitomycin C which is a reconstituted suspension for administration.

Example 9

To a 20% dichloromethane solution of lactic acid/glycolic acid copolymer (monomer ratio: 78.1/21.9, average mol. wt. 10000) is added 3 ml of a 20% aqueous gelatin solution containing 1.5 g of gentamycin sulfate (liquefied by warming). The mixture is further worked up in the same manner as Example 1 to give microcapsules.

These microcapsules are dried in vacuo and sieved, and 350 mg of the product is taken as a prolonged release preparation containing about 100 mg of gentamycin for use as a reconstituted suspension.

Example 10

In 10 ml of dichloromethane is dissolved 3 g of polylactic acid (average mol. wt. 15000) followed by addition of 3 ml of a 20% aqueous gelatin solution containing 43000 units of blood coagulation factor VIII and 15 mg of sodium citrate. The mixture is worked up in the same manner as Example 4 to give microcapsules.

This product is dispersed in 20 ml of dispersing medium and vials are filled with 2 ml portions to freeze dry to give a prolonged release injection for a reconstituted suspension containing about 3000 units of blood coagulation factor VIII in each vial.

Example 11

In 3 ml of a 20% aqueous gelatin solution (liquified by warming) is dissolved 2 g of sulpyrine and the solution is added to 10 ml of a 25% dichloromethane solution of lactic acid-glycolic acid copolymer (54.5/45.5, average mol. wt. 20000). Finally, the mixture is worked up in the same manner as Example 1 to give microcapsules.

Example 12

In 2.5 ml of 20% aqueous gelatin solution (liquified by warming) is dissolved 500 mg of morphine hydrochloride and the solution is added to 10 ml of a 20% dichloromethane solution of polylactic acid (average mol. wt. 15000). Thereafter, the same procedure as Example 1 is followed to give prolonged release mocrocapsules for injection.

Example 13

In 2.5 ml of 20% aqueous gelatin solution (liquified by warming) is dissolved 150 mg of sodium dichlofenac and the solution is added to 10 ml of a 20% dichloromethane solution of polylactic acid (average mol. wt. 15000). The mixture is worked up in the same manner as Example 1 to give microcapsules for injection.

Example 14

In 2.5 ml of 20% aqueous gelatin solution (liquified by warming) is dissolved 1 g of methylephedrine hydrochloride and the solution is added to 10 ml of a 20% dichloromethane solution of polylactic acid (average mol. wt. 50000). The mixture is worked up in the same manner as Example 1 to give methylephedrine microcapsules for injection.

Example 15

In 3.0 ml of 20% aqueous gelatin solution (liquified by warming) is dissolved 1 g of chloropromazine hydrochloride, and the solution is added to 10 ml of a 20% dichloromethane solution of lactic acid-glycolic acid copolymer (88.7/11.3, average mol. wt. 19000). The mixture is worked up in the same manner as Example 1 to give chlorpromazine hydrochloride microcapsules for injection.

Example 16

In 3.0 ml of 30% gelatin (dissolved by warming) is dissolved 50 mg of pridinol methanesulfonate and the solution is added to 10 ml of a 30% dichloromethane solution of lactic acid-glycolic acid copolymer (78.1/21.9, average mol. wt. 10000). The mixture is then worked up in the same manner as Example 1 to give pridinol methanesulfonate microsapcules for injection.

Example 17

Using 600 mg of chlordiazepoxide hydrochloride, the procedure of Example 11 is followed to give microcapsules.

Example 18

Using 800 mg of metroclcpramide, the procedure of Example 12 is followed to give metoclopramide microcapsules for injection.

Example 19

Using 1 g of imipramine, the procedure of Example 15 is followed go give imipramine microcapsules for injection.

Example 20

Using 750 mg of diphenhydramine hydrochloride, the procedure of Example 14 is followed to give diphenhydramide hydrochloride microcapsules for injection.

Example 21

Using 750 mg of etilefrin hydrochloride, the procedure of Example 15 is followed to give etilefrin hydrochloride microcapsules for injection.

Example 22

Using 300 mg of propranolol hydrochloride, the procedure of Example 14 is followed to give propranolol hydrochloride microcapsules for injection.

