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(54) Title: IN SITU FORMATION OF POLYMERIC MATERIAL (57) Abstract The invention provides a pharmaceutically acceptable polymeric material formed in situ at a body surface and a process for the preparation of material. The polymeric material is formed by applying an anionic polymer and a cationic polymer to the surface in the presence of water.		

In Situ Formation of Pharmaceutically Acceptable Polymeric Material

5 This invention relates to polymeric material, for example, coatings, films and gels, especially pharmaceutically acceptable bioadhesive coatings, films and gels and more specifically to improved methods for producing such coatings, films and gels.

10 Many polymers are known to be bioadhesive (i.e. able to adhere to biological surfaces, e.g. mucus, the skin, mucosal surfaces, epithelium etc.) and the value of this property is well recognised. For example, bioadhesives may be used to adhere active agents to specific sites in the body for local drug administration, or to coat particular parts of the body. However, when bioadhesives are applied to such surfaces in aqueous solution they may be easily washed off or mechanically removed, because the strength of adhesion
15 of each individual bioadhesive molecule to the surface is not very high. This may lead to further problems if the bioadhesive materials contain active agents intended for use at one particular site, but which are washed away to other sites.

20 Thus to improve the retention of bioadhesives at a surface they may be formed into films. Such films may be formed either by chemical crosslinking or by physical interaction of the bioadhesive molecules as they come out of the solution. However, all of the known methods of film formation have drawbacks with regard to their use at biological surfaces. For example, if bioadhesive films are formed before being applied to a surface (e.g. by
25 weaving polymer strands or by slow evaporation of aqueous solutions of the polymers) they will be awkward to apply to relatively inaccessible parts of the body (e.g. the back of the throat or the underside of the tongue); furthermore, for a number of biopolymers, much of the bioadhesive character of the films may be lost if they become too dry.

30 Alternatively, current methods for forming bioadhesive films directly on a surface require the use of volatile solvents, which quickly evaporate to leave a film, but which are not suitable for use on sensitive areas of a body (e.g. open wounds, mucosal surfaces, etc.).

35 A need exists for coatings, gels and/or films, especially bioadhesive coatings, gels and films, capable of being formed directly on surfaces which avoids the use of volatile solvents.



A further need exists for a formulation which is capable of forming a bioadhesive coating, film or gel in situ and which may be provided to the consumer in stable form in a single dosage form containing both components.

According to the present invention, there is provided a non-aqueous liquid formulation for forming a pharmaceutically acceptable polymeric material in situ at a body surface of a mammal, the formulation including

- i) a water soluble salt of alginic acid or a water soluble or water dispersible salt of polyacrylic acid (component a);
- ii) a cationic polymer (component b); and
- iii) a pharmaceutically acceptable inert filler or carrier selected from glycols, medium chain triglycerides, glycerides, evening primrose oil, neem tree oil and vegetable oils wherein component a) is capable of reacting with component b) to form the polymeric material in situ following application to or ingestion by the mammal.

The concentration of component a) in the bioadhesive coating, gels or films of the invention will depend upon a number of factors (e.g. the strength of the film, gel or coating to be produced, the solubility of the polymers, the required viscosity of the solution etc.). Generally the concentration will preferably be selected from the range 0.1 to 75% weight to volume (w/v), more preferably 0.5 to 25% w/v based on the composition as a whole.

Component b) may be selected from any cationic polymers that are water-soluble or dispersible and that will form a coating, film or gel in the presence of component a). Preferred cationic polymers include water-soluble chitosan salts (e.g. chitosan chloride, chitosan acetate), polylysine, chondroitin salts, diethylaminoethyl dextran and keratin.

Mixtures of component b) may be used to form the bioadhesive films of the invention, as long as they do not interact to form a film themselves until they have been added to component a).

