PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DSTM 16307-5	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/CA2007/000358	International filing date *(day/month/year)* 02 March 2007 (02-03-2007)	Priority date *(day/month/year)* 02 March 2006 (02-03-2006)

International Patent Classification (IPC) or national classification and IPC
IPC: ***A61K 9/48*** (2006.01) , ***A61K 47/12*** (2006.01) , ***A61K 47/36*** (2006.01) , ***A61K 47/42*** (2006.01) , *A61K 9/107* (2006.01)

Applicant
LABORATOIRES MAUVES INC. ET AL

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 3 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. [X] *(sent to the applicant and to the International Bureau)* a total of 11 sheets, as follows:
      [X] sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      [ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. 1 and the Supplemental Box.
   b. [ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - [X] Box No. I Basis of the report
   - [ ] Box No. II Priority
   - [ ] Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - [ ] Box No. IV Lack of unity of invention
   - [X] Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - [ ] Box No. VI Certain documents cited
   - [ ] Box No. VII Certain defects in the international application
   - [ ] Box No. VIII Certain observations on the international application

Date of submission of the demand 27 November 2007 (27-11-2007)	Date of completion of this report 30 June 2008 (30-06-2008)
Name and mailing address of the IPEA/CA Canadian Intellectual Property Office Place du Portage I, C114 - 1st Floor, Box PCT 50 Victoria Street Gatineau, Quebec K1A 0C9	Authorized officer Nasreddine Slougui 819- 956-6132

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2007/000358

Box No. I Basis of the report

1. With regard to the **language,** this report is based on:

[X] the international application in the language in which it was filed

[ ] a translation of the international application into , which is the language of a translation furnished for the purposes of:

[ ] international search (Rules 12.3(a) and 23.1(b))

[ ] publication of the international application (Rule 12.4(a))

[ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

[ ] the international application as originally filed/furnished

[X] the description:

[X] pages 1, 3-9 and 11-21 as originally filed/furnished

[ ] pages* 2 and 10 received by this Authority on 27 November 2007 (27.11.2007)

[ ] pages* received by this Authority on

[X] the claims:

[ ] pages as originally filed/furnished

[ ] pages* as amended (together with any statement) under Article 19

[X] pages* 22-30 received by this Authority on 27 November 2007 (27.11.2007)

[ ] pages* received by this Authority on

[X] the drawings:

[X] pages 1/4-4/4 as originally filed/furnished

[ ] pages* received by this Authority on

[ ] pages* received by this Authority on

[ ] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. [ ] The amendments have resulted in the cancellation of:

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

4. [ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

[ ] the description, pages

[ ] the claims, Nos.

[ ] the drawings, sheets/figs

[ ] the sequence listing *(specify):*

[ ] any table(s) related to sequence listing *(specify):*

5. [ ] This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 66.1(d-*bis*))

**If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/CA2007/000358

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-63	YES
	Claims	None	NO
Inventive step (IS)	Claims	1-63	YES
	Claims	None	NO
Industrial applicability (IA)	Claims	1-63	YES
	Claims	None	NO

2. Citations and explanations (Rule 70.7)

Cited refercnes:

D1: Srinivas et al, , J. Biomater. Sci. Polymer Edn. Vol. 12, No. 2, pp. 137-48 (2001)
D2: US 4082857 (P.LEINER & SONS LIMITED), 04 April 1978
D3: EP0447100 (KELCO INTERNATIONAL LIMITED), 18 September 1991

In D1, gelatin was anionized to increase the carboxylic acid groups through succinylation which is performed by using different amounts of succinic anhydride. This modified gelatin is used in the preparation of microspheres to study the controlled release of a drug: lysozyme, comparatively to a microsphere prepared with a non-modified gelatin.

D2 disclose gels and gelling systems of a polysaccharide and a chemically modified gelatin which can be prepared by reaction of gelatin with the anhydride of dicarboxylic acids such as succinic anhydride. D2 is related to the field of food preparation.

D3 discloses a controlled release formulation based on a gel matrix for a controlled release of a pharmaceutical, a foodstuff, or as a component of a diagnostic assay apparatus. The gel matrix is prepared from a polysaccharide.

