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TITLE

Sustained Release Pharmaceutical Compositions and the Preparation of Particles for use therein.

DESCIPTION:

The invention relates to a process for the preparation of particles designed to release an effective amount of active ingredient over a predetermined period of time, said particles comprising one or more active ingredients in admixture with a bioresorbable and/or biodegradable polymer or copolymer. The invention also relates to sustained release pharmaceutical preparations containing such particles.

In this specification, the term "active ingredient" is used to mean any therapeutically active substance or admixture which might advantageously be administered to man or other animals for the purpose of diagnosis, cure, mitigation, treatment or prevention of disease.

The preparation of microparticles and their use in pharmaceutical compositions for the sustained release of one or more active ingredients are well known. These known microparticles fall into two categories, microcapsules and microspheres.

Microcapsules are generally obtained by suspending or dissolving a polymer and/or copolymer in a solution and then evacuating the solvent; microcapsules are formed by a core with a rather high active ingredient content surrounded by a covering with a rather high polymer and/or copolymer content. Because complete solvent elimination is never possible, microcapsules contain at least traces of solvents in their composition; although, by this way, the encapsulation rate with respect to the active ingredient never reaches 100 %.

Microspheres are also generally formed using solvents and present a more regular repartition of the active ingredient in the polymer; the second step of their formation, e.g. extrusion and grinding implies the formation of an irregular external surface so that they are in fact not truly spheroidal; the presence of active ingredient on the external surface and the irregularity of the said surface do not permit precise control of the burst effect. Moreover as solvent has been used in the first step, the complete elimination is practically impossible.

In contradistinction, the particles according to the invention, which may be called microballs, are dry processed without use of any solvent. The solid composition obtained by dry admixture of the active ingredient and the polymer is manufactured by conventional techniques well known in the pharmaceutical art. The repartition of the active ingredient in the polymer is approximately the same as in the above defined microspheres. After grinding and sifting, the particles are suspended in a gel under energetic stirring. The gel is then heated with close control of temperature and time according to the employed constituents. The suspended particles fuse, and due to superficial tension tend to become spherical if the gel viscosity is sufficient; the viscosity must be such as to avoid agglomeration. This operation may be called "spheronization". When spheronization has been achieved, the suspension is very rapidly cooled (by dipping), and the gel is dissociated by addition of a washing agent which is neither a solvent of the polymer nor a solvent of the active ingredient. The smooth structure of the surface of the microballs ensures no retention of the washing agent.

The microballs of the invention are bioresorbable, non irritating pharmaceutical compositions consisting of one or more active ingredients intimately dispersed in a

bioresorbable polymer designed to release an effective amount of active ingredient over a predetermined period of time.

The microballs permit prolonged release of active ingredients for a controlled period of time from the sites of parenteral administration and minimize the frequency and thus the discomfort and inconvenience associated with conventional daily injection formulations. Unlike conventional depot injections, the microballs according to the invention undergo biodegradation in the body into normal or essentially normal metabolic products, are non reactive toward body tissues, and can be designed by controlling the weight average molecular weight and the number average molecular weight to undergo hydrolysis and to release the active ingredient from the depot at a desired rate.

The invention provides a process for the preparation of particles designed to release an effective amount of active ingredient over a predetermined period of time, said particles comprising one or more active ingredients in admixture with a bioresorbable and/or biodegradable polymer or copolymer being within a determined size range, the process comprising mixing the active ingredient(s) with the polymer or copolymer in the dry state; tabletting or extruding the resultant mixture; grinding the tablets or the extrudate; selecting ground particles within the determined size range; suspending them under stirring in a hydrophilic or hydrophobic gel or oil which has a viscosity at 60°C or over, the upper limit being defined by the stability of components, of from 40 to 500 mPa.s in the case of a hydrophilic gel or of from 3 000 to 12 500 mPa.s in the case of a hydrophobic gel; heating the gel to a temperature sufficient to melt the particles whereby microballs are formed; cooling the gel; and recovering the microballs by filtration.

The gel viscosity may be preferably comprised at 60°C or over, of from about 80 to about 200 mPa.s wherein hydrophilic gel is used, and of from 5 000 to 11 000 mPa.s wherein hydrophobic gel is used, and in a preferred embodiment, at about 100 mPa.s wherein hydrophilic gel is used and about 9 000 mPa.s wherein hydrophobic gel is used.

