Table 4: Mean values for parameters according to Example 1 in Table 1.

Properties	Value	±SD (n)
Weight (g/dosage film)	0.028	0.001 (4)
Thickness (mil)	2.1	0.12 (3)
PH	3.07	(1)
Density (g/cm2)	1.0485	0.009 (3)
% Water content	1.7	0.24 (2)
Dry tack (g)	0.674	0.110 (6)
Wet tack (g)	60.169	11.680 (6)
Tensile strength (psi)	5242	379 (5)
% Elongation	2.9	0.4 (5)
Modulus (psi)	266834	7910 (5)
Tear-propagation resistance (N)	0.02	0.00 (4)
Disintegration time (sec)	12	1 (3)
Dissolving time (sec)	41	5 (3)

Examples 4 - 8: Hydropropylmethylcellulose based quick dissolving intraoral film containing therapeutic agents

The films were prepared according to Examples 1 - 3. Therapeutic agents were added to the homogeneous mixture (coating solution) prior to forming the film.

Table 5:

Composition (coating solution)	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8
Nicotine		1.4			
Hydromorphone			2.92		
Oxybutynin				3.71	
Estradiol					1.49
Peppermint	1.0	1.0	1.0	1.0	1.0
Methocel E5(HPMC)	21.06	21.06	21.06	21.06	21.06
Propylene glycol	1.0	1.0	1.01	1.0	1.0
Aspartame	0.8	0.8	0.8	0.8	0.8
Citric acid	0.7	0.7	0.7	0.7	0.7
Cremphor EL40	1.0	1.0	1.0	1.0	1.0
Benzoic acid	0.013	0.013	0.013	0.013	0.013
FD&C blue #1	qs.				
FD&C yellow #5	qs.				
Water	74.43	73.03	71.51	70.72	72.94

Table 6: Properties of the film formed according to the formulation in Table 5

Properties	Ex. 4	Ex. 5	Ex. 6	Ex. 7	Ex. 8
Thickness (mil)	3.0	2.9	2.9	3.2	2.7
Density (g/cm^3)	1.18	1.19	1.13	1.20	1.16
Water content %	1.8	2.93	2.42	2.32	2.31
Dry tack (g)	0.67	0.608	0.619	1.215	0.671
Wet tack (g)	49.08	54.81	84.34	88.85	39.91
Tensile strength (psi)	4393	3373	4138	3549	3688
% Elongation (sec)	8.3	8.3	7.6	8.1	7.5
Modulus (psi)	45969	48168	42110	41745	53334
Tear resistance (N)	0.03	0.02	0.01	0.03	0.01
Disintegration (sec)	43.0	34.3	27.3	36.0	55.7
Dissolving time (sec)	73.7	64.3	58.0	65.7	111.3

Table 7: Compostion of the Sildenafil film (%wet base)

Composition	Percentage
Sildenafil citrate	28.93
Xylitol	3.21
Methocel E15	4.59
Propylene Glycol	3.67
Aspartame	0.46
Benzoic acid	0.0045
peppermint oil	0.46
Sodium EDTA	0.0045
Polyoxamer L-44	2.3
Water	55
polypro 5000	0.92

Table 8: Properties of the film formed according to the formulation in Table 7

Properties	**Ex. 9**
Thickness	3.2±0.1
Density (g/cm^3)	1.230
Dry tack (g)	1.21±0.19
Wet tack (g)	23.79±3.45
Tensile strength (psi)	421±49
% Elongation	4.0±0.7
Modulus (psi)	31822±6137
Tear resistence (N)	0.04±00
Disintegration (sec)	8.3±1.5
Dissolution (sec)	23.7±1.5

Example 9: A comparison of properties of dosage units using different

hydroxypropylmethylcellulose polymers

The properties of a dosage unit according to the invention may be modified by varying individual components. For example, the dissolution of the film may be prolonged by using hydroxypropylmethylcellulose (HPMC) with higher molecular weight as shown below in Table 9.

Table 9a: Properties of selected commercial hydroxypropylmethylcellulose polymers.

Property	**Methocel Type (Dow Pharmaceuticals)**						
	E3	**E5**	**K3**	**E15**	**A15**	**E50**	**F50**
% Methoxyl	29	29	22	29	30	29	28
% Hydroxypropyl	8.5	8.5	8.1	8.5	0	8.5	5.0
Viscosity 2% (cps)	2-4	4-6	2-4	12-18	12-18	40-60	40-60

* Each value is the mean S±D, n=6

Table 9b: Properties of films prepared according to Example 1, using different hydroxypropylmethylcellulose polymers

Property	E3	E5	K3	E15	A15	E50	F50
Dry tack (g)	0.61±0.08	0.67±0.110	0.82±0.12	0.66± 0.09	0.52±0.09	0.68±0.14	0.52±0.12
Wet tack (g)	93.4±8.95	60.169±11.6	60.2±8.77	65.4±17.8	18.4±3.0	79.1±17.1	64.1±11.2
Tensile strength (psi)	1921±442	5242±379	2043±268	4316±384	3351±165	3725±123	3905±590
% Elongation	4.2±1.2	2.9±0.4	3.8±0.8	16.9±4.3	11.1±2.4	11.4±2.4	15.0±3.4
Modulus (psi)	44368±864	266834±79	41737±816	46889±416	35914±964	41651±282	43644±942
Tear resistence (N)	0.040.01±	0.02±0	0.05±0.01	0.09±0.03	0.12±0.02	0.05±0.01	0.08±0.01
Disintegration (sec)	17.0±4.4	12±1	15.3±1.5	21.9±1.6	161.0±15.9	33.2±5.1	24.1±1.3
Dissolution (sec)	35.7±2.1	41±5	31.0±1.0	51.6±1.3	>600	71.6±3.3	62.1±2.8

