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APPLICATION NUMBER: ***60/778,104***
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET – Page 1 of 2

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. _____

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Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max):

FUNCTIONALIZED GELATIN AND METHOD FOR PRODUCING SAME

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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ENCLOSED APPLICATION PARTS *(check all that apply)*

☐ Application Data Sheet. See 37 CFR 1.76

☐ CD(s), Number of CDs _____

☑ Specification *Number of Pages* 14

☐ Other (specify) _____

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SIGNATURE _____ Date March 2, 2006

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TELEPHONE (514) 847-4293 Docket Number: 17111-3USPR CC/jl

FUNCTIONALIZED GELATIN AND METHOD FOR PRODUCING SAME

BACKGROUND OF THE INVENTION

Field of the invention

The invention relates to gelatin forms for encapsulation with greater bioavailability.

Description of the Prior Art

Gelatin has the potential advantages of great availability, low cost, no toxicity, and being easily modifiable. However, sensitivity to moisture of gelatin constitutes an important problem to dosage forms with hydrosoluble drugs. Generally, there are two forms of gelatin based capsules, soft and hard gelatin capsules.

Soft gelatin capsule is generally used for encapsulate the hydrophobe active molecules such as oils (i.e. primose oil) or liposoluble vitamins (i.e. vitamin E), while hard gelatin capsule has been used for drugs and herbal products, which are formulated either as powder or pellets.

The presence of other substances such as glycerol as plasticizer can also constitute a problem. The moisture uptake of soft gelatin capsules plasticized with glycerol is considerably higher than that for hard gelatin capsules. Another effect of the plasticizer has been reported by Armstrong et al. (1984. *J. Pharm. Pharmacol*, 36, 361-365) shown that migration of a drug into the shell of a soft gelatin capsule can occur which may result in drug degradation and difficulties in assay.

It's the reason that the applications for gelatin capsules generally are used for 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 SMEDDS (Self Emulsifying Drug Delivery System) 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).

Sensitivity to moisture is an aspect of 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.

By choosing an appropriate excipient the release rate of an active 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.

There is therefore a need for developing stable dosage forms during gastric transit and greater bioavailability at the absorption sites in intestine.

SUMMARY OF INVENTION

One object of the present invention is to provide a functionalized gelatin modified by adding carboxylate groups and/or by adding acyl chains for uses as carriers of bioactive agents under various forms (capsules, spheres, films, hydrogel, etc.). The addition of carboxylate groups consists in conferring to polymers a buffer capacity to neutralize the acid and the acyl chain constitute a barrier limiting the hydration of gastric fluid protecting thus the sensitive bioactive agents during gastric transit (pH 1.2-2.0).

BRIEF DESCRIPTION OF THE DRAWINGS

Having thus generally described the nature of the invention, reference will now be made to the accompanying drawings, showing by way of illustration, and a preferred embodiement thereof, and in which:

Fig. 1 illustrates the functionalization of gelatin: succinylation (a) and acylation (b); and

Fig. 2 illustrates the functionalization that could be carried out with alkenylsuccinic anhydride allowing the introduction of carboxylate groups including an acyl chain on the gelatin (R= alkenyl chain, C4-C18).

DETAILED OF INVENTION

In accordance with one embodiment of the present invention, there is provided an improved drug delivery device comprising soft and hard gelatin capsules and methods for producing the same. A gelatin device for administering pharmaceutical formulations comprises a gelatin capsule having a shell, which resists the gastric fluid. The prolonged dissolution of gelatin device is a that delay the release of bioactive agent in gastric fluid. These lipid compounds enable to improve the hydrophobicity of membrane which constitutes a barrier to limit the access of water and gastric fluid.

In one embodiment of the present invention, there is provided a method for the prevention of acid sensible drugs degradation by the addition of carboxylate groups on gelatin, which use as a trapper of proton. This process can neutralize the acid penetrated inside membrane protecting thus the bioactive agents.

In another embodiment of the invention, the addition of carboxylate groups on gelatine is achieved using functionalizing agents such as succinic anhydride, glutaric anhydride, maleic anhydride, isovaleric anhydride, diglycolic anhydride, monochloracetic acid, etc.

(Figure 1a). For acylation of gelatin, several functionalizing agents are used such as acyl chloride (palmitoyl chloride, steroyl chloride, myristoyl chloride, etc.), anhydride of fatty acids (myristic anhydride, palmitic anhydride, erucic anhydride, heptanoic anhydride, etc., Figure 1b).