Example 23

Using 250 mg of oxyfedrine hydrochloride, the procedure of Example 12 is followed to give oxyfedrine hydrochloride microcapsules for injection.

Example 24

Using 300 mg of pentolinium, the procedure of Example 11 is followed to give pentolonium microcapsules.

Example 25

Using 1 g of phenformin hydrochloride, the procedure of Example 13 is followed to give phenformin hydrochloride microcapsules.

Example 26

Using 2×10^6 units of sodium heparin, the procedure of Example 15 is followed to give sodium heparin microcapsules.

Example 27

Using 400 mg of adrenochrome monoaminoguanidine methanesulfonate, the procedure of Example 12 is followed to give adrenochrome monoaminoguanidine methanesulfonate microcapsules for injection.

Example 28

Using 800 mg of isoniazid, the procedure of Example 16 is followed to give isoniazid microcapsules for injection.

Example 29

Using 750 mg of prednisolone sodium phosphate, the procedure of Example 15 is followed to give prednisolone sodium phospnate microcapsules for injection.

Example 30

Using 100 mg of levallorphan tartrate, the procedure of Example 16 is followed to give levallorphan tartrate microcapsules for injection.

Claims

1. A prolonged release microcapsule, which is produced by preparing a water-in-oil emulsion comprising an inner aqueous layer containing a water-soluble drug and a drug retaining substance therefor and an oil layer containing a high polymer substance, then thickening or solidifying said inner aqueous layer to a viscosity of not lower than 5.0 Pas (5000 centipoises) and finally subjecting the resulting emulsion to in water drying.

2. A microcapsule as claimed in claim 1, wherein the water-soluble drug is a biologically active polypeptide.

3. A microcapsule as claimed in claim 2, wherein the biologically active polypeptide is (Pyr)Glu-His-Trp-Ser-Tyr-D-leu-Leu-Arg-Pro-NH-C_2H_5.

4. A microcapsule as claimed in claim 1, wherein the drug retaining substance is a natural high molecular weight compound.

5. A microcapsule as claimed in claim 4, wherein the natural high molecular weight compound is gelatin.

6. A microcapsule as claimed in claim 1, wherein the polymer substance in the oil layer is a copolymer of lactic acid and glycolic acid.

7. A microcapsule as claimed in claim 6, wherein the ratio of lactic acid:glycolic acid is 75:25.

8. A microcapsule as claimed in claim 1, wherein the inner aqueous layer is solidified.

9. A microcapsule as claimed in claim 1, wherein the average diameter is 2 to 200 µm.

10. A method for producing a prolonged release microcapsule of water-soluble drug which comprises preparing a water-in-oil emulsion comprising an inner aqueous layer containing said water-soluble drug and a drug retaining substance therefor and an oil layer containing a polymer substance, then thickening or solidifying said inner aqueous layer to a viscosity of not lower than 5.0 Pas (5000 centipoises) and finally subjecting the resulting emulsion to in water drying.

Patentansprüche

1. Mikrokapsel mit verlängerter Freisetzung, die hergestellt wird, indem eine Wasser-in-Öl-Emulsion zubereitet wird, die einen innere, wässerige Schicht, die ein wasserlösliches Arzneimittel und eine dasselbe zurückhaltende Substanz enthält und eine Ölschicht umfaßt, die eine hochpolymere Substanz enthält, dann die genannte innere, wässerige Schicht auf dine Viskosität von nicht weniger als 5,0 Pa.s (5000 Centipoise) verdickt oder verfestigt wird und schließlich die entstandene Emulsion der Trocknung in Wasser unterworfen wird.

2. Mikrokapsel nach Anspruch 1, worin das wasserlösliche Arzneimittel ein biologisch wirksames Polypeptid ist.

3. Mikrokapsel nach Anspruch 2, worin das biologisch aktive Polypeptid (Pyr)Glu-His-Trp-Ser-Tyr-D-leu-Leu-Arg-Pro-NH-C_2H_5 ist.

4. Mikrokapsel nach Anspruch 1, worin die das Arzneimittel zurückhaltende Substanz eine natürliche Verbindung mit hohem Molekulargewicht ist.