The invention relates also to microballs thus obtained, in a substantially spheroidal form and deprived of active ingredient on the external covering.

Pharmaceutically inert additives which can be ground with the polymer or copolymer include PvP, mannitol, carbowax, polyethylene glycols, glycerides and ethyl cellulose.

The melting, as previously stated, is at a temperature in excess of the glass temperature. For example, for a D,L lactic acid-co-glycolic acid copolymer (50:50), temperature may be 75°C. The process provides classical tablets or others forms well known in the pharmaceutical art, which may be cut to lenghts of, e.g., 1 cm for grinding. Grinding may be effected with a congealed grinding apparatus.

The gel may be hydrophobic or hydrophilic. Hydrophilic gels are such as PvP, carboxymethyl cellulose, poloxamer and water, are suitable for hydrophobic active ingredients and are common for industrial use. Stirring must be maintained throughout the suspension of the active

ingredient polymer mixture in the gel, essentially at the beginning of the process to disperse particles in the gel. Filtration may be through a 0.45 to 10 μm PTFE membrane for instance when preparation for injection is involved.

In the process of the invention only mechanical systems are used. The process of the invention is different from spray atomisation, pan coating, fluid bed coating, microencapsulation by coacervation and microencapsulation by solvent evaporation, none of which processes leads to homogeneous microballs.

Classes of active ingredient which may be used in the invention include agents affecting the central nervous system, e.g. narcotics such as morphine ; narcotic antagonists, such as naloxone ; antipsychotic agents, such as sodium pentobarbital, chlorpromazine ; antidepressives such as imipramine hydrochloride ; stimulants, such as methyl phenadate and nikethamide ; hallucinogens; analgesics such as mumorphan meperidine; and anorexigenic agents.

Other classes are pharmacodynamic agents, e.g. antihypertensive agents such as reserpine, and antianginal agents, such as papaverine, and drugs for the therapy of pulmonary disorders, such as theophylline ethylene diamine salt. Additional classes are chemotherapeutic agents, e.g. antiviral ; antiparasitic, such as emetine hydrochloride ; antifungal agents, such as cyclohexemide ; and anti-neoplastic agents, such as triethylene thiophosphoramide ; agents affecting metabolic diseases and endocrine functions, e.g., prostaglandins ; athersclerosins,such as heparin ; steroids and biologically related compounds ; polypeptides, such as bacitracin, polymyxin B sulfate ; natural and synthetic hormones, such as progesterone ; steroid and non steroidal anti-inflammatory agents, such as hydrocortisone ; and agents affecting thrombosis, such as

crystalline trypsin ; vitamins, such as vitamin B12 ; anti-epilepsy agents, such as phenobarbital, and the like. It should be understood that the specific drugs mentioned by name are illustrative and not limitative.

Endocrine agents comprise a particularly useful class of compounds in this invention and can be defined either as natural hormones or as synthetic drugs that to some extent act like, or antagonize, natural hormones, such as triptoreline or somatuline. Endocrine agents include, but are not limited to, both steroids and non steroids that function as fertility control agents ; progestogens, estrogens, androgens, antiandrogens, corticoids, anabolic agents and anti-inflammatory agents.

Any biodegradable polymer can be used for the microballs formulation. Illustrative, but non-limiting, examples include :

- homopolymers and copolymers of $\epsilon$ -caprolactone
- denatured proteins
- homopolymers and copolymers of lactic acid and glycolic acid
- poly ortho esters
- poly anhydrides
- poly ($\beta$ -hydroxybutyric acid)
- poly phosphazens
- poly alkylcyanoacrylates
- polycetals
- poly saccharides, cellulosic polymers
- polypeptides

When glycolic or lactic acids are used to prepare the polymer, it is clear that the polymer's hydrolysis products will include glycolic or lactic acids which are normal metabolites of the body. When the polymer is prepared from the other compounds listed above, the hydrolysis products

will be related in simple structure and will have non deleterious or untoward effect on the body.

Polymers and copolymers useful in the formulations of the invention may be prepared by the methods disclosed in US 2703316, US 2758987 and EP 0244114.

For this invention, different polymer parameters have been known for a good processing :

- the crystallinity,
- the amount and type of catalyst,
- the degree of polymerization,
- the average molecular weight in weight and in number,
- the polydispersity value, which corresponds to the ratio between the average molecular weight in weight and number,
- the glass temperature, or Tg.