The total amount of component b) in the bioadhesive coatings, films or gels of the invention will depend upon a number of factors including the amount of component a) used, the strength of film required, the effectiveness of component b), etc. Generally, the concentration will be selected from 0.1 to 75% w/v, more preferably 0.5 to 25% w/v of the composition as a whole.

The preferred amount may be easily determined by simple experimentation, however the total weight ratio of component a) to component b) will generally be from 1:10 to 10:1, more preferably 1:2 to 2:1.



The pharmaceutically acceptable inert filler or carrier of the invention may include a glycol, for example propylene glycol, a medium chain triglyceride oil, for example, Miglyol (RTM) (Huls Chemicals) and/or a glyceride, for example Transcutol (RTM) (Gattefosse).

5 The balance of the coating, film or gel may be any other pharmaceutically effective carriers, fillers and/or excipients.

Where component a) is a water soluble alginate salt component b) is preferably selected from water-soluble chitosan salts; diethylaminoethyl dextran and chondroitin sulphate; most preferably a water-soluble chitosan salt.

Where component a) is a water-soluble or dispersible carbomer salt, component b) is preferably selected from water-soluble chitosan salts; diethylaminoethyl dextran and chondroitin sulphate; most preferably a water-soluble chitosan salt.

15 The formulation of the invention may optionally further comprise one or more pharmaceutically active agents, for either local or systematic delivery depending upon the site of application of the coating, film or gel.

In the case of delivery to the mouth, for example, active agents may be included to provide a local effect such as an analgesic or antiseptic action and/or to provide a systemic effect (for example, an anti-histamine or an anti-nausea agent).

Suitable active agents for use in such coatings, films or gels of the invention include analgesics, anti-inflammatory agents and antipyretics (e.g. acetaminophen, ibuprofen, naproxen, diclofenac, ketoprofen, choline salicylate, benzydamine, buprenorphine, hydrocortisone, betamethasone); decongestants (e.g. pseudoephedrine, phenylephrine, oxymetazoline, xylometazoline); mineral salts (e.g. zinc gluconate, zinc acetate); cough suppressants (e.g. dextromethorphan, codeine, pholcodine); expectorants (e.g. guaiphenesin, n-acetylcysteine, bromhexine); antiseptics (e.g. triclosan chloroxylenol, cetylpyridinium chloride, benzalkonium chloride, amylmetacresol, hexylresorcinol, dichlorobenzyl alcohol, benzyl alcohol, dequalinium chloride, silver sulphadiazine); cardiovascular agents (e.g. glyceryl trinitrate); local anaesthetics (e.g. lignocaine, benzocaine); cytoprotectants (e.g. carbenoxolone, sucralfate, bismuth subsalicylate); anti ulcer agents (e.g. calcium carbonate, sodium bicarbonate, magnesium trisilicate, magaldrate, cimetidine, ranitidine, nizatidine, famotidine,



omeprazole, pantoprazole); antihistamines (e.g. loratidine, terfenadine, diphenhydramine, chlorphenhydramine, triprolidine, acrivastine); antinausea agents (e.g. prochlorperazine, sumatriptan), bowel regulatory agents (e.g. diphenoxylate, loperamide, sennosides); antifungal agents (e.g. clotrimazole);
 5 antibiotics (e.g. fusafungine, tyrothricin) and antipsoriasis agents (e.g. dithranol, calcipotriol).

Mixtures of the active agents may be included in the coatings, films or gels of the invention where appropriate.

10 The concentrations of the active agents will depend upon their standard dosages and whether they are for local or systemic release etc. Generally the suitable concentrations will be readily apparent to one skilled in the art of formulation (normally a concentration range of 0.001 to 10% w/v).

15 The formulations may optionally contain other suitable excipients depending upon the proposed site of application. Examples of suitable excipients include colours, pH adjusters, flavours, sweeteners, preservatives, suspending agents or plasticisers. The concentration of such excipients will be readily apparent to one skilled in the art of formulation (although they will normally be used in a concentration range of 0.001 to 10% w/v).