According to one embodiment of the present invention, there is provided that the addition of carboxylate groups including alkenyl chains on the gelatin is achieved in one step using the functionalizing agents such as: dodecenylsuccinic anhydride, nonenylsuccinic anhydride, 2-dodecen-1-yl)succinic anhydride, etc. (Figure 2).

In another embodiment of the invention, the gelatin modification is carried out just prior to make the capsule or prefunctionalized for «ready-to-use». In the last case, the functionalizing agent (preferably succinic anhydride) is added during the process of transformation of gelatin.

It is of interest to note that the reaction with succinic anhydride is rapid, low cost and no solvent use. Moreover, the secondary product obtained is succinic acid (resulting of anhydric acid and water) which occurring naturally in amber and important in the Krebs cycle. It is also use in pharmaceuticals and perfumes. The succinylated gelatin was known non toxic and considered GRAS for use in gelatin. Tosaki et al. (1968. Nippon Rinsho, 26, 5, 1227-1233) reported that succinylated gelatin can use as a plasma substitute. The latter was known under commercial name «Gelofusine».

In another embodiment of the invention, various additives are added in the formulations to improve the buffer capacity or the resistance of the gastric fluid. To improve the buffer capacity, several natural polymers are used such as polysaccharides possessing carboxylate groups such as alginate, hyaluronate, carboxymethylcellulose, etc. For the resistance of gastric fluid, numerous products are added: vegetal oils (canola oil, lin oil, soybean oil, etc.), mineral oils, polycaprolactone, etc. The latter are used as plasticizer which also improves the mechanical properties of gelatin membrane.

In another embodiment of the invention, the functionalized gelatin are incorporated in the capsule formulations to be used as supports or capsule to immobilize the bioactive agents such as bioactive peptides (bacteriocin, insulin, vaccines) or proteins (enzymes), bacterial cells, various drugs, etc. Their roles are to protect these bioactive agents during gastric transit and to deliver at action sites in intestine.

While the invention has been described in connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any variations, uses, or adaptations of the invention following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.

EXAMPLE I

Shell composition for use in constructing soft and hard gelatine capsules.

The present invention relates to an improved soft gelatin drug device. The invention also provides a shell composition for use in constructing soft or hard gelatin capsules includes gelatin in the range of approximately 40% to 50% by weight and a plasticizer ranging in amount from approximately 2% to 35% by weight according to hard or soft gelatin capsule process. Generally, a low quantity (approximatively 2 %) of hydrophilic plasticizer such as glycerol, sorbitol, polyethylene glycol, etc. was used for the hard gelatin capsule. A preferred plasticizer for use with the preferred capsule or shell formulation includes sorbitol, glycerol, polyethylene glycol or fatty acids, etc. Capsule formulations can also include other suitable additives such as alginate, hyaluronate, CMC, mineral oils, vegetal oils or flavoring agents which are utilized to impart specific characteristics.

EXAMPLE II

Functionalization of gelatine.

- *Succinylation of gelatin*

An amount of 40 g of gelatin was dissolved in 40 g of water at 60 °C under mildly stirring. 5 g of solid succinic anhydride were added over 30 minutes while the pH was maintained between 5.0-6.0 by addition of diluted sodium hydroxide. The mixture was stirred for 1 hour and suitable quantity of other ingredients is added.

- *Palmitoylation of gelatin*

An amount of 40 g of gelatin was dissolved in 40 g of water at 60 °C under mildly stirring. The pH was adjusted to 5.0-6.0 and 8-10 g of palmitoyl chloride were added over 30 minutes while the pH was maintained at 5.0-6.0 by addition of diluted quantity of other ingredients is added.

- *Palmitoylation and succinylation of gelatin*

The palmitoylation and succinylation of gelatin could be carried out at the same time and proceeded as described previously. Pratically, an amount of 40 g of gelatin was dissolved in 40 g of water at 60 °C under mildly stirring. The pH was adjusted to 5.0-6.0 and 5 g of succinic anhydric and 5 g of palmitoyl chloride were added over 30 minutes while the pH was maintained at 5.0-6.0 by addition of diluted quantity of other ingredients is added.

Preferably, the sorbitol and glycerol could be added in the same time as water (before palmitoylation or succinylation) in order to simplify the process and to facilitate the dissolution of gelatin.

