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(54) **METHOD OF PRODUCING
MICRO-CAPSULES FOR THE SUSTAINED
RELEASE OF DRUGS**

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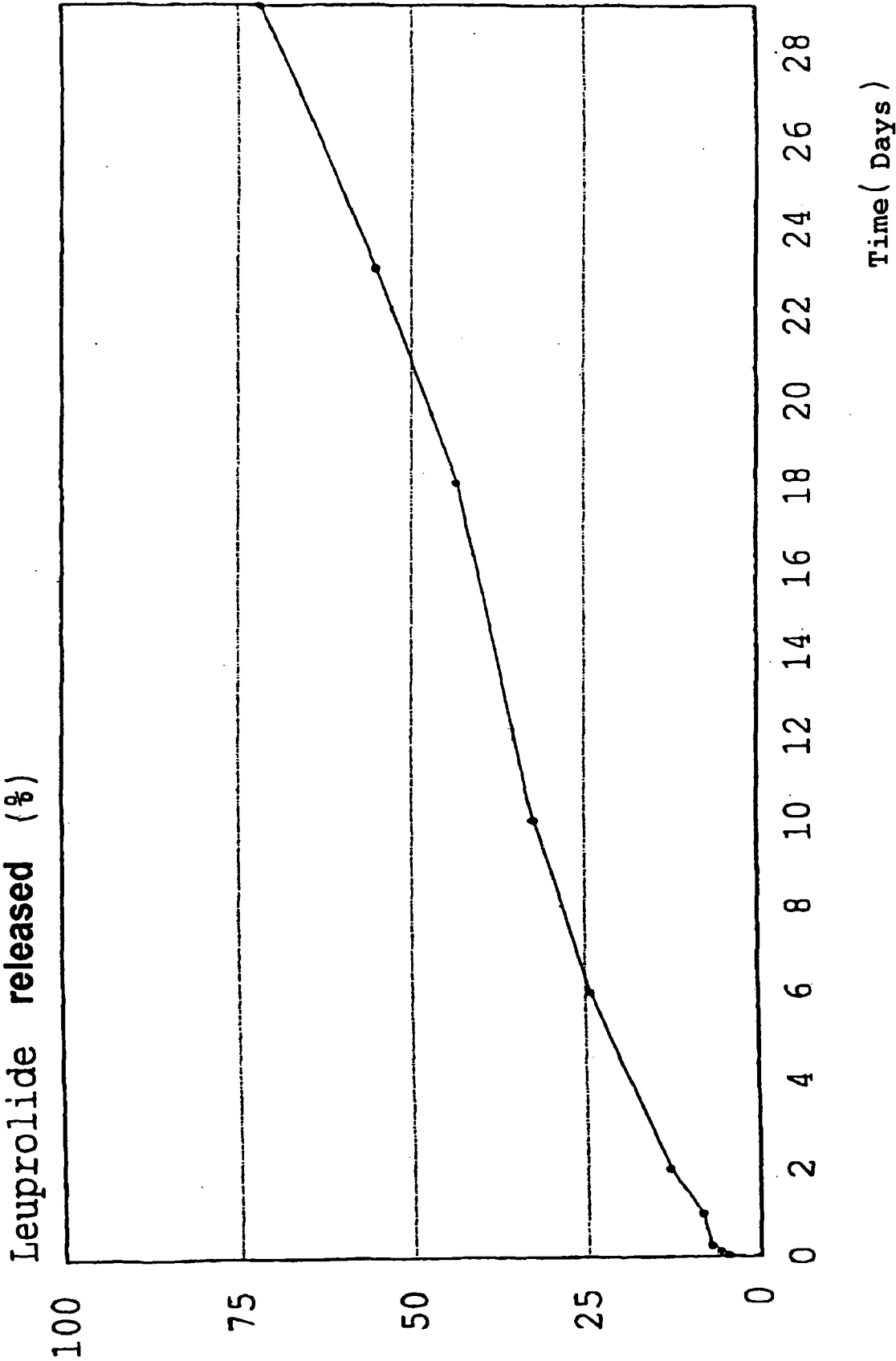
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(57) **ABSTRACT**

Micro-capsules for the slow release of drugs, consisting of a lactic-co-glycolic copolymer to which a plasticiser has been incorporated and which contain a drug of pharmaceutical interest within them.



METHOD OF PRODUCING MICRO-CAPSULES FOR THE SUSTAINED RELEASE OF DRUGS

[0001] The present invention relates to a new type of micro-capsule or micro-bead for the sustained administration of drugs and to a procedure for their preparation.

[0002] A large variety of administration systems have been proposed for drugs that require administration over a long time period. The strategy described in the literature as the most successful is that of micro-encapsulation of the drug to administer in a polymer material of the biodegradable and biocompatible polyester type, such as polylactic-co-glycolic (PLGA). There are a large number of bibliographic references to this strategy, such as: U.S. Pat. No. 5,445,832; ES 2009346; CH 661 206; CH 665 558; ES 2037621; U.S. Pat. No. 4,652,441; ES 2020890; U.S. Pat. No. 4,728,721; U.S. Pat. No. 5,330,767; U.S. Pat. No. 4,917,893; U.S. Pat. No. 4,652,441; EP 0 145 240; EP 0 2020 065; EP 0 190 833, among others for example.