20 In addition, the formulations of the present invention may optionally contain other suitable excipients depending upon the proposed site and/or mode of application. Examples of suitable excipients are as described above with the inclusion of granulating agents such as polyvinyl pyrrolidone, and/or magnesium stearate.

25 Preferably, the mammal is a human although it will be appreciated that the present invention can have application in animals.

The present invention thus provides formulations which can be used for preparing pharmaceutically acceptable bioadhesive coatings, gels and films in situ. Unexpectedly, some of the films formed by this process also
 30 have improved properties such as strength and adhesion as a result of their targeted delivery.

In one embodiment of the present invention, the formulation is presented as a non-aqueous liquid formulation in which both component a) and component b) are dispersed or suspended.

35 Such a formulation may be taken orally by drinking or pouring, or by spraying.



Another embodiment of the present invention relates to a formulation which employs a controlled-release capsule containing both component a) and component b) within a hard or soft capsule. The capsule is made from gelatin or a suitable equivalent and opens in the stomach to allow reaction of components a) and b) to form a bioadhesive film or gelatinous mass.

The novel formulations of the present invention are all one-component non-aqueous systems containing both component a) and component b). In situ, water which is present at (or which may be provided at) the delivery site is absorbed by the formulation, thereby enabling component a) and component b) to react to form a bioadhesive film or gel.

It will be appreciated by those skilled in the art that component a) and b) will not crosslink to form a bioadhesive coating, film or gel unless in an aqueous environment. Significant advantages accrue from keeping components a) and b) in a non-aqueous (and therefore noncrosslinking) environment, particularly insofar as the two components may be stored together without reacting therefore allowing simultaneous (and therefore quicker) application to a location in a single dosage form.

Components a) and b) may be applied to the surface by any suitable means, depending upon the nature and accessibility of the surface and on the nature of formulation which is appropriate for delivery to the surface. For example, where the surface is a relatively large area that may be suitably positioned (e.g. an external surface such as the back of a hand, etc.) a liquid formulation may be poured on, or may be applied by use of a dropper (e.g. an eye dropper), or may be painted on by use of a brush, or may be dispersed from a syringe. Where the film is intended to be formed in the oesophagus, the film could be produced by drinking a liquid formulation or by the ingestion of a tablet or capsule formulation.

Any conventional spraying devices may be used for spraying the liquid formulation, for example aerosol sprays, pump sprays or trigger sprays.

Most preferably the spray device will be a pump spray or a trigger spray.

The bioadhesive coatings, films or gels according to the invention in this case may act as a barrier to prevent further damage/contamination to wounded areas of skin (e.g. wounds, or sites of eczema etc.), to soothe sore areas of the body (e.g. sore throats etc.); or as systemic drug delivery films (e.g. transdermal films on intact skin, sublingual delivery films on the



underside of the tongue etc.). Such coatings, films or gels are particularly useful for local delivery of active agents, as they prevent the active agents from being washed away from the site of application, i.e. they minimise the effect of the active agent on the surrounding tissue (e.g. a topical anaesthetic in the throat).

The bioadhesive coatings, films or gels of the invention may be formed upon any surface of the mammalian body as required. Suitable surfaces include any region of the skin (for example to cover a wound or act as a drug delivery patch), the back of the throat or the oesophagus (e.g. to provide mechanical protection/soothing, or to deliver active agents locally or systematically); the underside of the tongue (as a sublingual dosage form for systemic delivery) or in the nasal cavity, vagina or rectum (as local drug delivery forms).

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

The invention will now be illustrated by the following Examples.

Example 1

Chitosan chloride (Seacure CL211 (RTM), Pronova Biopolymer a.s.)	2g
Sodium alginate (LFR5/60 (RTM), Pronova Biopolymer (a.s.)	10g
Flavours, sweeteners colours and preservatives	q.s.
Propylene glycol to	100g

The sodium alginate and chitosan chloride powders are dispersed in propylene glycol. The remaining ingredients are then added and mixed until dispersed to form a sprayable liquid formulation. The formulation is filled into a suitable spray pack and between 0.2 and 1.0ml of the suspension is sprayed onto the back of the throat to provide a soothing protective film. This formulation is of particular benefit to sore throat sufferers.