The instant application discloses a composition comprising a functionalised gelatin modified by adding carboxylates groups and/or acyl chains to be used as carriers for the controlled release of bioactive agents under various forms such as capsules, spheres, films and hydrogel. Furthermore, a negatively charged polysaccharide is used to formulate the composition as a matrix. A method of manufacturing said composition is also disclosed.

Novelty step:

None of the cited references discloses the composition with the specific ratios for the gelatin, functionalising agent and negatively charged polysaccharides; as well as the methods of preparation disclosed in claims 1-63 of the instant invention Therefore, novelty can be acknowledged for claims 1-63 according to Article 33(2) of PCT.

Inventive step:

D1 which appears to be the closest prior art does not disclose the presence of negatively charged polysaccharide in the gelatin composition nor it discloses a method of preparation of a gastric resistant gelatin composition using negatively charged saccharides. Whereas D2 is related to the field of food preparation and D3 does not disclose compositions containing gelatin. It would not be obvious for a person skilled in the art to reach the contemplated goal of the present alleged invention by combining the teachings of the different cited documents. Therefore, claims 1-63 of the present application appear to meet the criteria set by Article 33(3) of PCT for inventive step.

Industrial Applicability:

Claims 1-63 meet the criteria of industrial applicability according to Article 33)4) of PCT.

WHAT IS CLAIMED IS:

1. A gastric-resistant gelatin composition for use in the preparation of dosage forms, said gelatin composition comprising:

   30-60 % (w/w of the composition) of gelatin;

   0.1-10 % (w/w of the composition) of a functionalizing agent containing a carboxylate group or an acyl chain containing group, said functionalizing agent comprising i) a carboxylate group or an acyl chain containing group, and a reactive group capable of reacting the gelatin for attaching covalently said carboxylate group or said acyl chain containing group to the gelatin; and

   0.1-10 % (w/w of the composition) of a negatively charged polysaccharide.

2. The gelatin composition of claim 1, further comprising 0.5-15% (w/w of the composition) of a lipid.

3. The gelatin composition of claim 1, further comprising 0.5-10% (w/w of the composition) of an emulsifier.

4. The gelatin composition of any one of claims 1 to 3, wherein the polysaccharide is selected from the group consisting of alginate, hyaluronate, pectin, carrageenan, xanthan, and galactomanan or combination thereof.

5. The gelatin composition of any one of claims 1 to 3, wherein the polysaccharide is alginate.

6. The gelatin composition of any one of claims 1 to 3, wherein the lipid is selected from the group consisting of fatty acids, mineral oils, vegetal oils, and polycaprolactone.

7. The gelatin composition of claim 6, wherein said composition comprises a fatty acid chosen from stearic acid, oleic acid, palmitic acid, and mixtures thereof.

8. The gelatin composition of claim 6, wherein said composition comprises a vegetal oil chosen from canola oil, lin oil, soybean oil, and mixtures thereof.

9. The gelatin composition of any one of claims 1 to 3, wherein the emulsifying agent is selected from the group consisting of ionic and amphoteric compounds.

10. The gelatin composition of claim 9, wherein the emulsifying agent is selected from the group consisting of zwitterions, phosphatidylcholin, phosphatidylserine, phosphatidyl ethanolamine, and phsphatidylinositol, or a mixture thereof.

11. The gelatin composition of any one of claims 1 to 3, wherein the gelatin is porcine gelatin, bovine gelatin or fish gelatin, obtained from either skin, bones or cartilage.

12. The gelatin composition of any one of claims 1 to 3, wherein the functionalizing agent comprising a carboxylate group is selected from the group consisting of succinic anhydride, glutaric anhydride, maleic anhydride, isovaleric anhydride, diglycolic anhydride, and monochloracetic acid.

13. The gelatin composition of any one of claims 1 to 3, wherein the functionalizing agent comprising an acyl chain containing group is selected from the group consisting of acyl chloride, anhydride of fatty acids, dodecenylsuccinic anhydride, nonenylsuccinic anhydride, and 2-dodecen-1-yl-succinic anhydride.

14. The gelatin composition of claim 13, wherein the acyl chloride is selected from the group consisting of palmitoyl chloride, steroyl chloride, and myristoyl chloride.

15. The gelatin composition of claim 13, wherein the anhydride of fatty acids is selected from the group consisting of myristic anhydride, palmitic anhydride, erucic anhydride, and heptanoic anhydride.