[0003] These polymers have the peculiarity that they are degraded slowly within the body releasing the drug contained inside, and the products of this degradation (lactic acid and glycolic acid) are naturally present within the organism.

[0004] In the micro-capsules described in the literature of the state of the art it is very hard to achieve a satisfactory modulation of the encapsulated drug release, and to avoid an initial large drug release, as this can only be achieved by changing the composition of the polymer (the ratio of lactic-glycolic acid or the molecular weight thereof), which usually implies making important changes in the procedure for the production of the micro-capsules every time a modification in the drug release profile is desired.

[0005] In the article published by Pitt et al. in the Journal of Biomedical Materials Research, Vol. 13, pg 497-507, 1979, it is described that tributyl citrate accelerates the release of drugs, for example, progesterone, in microcapsules of polylactic polymers.

[0006] As a fruit of our research, we have surprisingly discovered that the addition of small amounts of citric acid esters, to the polymer constituting the micro-capsules, allows a very effective modulation of the liberation characteristics of the micro-capsules obtained, without the need to modify the composition of the polymer.

[0007] In the present specification the term modulating release from microcapsules is understood to mean a reduction in the initial release of encapsulated drug and a release of said drug that is almost linear in time. It is both surprising and unexpected, in view of that described by Pitt et al. that the incorporation of small amounts of citric acid ester into the microcapsule preparation of lactic-co-glycolic polymer that encapsulate a peptide of pharmaceutical interest allows the release of the drug to be almost linear and without the presence of sudden initial releases of the drug.

[0008] Therefore, the object of this invention consists of providing pharmaceutical of preparations micro-capsules of polymers of lactic and glycolic acid plastified with small quantities of citric acid esters and which contain peptides.

[0009] The present invention also comprises the preparation and use of the aforementioned microcapsules.

[0010] The citric acid esters useful for the purposes of the present invention are those normally used as plasticizers for pharmaceutical polymers, such as triethyl citrate, tributyl citrate and acetyl tributyl citrate. Use of triethyl citrate is preferable.

[0011] By peptides of pharmaceutical interest it is understood:

[0012] analogues of LHRH such as tryptoreline, leuprolide, gosereline, busereline or cetrorelix

[0013] analogues of somatostatin such as somatostatin or octreotide

[0014] analogues of human calcitonin such as salmon calcitonin or carbocalcitonin.

[0015] The preparation of the micro-capsules can be carried out following any of the methods described in the literature such as, for example, those described in the U.S. Pat. No. 3,773,919. By way of description and without limitation thereto, the different procedures for producing micro-capsules of the invention would be grouped into the following sections:

[0016] a) Method of Coacervation:

[0017] A solution of polymer is prepared along with tri-ethyl citrate in a suitable solvent. The drug to be encapsulated is suspended in the polymer and plasticiser solution and a non-solvent of the polymer is added to force deposition of the polymer on the drug crystals. Examples of these procedures without using plasticiser can also be found in documents such as ES 2009346 or EP 052 510.

[0018] b) Double Emulsion Methods:

[0019] The drug to be encapsulated is dissolved in water or in a solution of some other co-adjuvant in is emulsified in a solution of the polymer and the plasticiser in a suitable solvent such as dichloromethane for example. The resulting emulsion is in turn emulsified in water or in an aqueous solution of an emulsifier such as polyvinyl alcohol. Once this second emulsion has been carried out the solvent in which the polymer was dissolved is eliminated through evaporation or extraction. The resulting micro-capsules are obtained directly by filtration. Examples of these procedures that do not use the plasticiser can also be found in documents such as U.S. Pat. No. 4,652,441.

[0020] c) Simple Emulsion Method:

[0021] The drug to be encapsulated, the polymer and the plasticiser are dissolved together in a suitable solvent. This solution is emulsified in water or a solution of an emulsifier such as polyvinyl acid and the organic solvent eliminated by evaporation or extraction. The resulting micro-capsules are recovered by filtration. Examples of these procedures that do not use the plasticiser can also be found in documents such as U.S. Pat. No. 5,445,832.

[0022] d) Methods of Solvent Evaporation:

[0023] The drug to be encapsulated, the polymer and the plasticiser are dissolved together in a suitable solvent. This solution is evaporated to dryness and the resulting residue reduced down to a suitable size. Examples of this procedure, although not using the plasticiser, can be also be found in documents such as GB 2,209,937.

[0024] In the present invention, in all cases, the citric acid ester is deposited along with the polymer, plastifying it and advantageously modifying the hydrophobicity, flexibility and coating capacity characteristics of the polymer and the release profile of the micro-capsules obtained.

[0025] This is reducing the initial release of the encapsulated drug and making this release almost linear in time.

[0026] The present invention is now described by means of following, non-limiting examples:

EXAMPLE 1

[0027] Production of micro-capsules, containing leuprolide acetate, which presents a drug release profile suitable for one month.