Example 10: Enhancement of mucoadhesion

The enhancement of mucoadhesion was similarly applicable to films of varying thickness. The following formulations were prepared:

Table 10

Composition/Test results	Example 1	Example 10a	Example 10b
Composition of example 1	100%	99.9%	95%
Starch graft copolymer•	0	0.1%	5%
Mean Mucoadhesion Measurement (g)••	17.5	26.6	32.3
Standard deviation	7.8	4.7	4.0
Increase in mucoadhesion %	base value	52%	84.6%

• Starch graft copolymers were prepared by polymerization in water using 1:3 Amioca corn starch: acrylic acid (supplied by NSCC) and are described in further detail in US Patent 4,690,996 and Block and Graft Copolymerization, vol 1, R.J.Ceresa, ed. John Wiley and Sons 1973 both references herein incorporated by reference.

•• Mucoadhesion was tested using a tensile instrument (e.g. Texture Analyzer) which measures force of detachment of the invention product from a simulated mucosal tissue material. The mucosal-like material is prepared from a mixture of 3.25% gellan gum and 1.6% mucin in water. The product to be tested was brought into contact with the simulated mucosal surface for 5 seconds and detached. The force of detachment was measured as the value of mucoadhesion in grams force (g or gf). Test conditions used are as follows: speed of application=3mm/s, speed of detachment=2mm/s, force applied before detachment=150g, contact time=5s, contact surface =122.7mm^2

Example 11: Preparation of film using dry extrusion techniques

77.8g Polyethylene Oxide (Polyox®WSR N-10) was mixed using mechanical force and additional ingredients were added during the mixing as follows: 5.5g Estradiol, 3.7g Peppermint, 3.7g Propylene Glycol, 3.0g Aspartame, 2.6g Citric Acid, 3.7g Cremphor EL 40 and 0.05g Benzoic acid.. The temperature was maintained at about 70°C.

The blend was allowed to mix at 70°C until uniform. It was then forced through an extrusion die to form a film 5 mils in thickness. The film was then cut into dosage forms ready for packaging.

Example 12: Human clinical acute irritation study

An initial clinical irritation study of placebo samples formulated according to Example 1 was conducted. Six HPMC-based films were applied by each of 12 subjects within one hour. The site of application and the oral mucosae were evaluated for any acute irritation prior to each application, immediately after each application, one hour and 24 hours after last application. The following indications: erythema, edema, bullae, maceration and discharge were scored on a scale of 0-4. There was no measurable irritation for any of the sites examined and for any of the indications during each application, or one hour and 24 hours after the last application.

Each subject was asked to assess the mouth feel, product taste, sensation and dissolution time for each application. All twelve subjects did not experience any sensation for any application. All subjects described films gave them very smooth mouth feel and indicated the taste of freshness the film delivered into the oral cavity for each application. All subjects felt the dissolution time of the film was very short (<2 min).

The majority of the subjects stated a preference for the film compared with tablets or capsules. All of the subjects indicated that they preferred the film to solutions or syrups.

Example 13: Human pharmacokinetics study showing increased bioavailability of a active agent delivered by an dosage unit in the form of a film

A dissolving film suitable for administration via the oral mucosa and containing the active agent, sildenafil citrate, formulated according to Table 7. The properties of the

dosage unit are described in Table 8.

A two way crossover study was conducted comparing intraoral sildenafil, applied sublingually, with a commercial tablet (Viagra®) at the same dosage. The average plasma levels and the pharmacokinetics analysis are displayed in Figure 6 and Table 11. Figure 6 and Table 11 show that the bioavailability of the equivalent dosage from the dissolving film is about 25% higher than the bioavailability of the tablet.

Table 11: A comparison of pharmacokinetic parameters of Sildanedil film and Viagra film

Parameters	Sildanefil (S) film	Viagra (V) film	Ratio S/V	Statistical power
AUC*(0-t)	365.5	293.1	1.247	0.86
AUC (infinity)	378	310.4	1.218	0.88
Cmax	109.9	106.8	1.029	0.15
Tmax	1	1	1	0.08
Ke	0.354	0.285	1.245	0.32
T	1.99	2.56	0.775	0.23

* Area under the curve

What is claimed:

1. A dosage unit, comprising: a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent.

2. A dosage unit according to claim 1, wherein the film has a dry tack value of less than 3.5g.

3. A dosage unit according to claim 1, wherein the film has a dry tack value of less than 2.0g.

4. A dosage unit according to claim 1, wherein the film has a water content of 0.1%-10%.

5. A dosage unit according to claim 4, wherein the film has a water content of less than 5%.

6. A dosage unit according to claim 1, wherein the film has a wet tack value of greater than 35g.

7. A dosage unit according to claim 2, wherein the film has a wet tack value of greater than 35g.

8. A dosage unit according to claim 1, where the hydrocolloid has a gelation temperature that is greater than 70°C for a 2% polymer solution.