This ultimate parameter is important for the melting in a gelified vehicle. A control of the microball release profile is possible with polymer parameters listed above.

The relative proportions of the active ingredient and polymer can be varied over a wide range depending on the desired effect. The active ingredient can be present in an amount which will be released over controlled periods of time. This necessarily implies a quantity of active ingredient greater than the conventional single dose.

Proportions may range from 1 percent of active ingredient and 99 percent of the polymer to 99 percent of active ingredient and 1 percent of polymer. Ratios which have shown good results include 1 part of active ingredient to from 10 to 30 parts of polymer.

Pharmacokinetic results obtained by use of microballs, according to the invention, are unusually good, compared either to non spheroidal particles, or microcapsules prepared by usual methods. Microcapsules when parenterally administered to rats, present a release profile which is essentially biphasic with a "plateau" phase over a period of 20 days for triptoreline : the first phase presents an important active ingredient release, due to physiological fluid washing. The second phase is a sustained release of an effective amount of the active ingredient with a "plateau" phase. The duration of the "plateau" phase depends on the association active ingredient-polymer.

The microballs, according to the invention, present a limited burst effect compared to non spheroidal particles and allow in an aqueous physiological environment, an advantageous sustained release of active ingredient.

A Scanning Electron Microscopy study shows that microball surface is homogeneous without non-microencapsulated active ingredient cristals.

The composition of the invention may be formulated for injection by syringe into subcutaneous cellular tissue or muscular tissue, by suspending the microballs in a liquid vehicle. Suitable liquid vehicles include water, normal sodium chloride solution and oils such as sesame oil, peanut oil and vegetable oil. Adjuvants may be added as necessary or desirable. These may include dispersing agents such as polysorbate 80, thickening agents such as carboxymethyl cellulose, preservatives such as chlorbutanol or methyl paraben or propyl paraben, and suspending agents such as aluminium monostearate. Other adjuvants such as benzyl alcohol can also be included.

The following Examples illustrate the invention.

**EXAMPLE 1**

In this example and also in Examples 2 to 4 and 7 to 13, a poly (lactide-co-glycolide) was used with the following characteristics :

- polymer inherent viscosity range in chloroform (0.1% w/v) : 0.1 - 5.0 dl/g
- proportion of lactide (D,L or L) : 50 to 100 %
- proportion of glycolide : 0 to 50 %
- average molecular weight range

$\overline{Mw}$ : 1000 to 200 000

$\overline{Mn}$ : 100 to 100 000

- polydispersity value range

P : 2 to 10

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh 0.4 dl/g in chloroform (0.1 % w/v) ; Tg : 40°C by DSC (differential scanning calorimetry)]. 10 g was ground and mixed with 250 mg of D-Trp6 LHRH Acetate. The mixture was melted at 75°C. Tablets were ground. Resulting particles 0.5 to 200 microns in size were suspended in a carboxymethyl cellulose Na gel (10 % w/w in pure water).

Controlled heating (20°C, 80°C, 20°C) allows a progressive melting of the particles which become microcapsules of PLGA 50/50 containing an hormone analog.

**EXAMPLE 2**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 1 g of D-Trp6 LHRH Acetate.

**EXAMPLE 3**

Poly (D, L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.4 dl/g in chloroform ; Tg : 40°C by DSC] 10 g was similarly used with 250 mg of D-Trp6 LHRH Pamoate.

**EXAMPLE 4**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 1 g of D-Trp6 LHRH Pamoate.

**EXAMPLE 5**

Poly - L - Lactide [$\eta$ inh : 1.2 dl/g in chloroform ; Tg = 60°C by DSC] 10 g was similarly used with 1.8 g of Somatuline Acetate. Melting temperature is a little higher ; 85°C.

**EXAMPLE 6**

Poly - L - Lactide [$\eta$ inh : 1.2 dl/g in chloroform ; Tg : 60°C by DSC] 10 g was similarly used with 1.8 g of Somatuline Pamoate.

**EXAMPLE 7**

Poly (D,L lactide-co-glycolide) 75/25 [$\eta$ inh : 1.03 dl/g in chloroform ; Tg : 55°C by DSC] 10 g was similarly used with 1 g of D-Trp6 LHRH Acetate. Melting temperature is 82°C.