Example 2

A formulation identical to that of Example 1 but including 0.66% lignocaine hydrochloride was prepared. 0.5ml of a solution of the formulation was sprayed onto the back of the throat to provide a soothing protective film. The film also delivered a dose of 3.3mg of lignocaine hydrochloride to provide a local anaesthetic effect.

Example 3

A formulation identical to the formulation of Example 2 but further including Benzocaine 0.2g, Amylometacresol 0.16g, and Dichlorobenzyl alcohol 0.24g was prepared in the manner described in Example 1. 0.5ml of a solution of the formulation was sprayed onto the back of the throat to provide a soothing protective film which also delivered a dose of local anaesthetic and an anti-bacterial agent. This formulation provided a treatment of sore throats.

Example 4

The formulation of Example 4 is identical to the formulation of Example 3, except that the propylene glycol base was replaced by a medium chain triglyceride oil (Miglyol, Huls Chemicals).

Example 5

The formulation of Example 5 is identical with the formulation of Example 3, except that the propylene glycol base is replaced by Transcutol (a glyceride-based liquid from Gattefosse).

Example 6

Carbomer (Carbopol 974P (RTM), B.F.

Goodrich) 0.25g

Chitosan chloride (Seacure CL211(RTM),

Pronova Biopolymer a.s) 2g

Flavours, sweeteners colours and preservatives

q.s.

Medium chain triglyceride oil (Miglyol 812).

100g



The chitosan chloride powders are dispersed in propylene glycol. The remaining ingredients are then added and mixed until dispersed. The resulting dispersion is filled into a suitable spray pack. Between 0.2 and 1.0ml of the suspension was sprayed onto the back of the throat to provide a soothing protective film. The film soothes sore throats. Further examples of non-aqueous liquid-bases which may be used alone or in combination are: Polyethylene glycol 200 to 400, evening primrose oil, neem tree oil, vegetable oils such as arachis oil and tea tree oil.

Example 7

Chitosan chloride (Seacure CL211(RTM), Pronova Biopolymer a.s)	8mg
Sodium alginate (LFR5/60 (RTM), Pronova Biopolymer a.s.)	17mg
Triclosan	25mg
Lecithin	5mg
Colloidal silicon dioxide	4.5mg
Medium chain triglyceride oil	500mg

The ingredients were mixed together and filled into a hard gelatin capsule shell using conventional liquid filling equipment for liquid filling hard gelatin capsules. The capsule was dispersed in 0.1M hydrochloric acid at 37°C in order to simulate gastric conditions. The capsule ruptures and the contents gel to form a matrix due to the interaction of the polymers. The bulk of the gelled matrix remains intact for over 12 hours, slowly releasing the triclosan by diffusion and erosion processes. On ingestion, the capsule provided slow release of the drug into the stomach to provide a continued concentration of triclosan in the stomach for several hours; this provided an effective treatment of H.Pylori infections.

Example 8

Chitosan chloride (Seacure CL211 (RTM), Pronova Biopolymer a.s.)	8mg
Sodium alginate (LFR5/60 (RTM) Pronova Biopolymer a.s.)	17mg



Pseudoephedrine Hydrochloride	120mg
Lecithin	5mg
Colloidal silicon dioxide	4.5mg
Medium chain triglyceride oil	500mg

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The ingredients were mixed together and filled into a hard gelatin capsule shell using conventional liquid filling equipment for liquid filling hard gelatin capsules. The resulting capsule provides a slow release of water soluble drug over the period of 12 hours, with the advantage of reducing the required dosing frequency as compared with standard dosage forms such as tablets.