9. A dosage unit according to claim 1, wherein the hydrocolloid has a hydration rate in 24 hours of 5-20% at 75% humidity at room temperature.

10. A dosage unit according to claim 1, wherein the hydrocolloid is present at a concentration in the range of 5%-99%.

11. A dosage unit according to claim 1, wherein the hydrocolloid is a polymer selected from the group consisting of a natural, semi-natural and synthetic biopolymer.

12. A dosage unit according to claim 11, wherein the hydrocolloid is selected from the group consisting of a polysaccharide and a polypeptide.

13. A dosage unit according to claim 11, wherein the hydrocolloid is a hydroxypropylmethylcellulose polymer.

14. A dosage unit according to claim 11, wherein the hydroxypropylmethyl-cellulose polymer has a molecular weight of less than 200,000.

15. A dosage unit according to claim 1, wherein the film further includes one or more of an emulsifier, a plasticizer, a taste modifying agent, a water soluble inert filler, a preservative, a coloring agent and a stabilizer.

16. A dosage unit according to claim 15, wherein the emulsifier has a concentration in the range of 0.1 – 10 %w.

17. A dosage unit according to claim 15, wherein the taste modifying agent consists of one or more of a sweetening agent, a flavoring agent and a taste masking agent.

18. A dosage unit according to claim 15, wherein the film contains the water soluble inert filler has a concentration in the range of 0.5 to 50%.

19. A dosage unit according to claim 15, wherein the preservative has a concentration in the range of 0.01 to 10%.

20. A dosage unit according to claim 1 wherein the active agent is present at a concentration in the range of 0.01 to 75%.

21. A dosage unit according to claim 1, wherein the active agent is selected from the group consisting of a therapeutic agent, a dietary supplement and a hygiene aid.

22. A dosage unit according to claim 21, wherein the therapeutic agent is sildenafil citrate.

23. A dosage unit according to claim 21, wherein the therapeutic agent is selected from the group consisting of nicotine, hydromorphone, oxybutynine and estradiol.

24. A dosage unit according to claim 1, wherein the film has a dry film thickness in the range of 1-20 mil.

25. A dosage unit according to claim 24, wherein the film has a dry film thickness less than 10 mils.

26. A dosage unit according to claim 1, wherein the film has a tensile strength greater than 1500psi.

27. A dosage unit according to claim 1, wherein the film has a % elongation less than 20%.

28. A dosage unit according to claim 1, wherein the film disintegrates in a range from 1-300 seconds.

29. A dosage unit according to claim 1, wherein the film has a modulus in a range from 35,000-300,000 psi.

30. A dosage unit according to claim 1, wherein the film has a dissolving

time in a range from 10-600 seconds.

31. A dosage unit according to claim 1, wherein the film has a tensile strength greater than 1,500 psi, a % elongation less than 20%, a disintegration time in a range from 1-300 seconds and a dissolution time in a range from 10-600 seconds.

32. A dosage unit according to claim 1, wherein the film has an effective wettability profile in the absence of a mixture of two nonionic surfactants.

33. A dosage unit according to claim 1, wherein the active agent is encapsulated within a polymer, wherein the polymer is chemically or physically distinct from the hydrocolloid, the encapsulated agent being dispersed within the film.

34. A dosage unit according to claim 1, wherein the dosage unit comprises more than one active agent.

35. A dosage unit according to claim 1, wherein the dosage unit further comprises a mucosal adhesion enhancer, the mucosal adhesion enhancer being located in the film.

36. A dosage unit according to claim 35, wherein the mucosal adhesion enhancer
is a starch graft copolymer.

37. A dosage unit according to claim 35, wherein the mucosal adhesion enhancer
is present at 0%-50% by weight.

38. A method of making a dosage unit suitable for mucosal administration, comprising:

(a) dissolving a hydrocolloid in a solvent so as to form a substantially homogeneous preparation;

(b) adding to the hydrocolloid preparation, an active agent and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer and a buffering agent to form a coatable or extrudable mixture; and

c) forming a mucosal surface-coat forming film from the mixture for packaging as a dosage unit.

39. A method according to claim 38, wherein step (b) further comprises coating the mixture onto a backing film.

40. A method of making a dosage unit suitable for mucosal administration, comprising:

(a) combining, in any order, in a vessel having a heating source and a mechanical mixing device, a hydrocolloid, an active agent, and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer, and a buffering agent;

(b) mixing the combined ingredients during and after the addition of the ingredients to the vessel and applying an effective amount of heat for melting a substantial portion of the mixture; and

(c) forming the mixture into a film.

41. A method according to claim 40, wherein step (b) further comprises coating or extruding the mixture onto a backing film.

42. A method according to claim 40, wherein step (c) further comprises removing the flexible film from the backing film and die cutting the film to form the dissolving dosage unit.

43. A method for administering an active agent to a subject, comprising:

(a) obtaining a water-soluble hydrocolloid, mucosal surface coat-forming- film, such film including an effective dose of an active agent: and

(b) placing the film on a mucosal surface in the subject so as to release the active agent.