16. The gelatin composition of any one of claims 1 to 3, wherein the functionalizing agent is succinic anhydride.

17. The gelatin composition of any one of claims 1 to 3, further comprising at least one other ingredients selected from the group consisting of a plastifier, an antibacterial agent, a flavoring agent, a coloring agent, a sweetener, and an antioxidant.

18. The gelatin composition of claim 17, wherein said plastifier is selected from the group consisting of glycerol, propylen glycol, and sorbitol.

19. The gelatin composition of claim 17, wherein said antibacterial agent is selected from the group consisting of propionic acid, sorbic acid, and benzoic acid.

20. The gelatin composition of claim 17, wherein said antioxidant is selected from the group consisting of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

21. Use of the gelatin composition as defined in any one of claims 1 to 20, for the manufacture of a dosage form selected from the group consisting of capsules, spheres, films, and hydrogels.

22. Use of the gelatin composition as defined in any one of claims 1 to 20, for encapsulating or entrapping a bioactive agent.

23. The use of claim 22, wherein the bioactive agent in selected from the group consisting of a bioactive peptide, a protein, bacteria, and a pharmaceutical drug.

24. A method for manufacturing a gelatin composition for use in the preparation of dosage forms, said method comprising the steps of:

i) dispersing 30-60 % (w/w of the composition) of gelatin in a solution of 0.1-10 % (w/w of the composition) of a negatively charged polysaccharide to create an emulsion; and

ii) stirring into said emulsion 0.1-10 % (w/w of the composition) of a functionalizing agent containing a carboxylate group or an acyl chain containing group and a reactive group capable of reacting the gelatin for attaching covalently said carboxylate group or said acyl chain containing group to the gelatin, for a time sufficient for said functionalizing agent to attach covalently said carboxylate group or said acyl chain containing group to the gelatin to obtain an emulsion of functionalized gelatin in the solution of the negatively charged polysaccharide.

25. The method of claim 24, further comprising in step i) the addition of 0.5-15% (w/w of the composition) of a lipid before dispersing said gelatin in the solution.

26. The method of claim 25, further comprising in step i) the addition of 0.5-10% (w/w of the composition) of an emulsifier before dispersing said gelatin in the solution.

27. The method of any one of claims 24 to 26, wherein the polysaccharide is selected from the group consisting of alginate, hyaluronate, pectin, carrageenan, xanthan, and galactomanan or a combination thereof.

28. The method of any one of claims 24 to 26, wherein the polysaccharide is alginate.

29. The method of any one of claims 24 to 26, wherein the lipid is selected from the group consisting of fatty acids, mineral oils, vegetal oils, and polycaprolactone.

30. The method of claim 29, wherein said composition comprises a fatty acid chosen from stearic acid, oleic acid, palmitic acid, and mixtures thereof.

31. The method of claim 29, wherein said composition comprises a vegetal oil chosen from canola oil, lin oil, soybean oil, and mixtures thereof.

32. The method of any one of claims 24 to 26, wherein the emulsifying agent is selected from the group consisting of ionic and amphoteric compounds.

33. The method of claim 32, wherein the emulsifying agent is selected from the group consisting of zwitterions, phosphatidylcholin, phosphatidylserine, phosphatidyl ethanolamine, and phsphatidylinositol, or a mixture thereof.

34. The method of any one of claims 24 to 26, wherein the gelatin is porcine gelatin, bovine gelatin or fish gelatin, obtained from either skin, bones or cartilage.

35. The method of any one of claims 24 to 26, wherein the functionalizing agent comprising a carboxylate group is selected from the group consisting of succinic anhydride, glutaric anhydride, maleic anhydride, isovaleric anhydride, diglycolic anhydride, and monochloracetic acid.

36. The method of any one of claims 24 to 26, wherein the functionalizing agent comprising an acyl chain containing group is selected from the

group consisting of acyl chloride, anhydride of fatty acids, dodecenylsuccinic anhydride, nonenylsuccinic anhydride, and 2-dodecen-1-yl-succinic anhydride.

37. The method of claim 36, wherein the acyl chloride is selected from the group consisting of palmitoyl chloride, steroyl chloride, and myristoyl chloride.

38. The method of claim 36, wherein the anhydride of fatty acids is selected from the group consisting of myristic anhydride, palmitic anhydride, erucic anhydride, and heptanoic anhydride.