- *Alkenylsuccinylation: nonenylsuccinylation of gelatin*

The nonenylsuccinyl gelatin is synthetized as described previously in section.

EXAMPLE III

FTIR analysis.

The succinylated gelatin was achieved by FTIR analysis and FTIR spectra were recorded on a Spectrum One (PerkinElmer) instrument equipped with an UATR (Universal Attenuated Total Reflectance) device for native and functionalized gelatin in film form (50-60 μm), in the spectral region (4000–650 cm^{-1}) with 64 scans recorded at a 4 cm^{-1} resolution. For succinyl gelatin, the absorption bands about 1600 and 1410 cm^{-1} can be assigned to carboxylate anions (asymmetric and symmetric stretching vibrations) and in the region 1750-1700 cm^{-1} assigned for carbonyl (C=O) stretching vibration. In concerning the acylation, an increase of absorption at spectral region 2920–2850 cm^{-1} can be also noted due to the presence of overlapping (C-H) stretching vibrations of palmitoyl chain (-CH_2-, -CH_3) and at spectral region 1750-1700 cm^{-1} assigned for carbonyl stretching vibration.

EXEMPLE IV

Gelatin capsule compositions.

Below are illustrating several gelatin capsule compositions according with the present invention. The compositions presented below illustrate particular embodiment of the invention and is not intended to limit the scope of the specification.

Composition 1	
Fill Ingredients	% by wt.
Gelatin	35-45
Sorbitol	5-15
Succinic anhydride	1-10
Purified water	10-30

Composition 2	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-10
Succinic anhydride	1-10
Glycerol	1-5
Purified water	10-30

Composition 3	
Fill Ingredients	% by wt.
Gelatin	35-45
Sorbitol	5-10
Succinic anhydride	1-10
Palmitoyl chloride	1-5
Purified water	10-30

Composition 4	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-10
Glutaric anhydride	1-10
Palmitoyl chloride	1-5
Glycerol	1-5
Purified Water	10-25

Composition 5	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-10
Succinic anhydride	1-10
Mineral Oil, light or heavy	1-5
Purified water	10-30

Composition 6	
Fill Ingredients	% by wt.
Gelatin	30-45
Sorbitol	5-10
Glutaric anhydride	1-10
Canola Oil	1-5
Purified water	10-30

Composition 7	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
Succinic anhydride	1-10
Alginic acid, sodium salt	1-5
Mineral Oil, light or heavy	1-5
Purified water	10-30

Composition 8	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
2-Dodecen-1-ylsuccinic anhydride	1-10
Xanthan Gum	1-5
Glycerol	1-5
Soya Bean Oil	1-5
Purified water	1-25

Composition 9	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
Succinic anhydride	1-10
Alginic acid, sodium salt	1-5
Glycerol	1-5
Mineral Oil, light or heavy	1-5
Purified water	10-25

Composition 10	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
Succinic anhydride	1-10
Alginic acid, sodium salt	1-5
Glycerol	1-5
Lin Oil	1-5
Purified water	10-25

Composition 11	
Fill Ingredients	% by wt.
Gelatin	30-45
Sorbitol	5-10
Succinic anhydride	1-10
Hyaluronic acid, sodium salt	1-5
Purified water	10-30

Composition 12	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
Maleic anhydride	1-10
Arabic Gum	1-5
Glycerol	1-5
Purified water	10-30

Composition 13	
Fill Ingredients	% by wt.
Gelatin	30-40
Sorbitol	5-10
Succinic anhydride	1-10
Karaya Gum	1-5
Glycerol	1-5
Mineral Oil, light or heavy	1-5
Purified water	10-25

Composition 14	
Fill Ingredients	% by wt.
Gelatin	20-40
Sorbitol	5-10
Succinic anhydride	1-10
Sodium carboxymethylcellulose	1-5
Glycerol	1-5
Peanut Oil	1-5
Purified water	10-25

Composition 15	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-15
Myristoyl Chloride	1-10
Purified water	10-30

Composition 16	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-15
Hexanoyl Chloride	1-10
Glycerol	1-5
Purified water	10-25

Composition 17	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-15
4-Pentenoyl Chloride	1-5
Alginic acid, sodium salt	1-5
Purified water	10-30

Composition 18	
Fill Ingredients	% by wt.
Gelatin	20-45
Sorbitol	5-10
Heptanoyl Chloride	1-10
Alginic acid, sodium salt	1-5
Glycerol	1-5
Purified water	10-25

ABSTRACT

The invention pertains to functionalize the gelatin for encapsulation of the bioactive agent. The functionalization consists to add functional groups (i.e. carboxyl and/or acyl) in order to improve the resistance of the capsular membrane protecting thus the bioactive agents during gastric transit and deliver the bioactive agents at the action sites in intestine.