44. A method according to claim 43, wherein the film has a dry tack value of less than 3.5g.

45. A method according to claim 43, wherein the film has a water content of 0.1%-10%.

46. A method according to claim 43, wherein the hydrocolloid has a hydration rate in 24 hours of 5-20% at 75% humidity at room temperature.

47. A method according to claim 43, wherein the hydrocolloid is present at a concentration in the range of 5-99%.

48. A method according to claim 43, wherein the hydrocolloid is a hydroxypropylmethylcellulose polymer.

49. A method according to claim 48, wherein the hydroxypropylmethylcellulose polymer has a molecular weight of less than 200,000.

50. A method according to claim 43, wherein the hydrocolloid mixture further includes one or more of an emulsifier, a plasticizer, a taste modifying agent, a water soluble inert filler, a preservative, a coloring agent and a stabilizer.

51. A method according to claim 43, wherein the active agent is present at a concentration in the range of 0.01 to 75%.

52. A method according to claim 43, wherein the active agent is selected from the group consisting of a therapeutic agent, a dietary supplement and a hygiene aid.

53. A method according to claim 52, wherein the therapeutic agent is sildenafil citrate.

54. A method according to claim 52, wherein the therapeutic agent is selected from the group consisting of nicotine, hydromorphone, oxybutynine and estradiol.

55. A method according to claim 43, having a dry film thickness in the range of 1-20 mil.

56. A dosage unit, comprising: a water soluble hydrocolloid and an effective dose of sildenafil citrate in a mucosal-surface contacting film.

57. A dosage unit according to claim 56, wherein the sildenafil citrate forms a solid dispersion with xylitol.

58. A method of treating erectile dysfunction; comprising:

(a) obtaining a film including a solid dispersion of an effective dose of sildenafil and xylitol in a water soluble hydrocolloid; and

(b) applying the film to an oral mucosal surface.

59. A method according to claim 58, wherein the film substantially completely dissolves at the oral mucosal surface in 10-600 seconds.

60.A method according to claim 59, wherein the film substantially completely dissolves within 200 seconds.

61. A method of making a dosage unit for mucosal administration, suitable for treating erectile dysfunction , comprising:

(a) combining, in any order, in a vessel having a heating source and a mechanical mixing device, a hydrocolloid, a solid dispersion of sildenafil and xylitol, and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a coloring agent, a preservative, a permeation enhancer, a stabilizer, and a buffering agent;

(b) mixing the combined ingredients during and after the addition of the ingredients to the vessel and applying an effective amount of heat for melting a substantial portion of the mixture; and

(c) forming the mixture into a film.

62. A method according to claim 61, wherein the ratio of sildenafil to xylitol is 9/1.

63. A method according to claim 61, wherein the water solubility of sildenafil is at least 20 mg/ml.

64. A method according to claim 63, wherein the water solubility of sildenafil is about 50 mg/ml.

65. A dosage unit, comprising: an effective dose of sildenafil citrate; the sildenafil citrate being formed in a solid dispersion with a water soluble inert filler, the solid dispersion being mixed with film forming reagents including a hydropolymer so as to form a film, the film being capable of dissolving on a mucosal surface so as to release the sildenafil citrate.

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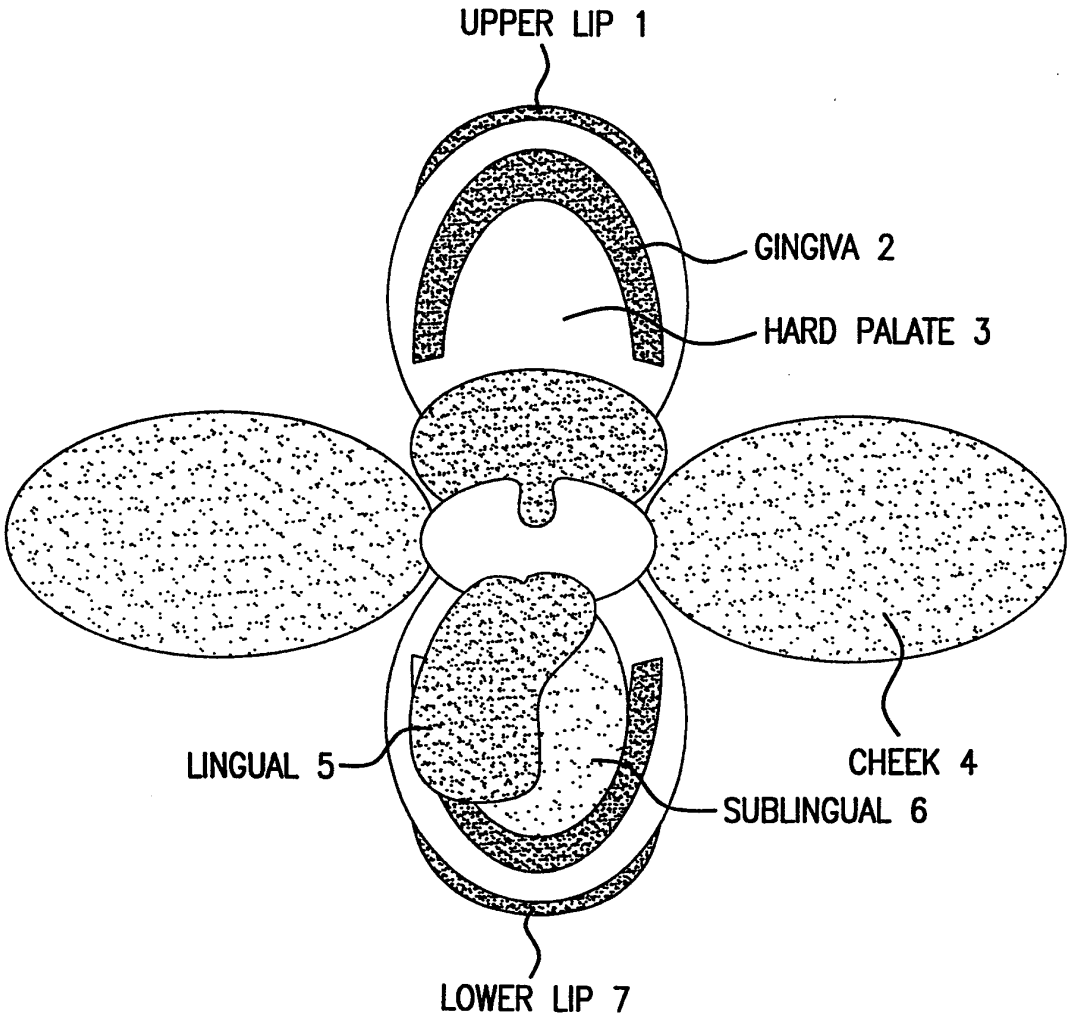