39. The method of any one of claims 24 to 26, wherein the functionalizing agent is succinic anhydride.

40. The method of any one of claims 24 to 26, further comprising a step iii) of adding an additive selected from the group consisting of a plasticizer an antibacterial agent, a flavoring agent, a coloring agent, a sweetener, and an antioxidant.

41. The method of claim 40, wherein said plasticizer is selected from the group consisting of glycerol, propylen glycol, and sorbitol.

42. The method of claim 40, wherein said antibacterial agent is selected from the group consisting of propionic acid, sorbic acid, and benzoic acid.

43. The method of claim 40, wherein said antioxidant is selected from the group consisting of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

44. A method for manufacturing a gelatin composition for use in the preparation of dosage forms, said method comprising the steps of:

i) Contacting 0.1-10 % (w/w of the composition) of a functionalizing agent containing a carboxylate group or an acyl chain containing group and a reactive group capable of reacting the gelatin for attaching covalently said carboxylate group or said acyl chain containing group to the gelatin, with a solution of 30-60 % (w/w of the composition) of gelatin for a time sufficient for said functionalizing agent to attach covalently said carboxylate group or said acyl chain containing group to the gelatin to obtain a solution of functionalized gelatin; and

ii) Adding to the solution of functionalized gelatin a solution of 0.1-10 % (w/w of the composition) of a negatively charged polysaccharide for completing said composition.

45. The method of claim 44, further comprising at step ii) the addition of 0.5-15% (w/w of the composition) of a lipid to the negatively charged polysaccharide.

46. The method of claim 45, further comprising at step ii) the further addition of 0.5-10% (w/w of the composition) of an emulsifier to the negatively charged polysaccharide.

47. The method of any one of claims 44 to 46, wherein the polysaccharide is selected from the group consisting of alginate, hyaluronate, pectin, carrageenan, xanthan, and galactomanan or a combination thereof.

48. The method of any one of claims 44 to 46, wherein the polysaccharide is alginate.

49. The method of any one of claims 44 to 46, wherein the lipid is selected from the group consisting of fatty acids, preferably stearic acid, oleic acid and palmitic acid, mineral oils, vegetal oils, preferably canola oil, lin oil, soybean oil, and polycaprolactone.

50. The method of claim 49, wherein said composition comprises a fatty acid chosen from stearic acid, oleic acid, palmitic acid, and mixtures thereof.

51. The method of claim 49, wherein said composition comprises a vegetal oil chosen from canola oil, lin oil, soybean oil, and mixtures thereof.

52. The method of any one of claims 44 to 46, wherein the emulsifying agent is selected from the group consisting of ionic and amphoteric compounds.

53. The method of claim 52, wherein the emulsifying agent is selected from the group consisting of zwitterions, phosphatidylcholin, phosphatidylserine, phosphatidyl ethanolamine, and phsphatidylinositol, or a mixture thereof.

54. The method of any one of claims 44 to 46, wherein the gelatin is porcine gelatin, bovine gelatin or fish gelatin, obtained from either skin, bones or cartilage.

55. The method of any one of claims 44 to 46, wherein the functionalizing agent comprising a carboxylate group is selected from the group consisting of succinic anhydride, glutaric anhydride, maleic anhydride, isovaleric anhydride, diglycolic anhydride, and monochloracetic acid.

56. The method of any one of claims 44 to 46, wherein the functionalizing agent comprising an acyl chain containing group is selected from the group consisting of acyl chloride, anhydride of fatty acids, dodecenylsuccinic anhydride, nonenylsuccinic anhydride, and 2-dodecen-1-yl-succinic anhydride.

57. The method of claim 56, wherein the acyl chloride is selected from the group consisting of palmitoyl chloride, steroyl chloride, and myristoyl chloride.

58. The method of claim 56, wherein the anhydride of fatty acids is selected from the group consisting of myristic anhydride, palmitic anhydride, erucic anhydride, and heptanoic anhydride.

59. The method of any one of claims 44 to 46, wherein the functionalizing agent is succinic anhydride.

60. The method of any one of claims 44 to 46, further comprising a step iii) of adding an additive selected from the group consisting of a plastifier, an antibacterial agent, a flavoring agent, a coloring agent, a sweetener, and an antioxidant.