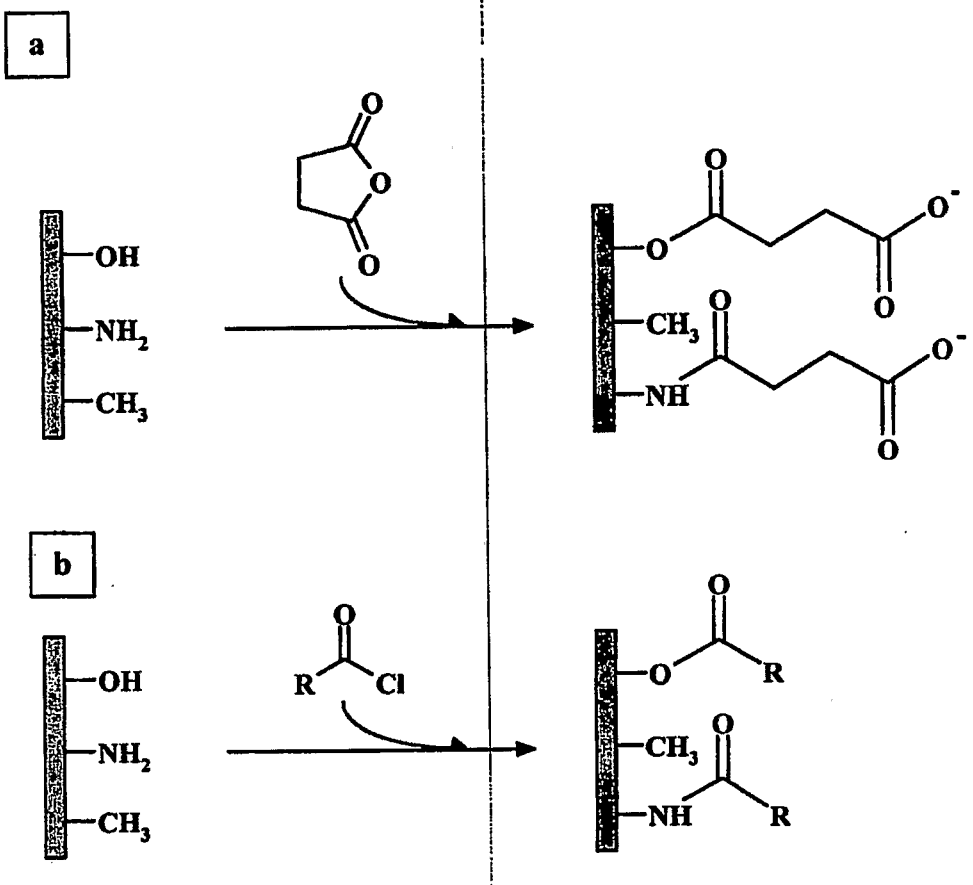

Figure 1

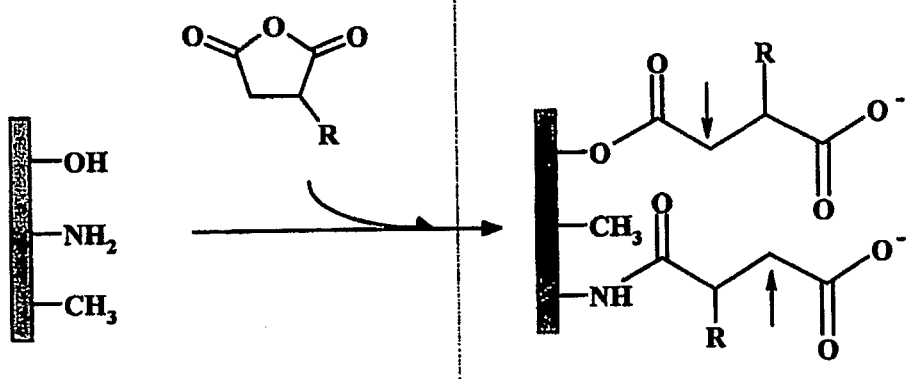

Figure 2