FIG.1

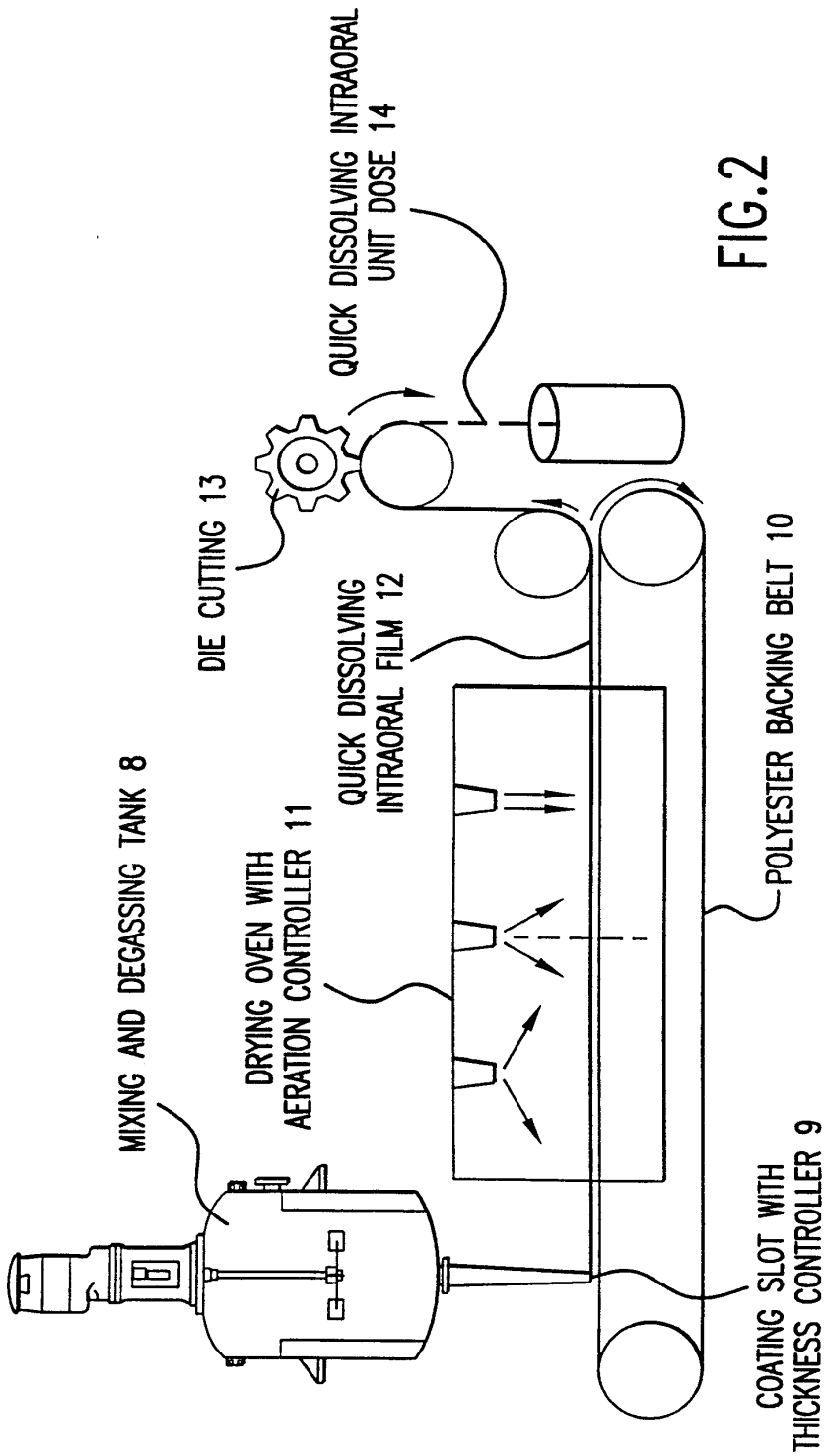


FIG.2

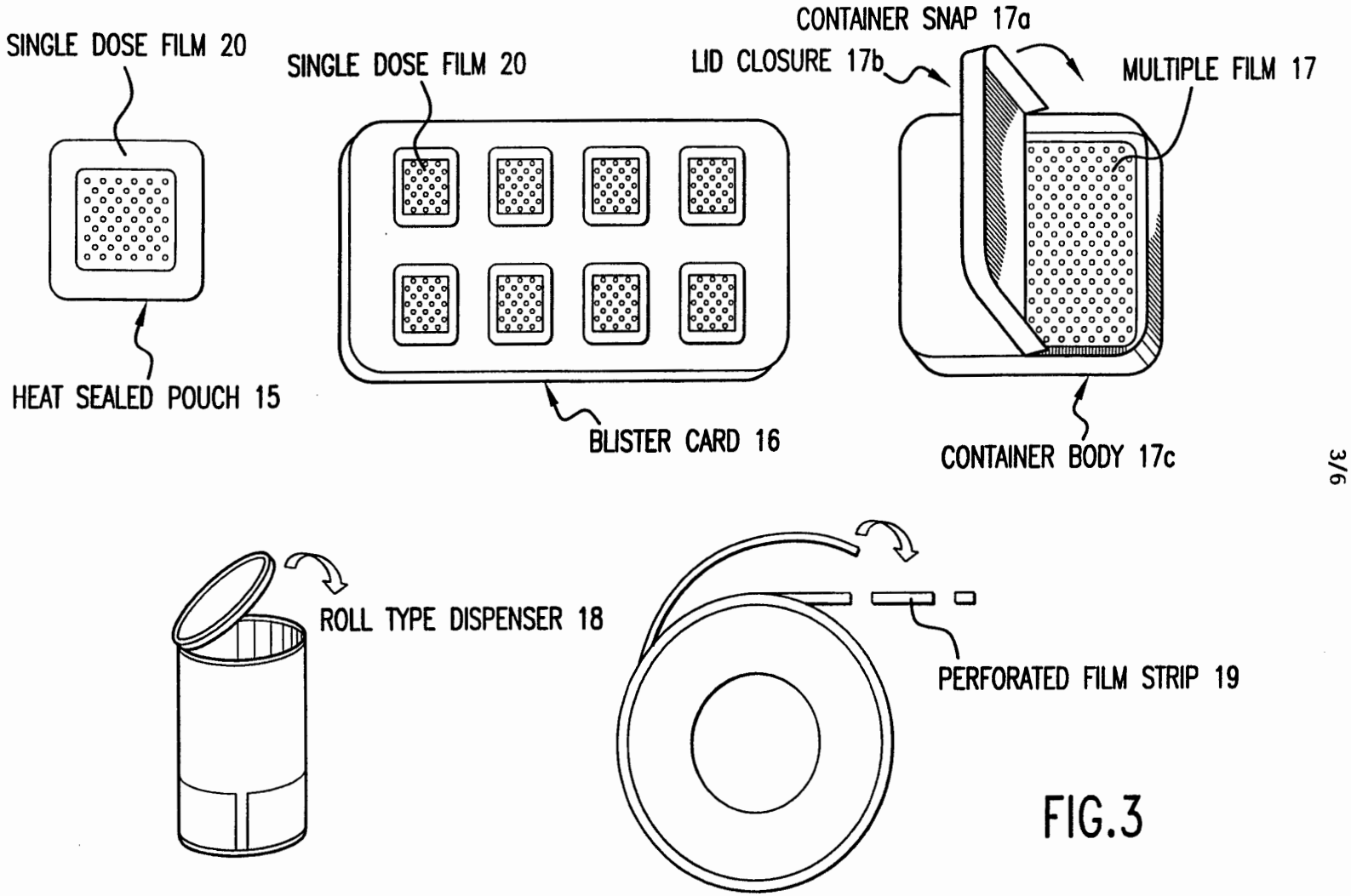


FIG.3