[0028] 3 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw=50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 67 mg of leuprolide acetate are added and then suspended by sonication.

[0029] 63 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of n-heptane and stirred for 1 hour.

[0030] The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 2

[0031] Production of micro-capsules with one-month release containing octreotide acetate.

[0032] 2 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw=50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 67 mg of octreotide acetate are added and then suspended by sonication.

[0033] 70 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of n-heptane and stirred for 1 hour.

[0034] The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 3

[0035] Production of micro-capsules with a three-month release profile containing Triptoreline acetate.

[0036] 2 g of tri-ethyl citrate and 1.45 g of lactic-co-glycolic polymer (mw=50000 with monomer ratio of 1/1) are dissolved in 50 ml of dichloromethane. When the polymer is fully dissolved 45 mg of triptoreline acetate are added and then suspended by sonication.

[0037] 70 g of silicone of 350 cts is added slowly with intensive stirring. And when all the silicone has been added the content of the reactor is poured onto 2.5 l of heptane and stirred for 1 hour.

[0038] The micro-capsules are recovered by filtration and dried under vacuum for 48 hours.

EXAMPLE 4

[0039] In vitro determination of the drug release by the micro-capsules obtained. MATERIAL NEEDED:

[0040] 12 plastic 10-ml tubes with lid.

[0041] 1 rack for tubes.

[0042] Procedure:

[0043] Approximately 10 mg of micro-capsules containing leuprolide obtained according to example I are weighed into 12 10-ml tubes.

[0044] To each tube 2 ml of phosphate buffer 1/30 M and pH=7.0 are added.

[0045] Each tube is gently shaken to suspend the micro-capsules in the buffer, the tubes are sealed and placed in an oven at 37° C.

[0046] Taking samples for the control of the hydrolysis is carried out in accordance with the following table:

TABLE 1

Taking samples for analysis of leuprolide released.		
Time	Tube no.	Type of analysis
1 h	1, 2	Supernatant
3 h	3	Supernatant
6 h	4	Supernatant
1 d	5 and 6	Pellet
2 d	7	Pellet
4 d	8	Pellet
Point	Tube no.	Type of analysis
8 d	10	Pellet
11 d	1 and 11	Pellet
14 d	2	Pellet
18 d	3 and 12	Pellet
23 d	9	Pellet
29 d	4 and 5	Pellet

[0047] The analysis of leuprolide released is carried out by HPLC in the following conditions:

1-11. (canceled)

12. A method for producing microcapsules which comprises the steps of:

- dissolving a lactic co-glycolic copolymer and a citric acid ester derivative in a solvent in which said lactic co-glycolic copolymer and said citric acid ester derivative are soluble to form a solution;
- adding a peptide of pharmaceutical interest to the solution to form a peptide suspension in said solution;
- adding an alkyl derivative to the solution to produce deposition of the lactic co-glycolic copolymer and the citric acid ester derivative on the peptide;
- adding the suspension obtained in step (c) to a solution in which said lactic co-glycolic copolymer and citric acid ester are not soluble to harden and precipitate microcapsules thus formed; and
- isolating the microcapsules thus formed;

wherein said citric acid ester derivative is added in an amount sufficient to regulate the release rate of said

peptide of pharmaceutical interest from said microcapsules once said microcapsules are within the body of a subject.

13. The method for producing microcapsules according to claim 12, wherein the citric acid ester used in forming said microcapsules is selected from triethyl citrate, tributyl citrate and acetyl tributyl citrate.

14. The method for producing microcapsules according to claim 13, wherein the citric acid ester used in forming said microcapsules is triethyl citrate.

15. The method for producing microcapsules according to claim 14, wherein the amount of said triethyl citrate is between 0.1% and 60% by weight of the copolymer.

16. The method for producing microcapsules according to claim 12, wherein the ratio between lactate and glycolate units in the lactic co-glycolic copolymer is between 100:0 and 10:90, both inclusive.

17. The method for producing microcapsules according to claim 16, wherein said alkyl derivative is silicon oil.

18. The method for producing microcapsules according to claim 12, wherein the peptide of pharmaceutical interest encapsulated within said microcapsules is an analogue of LHRH.

19. The method for producing microcapsules according to claim 18, wherein the analogue of LHRH encapsulated

within said microcapsules is selected from tryptoreline, leuprolide, gosereline, busereline and cetorelix.

20. The method for producing microcapsules according to claim 12, wherein the peptide of pharmaceutical interest encapsulated within said microcapsules is somatostatine or an analogue thereof.

21. The method for producing microcapsules according to claim 20, wherein the analogue of somatostatine encapsulated within said microcapsules is octreotide.

22. The method for producing microcapsules according to claim 12, wherein the peptide of pharmaceutical interest encapsulated within said microcapsules is analogue of human calcitonine.

23. The method for producing microcapsules according to claim 22, wherein the analogue of human calcitonin encapsulated within said microcapsules is salmon calcitonine or carbocalcitonine.

24. A pharmaceutical composition comprising microcapsules prepared according to claim 12 and a pharmaceutically acceptable carrier.

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