**EXAMPLE 8**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 1.4 g of corticotropine (ACTH 1 - 39).

**EXAMPLE 9**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 250 mg of D-Trp6 LHRH Acetate spray dried.

**EXAMPLE 10**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 1.8 g of Somatuline Acetate spray dried.

**EXAMPLE 11**

Poly (D,L lactide-co-glycolide 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 500 mg of [D-Trp6, des Gly10] - LHRH Ethylamide.

**EXAMPLE 12**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.8 dl/g in chloroform ; Tg : 44°C by DSC] 10 g was similarly used with 250 mg of Nafareline Acetate.

**EXAMPLE 13**

Poly (D,L lactide-co-glycolide) 50/50 [$\eta$ inh : 0.4 dl/g in chloroform (0.1 % w/v) ; Tg : 40°C by DSC] 10 g was ground and mixed with 250 mg of D-Trp6 LHRH Acetate. The mixture was melted at 75°C. Tablets were ground. Resulting particles 0.5 to 200 microns in size are suspended in silicone oil (viscosity : corresponding to 9 000 mPa.s at 60°C). Controlled heating (20°C, 80°C, 20°C) allows a progressive melting of the particles which become microballs of PLGA 50/50 containing an hormone analog.

**EXAMPLE 14**

Poly (ε - caprolactone-co-D, L lactide) 20/80 [$\eta$ inh : 0.5 dl/g in chloroform ; Tg : 18°C by DSC] 10 g was similarly used with 250 mg of D-Trp6 LHRH Acetate. Melting temperature is lower : 35°C.

CLAIMS

1. A process for the prepration of particles designed to release an effective amount of active ingredient over a predetermined period of time, said particles comprising one or more active ingredients in admixture with a bioresorbable and/or biodegradable polymer or copolymer being within a determined size range, the process comprising mixing the active ingredient(s) with the polymer or copolymer in the dry state; tabletting or extruding the resultant mixture; grinding the tablets or the extrudate; selecting ground particles within the determined size range; suspending them under stirring in a hydrophilic or hydrophobic gel or oil which has a viscosity at 60°C or over, the upper limit being defined by the stability of components, of from 40 to 500 mPa.s in the case of a hydrophilic gel or of from 3 000 to 12 500 mPa.s in the case of a hydrophobic gel; heating the gel to a temperature sufficient to melt the particles whereby microballs are formed; cooling the gel; and recovering the microballs by filtration.

2. A process according to claim 1 in which a hydrophilic gel having a viscosity of from 80 to 200 mPa.s at 60°C or over is used.

3. A process according to claim 2 in which the gel viscosity is about 100 mPa.s at 60°C or over.

4. A process according to any preceding claim in which the gel is a carboxymethylcellulose sodium in water gel.

5. A process according to claim 1 in which a hydrophobic gel having a viscosity of from 5 000 to 11 000 mPa.s at 60°C or over is used.

6. A process according to claim 5 in which the gel viscosity is about 9 000 mPa.s at 60°C or over.

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7. A process according to claim 5 or claim 6 in which the gel is a silicone oil.

8. A process according to any preceding claim in which D,L-lactic acid co-glycolic acic copolymer is used.

9. A process according to any preceding claim in which a pharmaceutically inert additive is dry mixed with the active ingredient(s) and the polymer or copolymer.

10. A process according to any preceding claim in which the particles prepared have a size range of from 0.5 to 200 microns.

11. A process according to any preceding claim in which the particles prepared have a size range of from 20 to 180 microns.

12. A process according to any preceding claim in which the particles prepared have 1 part by weight of active ingredient per 10 to 30 parts by weight of polymer or copolymer.

13. A process according to claim 1, the process being substantially as described herein with reference to any of the Examples.

14. Particles prepared according to any preceding claim, in a substantially spheroidal form and substantially deprived of active ingredient on the external covering.

15. Particles according to claim 14 being substantially free of water.

16. A sustained release pharmaceutical composition comprising particles prepared according to any of claims 1 to 13.

17. A composition according to claim 16 for parenteral administration in which the particles are suspended in a liquid vehicle.

18. A composition according to claim 17 in which the liquid vehicle is water, normal sodium chloride solution, sesame oil, peanut oil or vegetable oil.

19. A composition according to claim 17 or claim 18 further comprising one or more of a dispersing agent, a thickening agent, a preservative and a suspending agent.