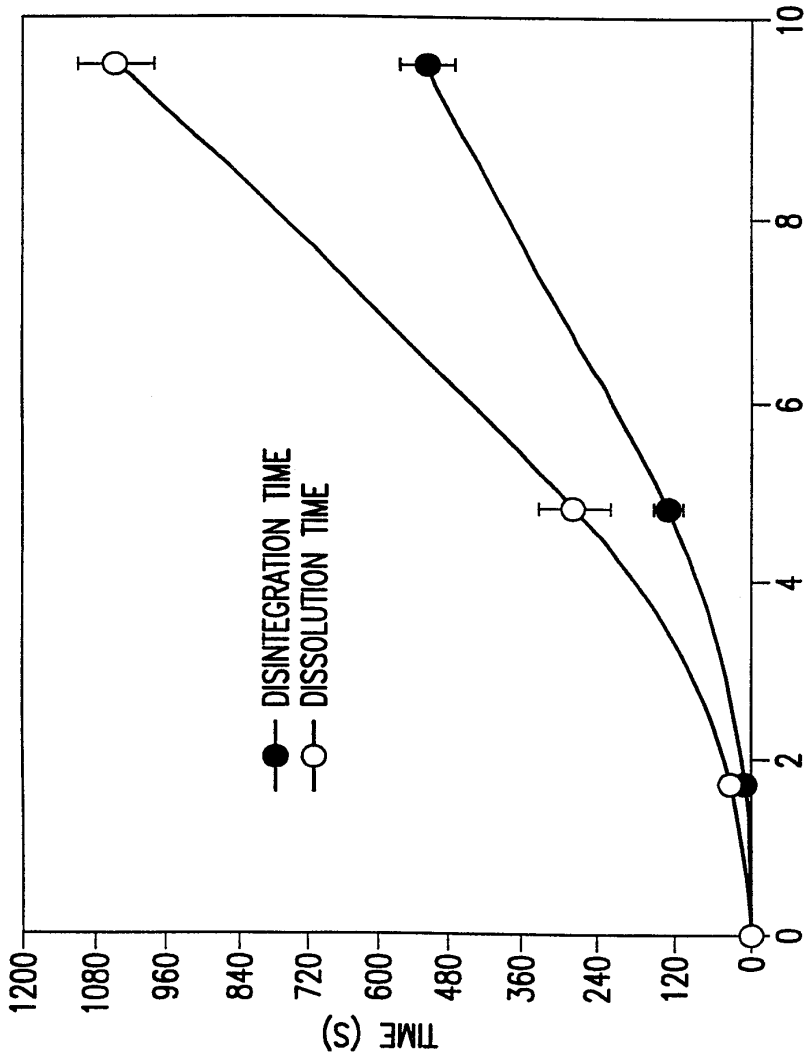
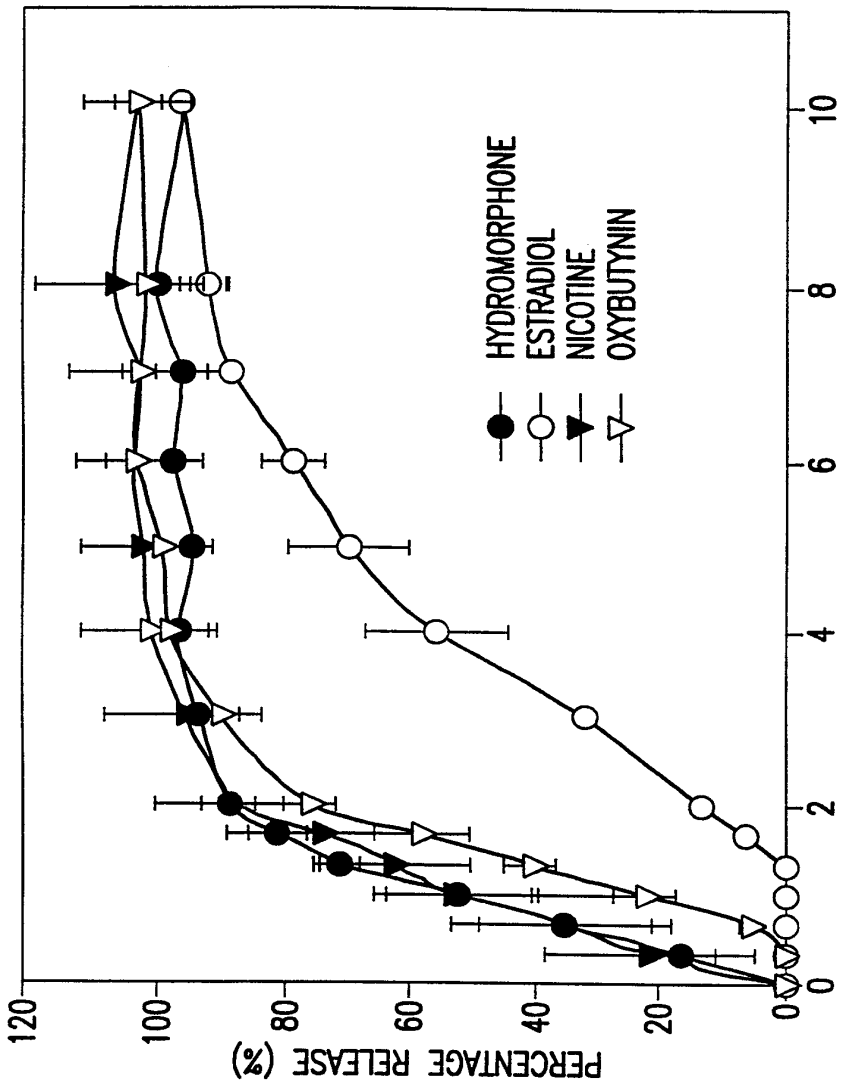


FIG.4


HYDROMORPHONE
ESTRADIOL
NICOTINE
OXYBUTYNIN
PERCENTAGE RELEASE (%)
TIME (MIN)
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20
40
60
80
100
120
0
2
4
6
8
10