61. The method of claim 60, wherein said plastifier is selected from the group consisting of glycerol, propylen glycol, and sorbitol.

62. The method of claim 60, wherein said antibacterial agent is selected from the group consisting of propionic acid, sorbic acid, and benzoic acid.

63. The method of claim 60, wherein said antioxidant is selected from the group consisting of butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

[0006] It is for the above reason that the applications for gelatin capsules generally are used mostly, if not limited to poorly water soluble drugs. The challenge is to find innovative ways of developing bioavailable and stable dosage forms. Excipient suppliers, encouraged by the potential opportunities in this field, are developing new materials comprising mixtures of functional excipients. An example is the introduction of Self Emulsifying Drug Delivery System (SMEDDS) by Gattefossé. Undoubtedly this approach was stimulated by the work performed by Sandoz, on the microemulsion formulation of cyclosporin A (Kovarik et al., 1994. *J. Pharm. Sci.*, 83, 444-446).

[0007] Sensitivity to moisture is an aspect of a formulation which can be minimized by incorporating the drug into either a hydrophilic or lipophilic matrix. For example, the antibiotic vancomycin hydrochloride is highly hygroscopic and to achieve acceptable stability it needed to be formulated as a lyophilized powder for reconstitution. Bowtle et al. (1988, *Pharm. Technol.* 12, 86-97) successfully developed a hard gelatin capsule filled with a PEG 6000 matrix of the drug. This capsule formulation produced faecal, plasma and urine levels of the antibiotic that were similar to those obtained with the solution (Lucas et al., 1987. *J. Clinical Pharmacy and Therapeutics*, 12, 27-31) and is marketed by *Eli Lilly* as Vancocin® HCL.

[0008] By choosing an appropriate excipient the release rate of an active ingredient can be modified. For example Gelucire®, which is available as a semi-solid and can be mixed to obtain different drug release rates (Howard and Gould, 1987. *Drug Dev. Ind. Pharm.* 13, 1031-1045). Seta et al. (*Int. J. Pharm.* 41, 263-269) compared the bioavailability of an oily semi-solid matrix of Captopril in hard gelatin capsules with that of a tablet. This product is marketed by Sankyo in Japan as Captoril®, and provides the patient with a more convenient dosage regime.

[0009] The challenge is to find simple yet innovative ways of developing stable dosage forms during gastric transit and greater bioavailability at the absorption sites in intestine.

[0042] The lists of functionalizing agents noted herein is not meant be exhaustive, but simply indicative of the groups of agents that one skilled in the art may choose from. Furthermore, the gelatin functionalization could be carried out just prior to make the capsule or pre-functionalized for «ready-to-use». In the last case, the functionalizing agent (preferably succinic anhydride) is added during the process of extraction and transformation of gelatin. In general, the amount of functionalizing agent added in the mixing solution is varied from about 0.1-10%.

[0043] It is of interest to note that the reaction with succinic anhydride is rapid and can be made at a low cost without using a solvent. Moreover, the secondary product obtained in a gastric acid attack is succinic acid (resulting of succinic acid and water) which occurs naturally in the Krebs cycle. It is also used in pharmaceuticals and perfumes. The succinylated gelatin is known to be non-toxic and is considered GRAS (Generally Recognized As Safe) for use in gelatin. Tosaki et al. (Nippon Rinsho, 26, 5, 1227-1233, 1968) reported that succinylated gelatin can use as a plasma substitute. The latter was known under commercial name «Gelofusine™».

Other ingredients

[0044] The gelatin dosage forms of the present invention can include other additives. For example, plasticizer such as glycerol, propylen glycol, sorbitol, etc. is optionally added to improve the rheological (viscoelasticity) properties of capsules. An antibacterial agent such as propionic acid, sorbic acid, benzoic acid, etc. could also be used to prevent bacteria contaminations. The addition of flavoring agent, coloring agent or sweetener is also possible to mask the odor or taste of the bioactive agent or impart specific characteristics and in in certain cases, an antioxidant such as butylated hydroxyanisole (BHA) or butylated hydroxytoluene (BHT) can be added to protect bioactive agents sensitive to the oxidation. It is important to note that the total amount of these other ingredients are generally used in the formulation in relatively small quantities varying from about 0 to about 15%.