5. Mikrokapsel nach Anspruch 4, worin die natürliche Verbindung mit hohem Molekulargewicht Gelatine ist.

6. Mikrokapsel nach Anspruch 1, worin die polymere Substanz in der Ölschicht ein Copolymer von Milchsäure und Glycolsäure ist.

7. Mikrokapsel nach Anspruch 6, worin das Verhältnis Milchsäure:Glycolsäure 75:25 ist.

8. Mikrokapsel nach Anspruch 1, worin die innere wässerige Schicht verfestigt ist.

9. Mikrokapsel nach Anspruch 1, worin der durchschnittliche Durchmesser 2 bis 200 µm beträgt.

10. Verfahren zur Herstellung einer Mikrokapsel mit verlängerter Freisetzung auf der Basis eines wasserlöslichen Arzneimittels, das die Zubereitung einer Wasser-in-Öl-Emulsion umfaßt, die eine innere wasserige Schicht, die das genannte wasserlösliche Arzneimittel und eine das Arzneimittel zurückhaltende Substanz enthält und eine eine polymere Substanz enthaltende Ölschicht umfaßt, dann die genannte innere wässerige Schicht auf eine Viskosität von nicht weniger als 5,0 Pa.s (5000 Centipoise) verdickt oder verfestigt wird und schließlich die entstandene Emulsion der Trocknung in Wasser unterworfen wird.

Example 29

Using 750 mg of prednisolone sodium phosphate, the procedure of Example 15 is followed to give prednisolone sodium phosphate microcapsules for injection.

Example 30

Using 100 mg of levallorphan tartrate, the procedure of Example 16 is followed to give levallorphan tartrate microcapsules for injection.

Claims

1. A prolonged release microcapsule, which is produced by preparing a water-in-oil emulsion comprising an inner aqueous layer containing a water-soluble drug and a drug retaining substance therefor and an oil layer containing a high polymer substance, then thickening or solidifying said inner aqueous layer to a viscosity of not lower than 5.0 Pas (5000 centipoises) and finally subjecting the resulting emulsion to in water drying.

2. A microcapsule as claimed in claim 1, wherein the water-soluble drug is a biologically active polypeptide.

3. A microcapsule as claimed in claim 2, wherein the biologically active polypeptide is (Pyr)Glu-His-Trp-Ser-Tyr-D-leu-Leu-Arg-Pro-NH-C_2H_5.

4. A microcapsule as claimed in claim 1, wherein the drug retaining substance is a natural high molecular weight compound.

5. A microcapsule as claimed in claim 4, wherein the natural high molecular weight compound is gelatin.

6. A microcapsule as claimed in claim 1, wherein the polymer substance in the oil layer is a copolymer of lactic acid and glycolic acid.

7. A microcapsule as claimed in claim 6, wherein the ratio of lactic acid:glycolic acid is 75:25.

8. A microcapsule as claimed in claim 1, wherein the inner aqueous layer is solidified.

9. A microcapsule as claimed in claim 1, wherein the average diameter is 2 to 200 µm.

10. A method for producing a prolonged release microcapsule of water-soluble drug which comprises preparing a water-in-oil emulsion comprising an inner aqueous layer containing said water-soluble drug and a drug retaining substance therefor and an oil layer containing a polymer substance, then thickening or solidifying said inner aqueous layer to a viscosity of not lower than 5.0 Pas (5000 centipoises) and finally subjecting the resulting emulsion to in water drying.

Patentansprüche

1. Mikrokapsel mit verlängerter Freisetzung, die hergestellt wird, indem eine Wasser-in-Öl-Emulsion zubereitet wird, die einen innere, wässerige Schicht, die ein wasserlösliches Arzneimittel und eine dasselbe zurückhaltende Substanz enthält und eine Ölschicht umfaßt, die eine hochpolymere Substanz enthält, dann die genannte innere, wässerige Schicht auf dine Viskosität von nicht weniger als 5,0 Pa.s (5000 Centipoise) verdickt oder verfestigt wird und schließlich die entstandene Emulsion der Trocknung in Wasser unterworfen wird.