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Example 9

Chitosan chloride (Seacure CL211 (RTM),

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Pronova Biopolymer a.s.) 10mg

Sodium alginate (LFR5/60 (RTM),

Pronova Biopolymer a.s.) 30mg

Triclosan 25mg

Gelucire 53/60 (RTM) (Gattefosse) 300mg

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The Gelucire 53/60 was melted and the remaining ingredients were added to the melt and dispersed. The resulting mixture was filled into hard gelatin capsules and allowed to set. On ingestion, the capsule slowly released the contents from the waxy matrix which had gelled at the surface due to the interaction of the polymers.

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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A non-aqueous, liquid, formulation for forming a pharmaceutically acceptable polymeric material in situ at a body surface of a mammal, the formulation including
 - 5 i) a water soluble salt of alginic acid or a water soluble or water dispersible salt of polyacrylic acid (component a);
 - ii) a cationic polymer (component b) and;
 - iii) a pharmaceutically acceptable inert filler or carrier selected from glycols, medium chain triglycerides, glycerides, evening primrose oil, neem tree oil and vegetable oils, wherein component a) is capable of reacting with component b) to form the pharmaceutically acceptable polymeric material in situ at a body surface following application to or ingestion by a mammal.
2. A formulation as claimed in claim 1 wherein the polymeric material is a bioadhesive coating, film or gel.
- 15 3. A formulation as claimed in any one of the preceding claims wherein the concentration of component a) in the polymeric material is 0.1 to 75% weight per volume (w/v).
4. The formulation according to claim 3 wherein the concentration of component a) is 0.5 to 25% w/v.
- 20 5. A formulation as claimed in any one of the preceding claims wherein component b) is selected from the group comprising: water-soluble chitosan salts, polylysine, chondroitin salts, diethylaminoethyl dextran and keratin.
6. A formulation as claimed in any one of the preceding claims wherein the concentration of component b) in the polymeric material is 0.1 to 75% weight per volume (w/v).
- 25 7. The formulation according to claim 6 wherein the concentration of component b) is 0.5 to 25% w/v.
8. A formulation as claimed in any one of the preceding claims wherein the polymeric material further comprises one or more active agents selected from the group consisting of acetaminophen, ibuprofen, naproxen, diclofenac, ketoprofen, choline salicylate, benzydamine, buprenorphine, hydrocortisone, betamethasone; decongestants including pseudoephedrine, phenylephrine, oxymetazoline and xylometazoline; mineral salts including zinc gluconate and zinc acetate; cough suppressants including dextromethorphan, codeine and phlocodine; expectorants including guaiphenesin, n-acetylcysteine and bromhexine; antiseptics including
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triclosan, chloroxylenol, cetylpyridinium chloride, benzalkonium chloride, amylmetacresol, hexylresorcinol, dichlorobenzyl alcohol, benzyl alcohol, dequalinium chloride and silver sulphadiazine; cardiovascular agents including glyceryl trinitrate; local anaesthetics including lignocaine and benzocaine; cytoprotectants including carbenoxolone, sucralfate and bismuth subsalicylate; antiulcer agents including calcium carbonate, sodium bicarbonate, magnesium trisilicate, magaldrate, cimetidine, ranitidine, nizatidine, famotidine, omeprazole and pantoprazole; antihistamines including loratidine, terfenadine, diphenhydramine, chlorphenhydramine, triprolidine and acrivastine; antinausea agents including prochlorperazine and sumatriptan; bowel regulatory agents including diphenoxylate, loperamide and sennosides; antifungal agents including clotrimazole; antibiotics including fusafungine; tyrothricin and antipsoriasis agents including dithranol and calcipotriol and mixtures thereof.

9. A formulation as claimed in any one of the preceding claims, wherein the body surface is the surface of a human body.

10. A non-aqueous, liquid, formulation for forming a pharmaceutically acceptable polymeric material in situ at a body surface substantially as hereinbefore described with reference to Examples 17 to 24 and 28 to 30.

Dated this tenth day of July 2001

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