2. Mikrokapsel nach Anspruch 1, worin das wasserlösliche Arzneimittel ein biologisch wirksames Polypeptid ist.

3. Mikrokapsel nach Anspruch 2, worin das biologisch aktive Polypeptid (Pyr)Glu-His-Trp-Ser-Tyr-D-leu-Leu-Arg-Pro-NH-C_2H_5 ist.

4. Mikrokapsel nach Anspruch 1, worin die das Arzneimittel zurückhaltende Substanz eine natürliche Verbindung mit hohem Molekulargewicht ist.

5. Mikrokapsel nach Anspruch 4, worin die natürliche Verbindung mit hohem Molekulargewicht Gelatine ist.

6. Mikrokapsel nach Anspruch 1, worin die polymere Substanz in der Ölschicht ein Copolymer von Milchsäure und Glycolsäure ist.

7. Mikrokapsel nach Anspruch 6, worin das Verhältnis Milchsäure:Glycolsäure 75:25 ist.

8. Mikrokapsel nach Anspruch 1, worin die innere wässerige Schicht verfestigt ist.

9. Mikrokapsel nach Anspruch 1, worin der durchschnittliche Durchmesser 2 bis 200 µm beträgt.

10. Verfahren zur Herstellung einer Mikrokapsel mit verlängerter Freisetzung auf der Basis eines wasserlöslichen Arzneimittels, das die Zubereitung einer Wasser-in-Öl-Emulsion umfaßt, die eine innere wasserige Schicht, die das genannte wasserlösliche Arzneimittel und eine das Arzneimittel zurückhaltende Substanz enthält und eine eine polymere Substanz enthaltende Ölschicht umfaßt, dann die genannte innere wässerige Schicht auf eine Viskosität von nicht weniger als 5,0 Pa.s (5000 Centipoise) verdickt oder verfestigt wird und schließlich die entstandene Emulsion der Trocknung in Wasser unterworfen wird.

* C L M S *

Revendications

1. Microcapsule à libération prolongée, qui est produite en effectuant une émulsion d'eau dans l'huile, comprenant une couche aqueuse interne contenant un médicament soluble dans l'eau et une substance appropriée retenant ce médicament et uen couche d'huile contenant un haut polymère, puis en faisant épaissir ou solidifier ladite couche aqueuse interne jusqu'à une viscosité non inférieure à 5,0 Pas (5000 centipoises) et finalement en soumettant l'émulsion ainsi formée à un séchage dans l'eau.

2. Microcapsule selon la revendication 1, dans laquelle le médicament soluble dans l'eau est un polypeptide biologiquement actif.

3. Microcapsule selon la revendication 2, dans laquelle le polypeptide biologiquement actif est (Pyr)Glu-His-Trp-Ser-Tyr-D-leu-Leu-Arg-Pro-NH-C_2H_5.

4. Microcapsule selon la revendication 1, dans laquelle la substance 1, dans laquelle la substance retenant le médicament est un composé naturel de poids moléculaire élevé.

5. Microcapsule selon la revendication 4, dans laquelle le composé naturel de poids moléculaire élevé est la gélatine.

6. Microcapsule selon la revendication 1, dans laquelle le polymère de la couche d'huile est un copolymère d'acide lactique et d'acide glycolique.

7. Microcapsule selon la revendication 6, dans laquelle la proportion d'acide lactique et d'acide glycolique est de 75 à 25.

8. Microcapsule selon la revendication 1, dans laquelle la coche aqueuse interne est solidifiée.

9. Microcapsule selon la revendication 1, dans laquelle le diamètre moyen est de 2 à 200 µm.

10. Procédé de préparation d'une microcapsule à libération prolongée d'un médicament soluble dans l'eau, selon lequel on effectue une émulsion d'eau dans l'huile, comprenant une couche aqueuse interne contenant ce médicament soluble dans l'eau et une substance appropriée retenant ce médicament et une couche d'huile contenant un polymère, puis on fait épaissir ou solidifier ladite couche aqueuse interne jusqu'à une viscosité non inférieure à 5,0 Pas (5000 centipoises) et finalement on soumet l'émulsion ainsi formée à un séchage dans l'eau.