FIG.5

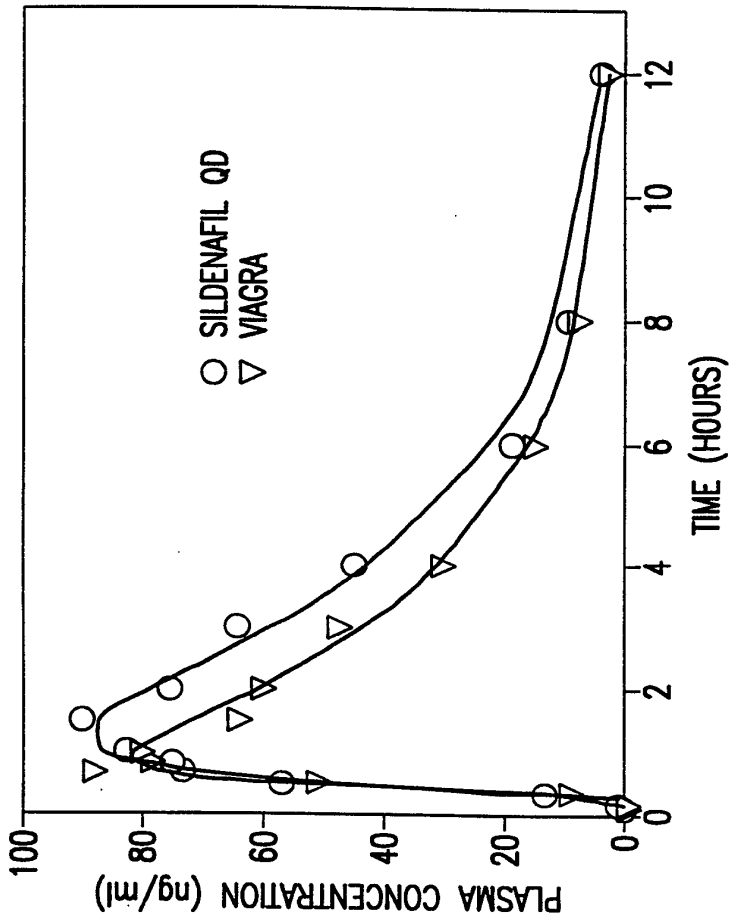
SILDENAFIL QD
VIAGRA
PLASMA CONCENTRATION (ng/ml)
TIME (HOURS)
0
20
40
60
80
100
2
4
6
8
10
12

FIG.6

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(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

(57) Abstract: Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film-forming polymer, such as pullulan, and a taste masked pharmaceutically active agent, such as dextromethorphan. The taste masking agent is preferably a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene, such as AMBERLITE. Methods for producing the films are also disclosed.

FAST DISSOLVING ORALLY CONSUMABLE FILMS CONTAINING AN ION EXCHANGE RESIN AS A TASTE MASKING AGENT

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films containing an agent to mask the taste of a pharmaceutically active agent therein, and more specifically to such films containing an ion exchange resin as the taste masking agent.

BACKGROUND OF THE INVENTION

It has been known to administer pharmaceutically active agents in an edible film vehicle.

For example, WO 99/17753 discloses rapidly dissolving films for delivery of drugs to be adsorbed in the digestive tract.

WO 98/26780 discloses a flat, foil, paper or wafer type presentation for the application and release of active substances in the buccal cavity. The specific active ingredient disclosed in WO 98/26780 is buprenorphine.

WO 98/20862 discloses a film for use in the oral cavity that can contain a cosmetic or pharmaceutical active substance.

WO 98/26763 discloses a flat, foil, paper or wafer like presentation for release of active substances into the buccal cavity. The particular active disclosed is apomorphine.

U.S. Patent Application No. 09/395,104 also discloses the delivery of pharmaceutical agents in a edible film vehicle.

U.S. Patent No. 5,411,945 to Ozaki et al. discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15).

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

It has also been known to combine ion exchange resins with pharmaceutically active agents to provide sustained release formulations.

For example, U.S. Patent No. 6,001,392 to Wen et al. discloses a controlled-release syrup suspension for oral administration containing dextromethorphan adsorbed to a polystyrene sulfonate ion exchange resin. Pharmaceutical films are not disclosed.

U.S. Patent No. 5,980,882 to Eichman discloses a method for improving the stability of a pharmaceutical composition that contains a drug-resin complex, comprising adding a chelating agent in an amount effective to reduce the rate of degradation of the drug in the drug-resin complex. Although Eichman teaches that complexing a drug with an ion exchange resin can mask the taste of the drug. Pharmaceutical films are not disclosed.

The inventors are not aware of any suggestion in the published art that ion exchange resins can act as taste masking agents in a fast dissolving orally consumable film. Accordingly, an object of this invention is to provide fast dissolving orally consumable films containing an ion exchange resin to mask the taste of a pharmaceutically active agent therein.

All references cited herein are incorporated herein by reference in their entireties.

SUMMARY OF THE INVENTION

The invention provides a consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein the film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

Also provided is a method for preparing the consumable film of the invention, comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide the film.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The invention provides a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver a pharmaceutically active agent. Preferred films according to the invention comprise a pharmaceutically active agent, an ion exchange resin, a film-forming agent, and at least one of the following additional ingredients: water, antimicrobial agents, plasticizing agents, flavoring agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, triglycerides, preservatives, polyethylene oxides, propylene glycol, and the like.

The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

The expression "pharmaceutically active agents" as used herein is intended to encompass agents other than foods, which promote a structural and/or functional change in and/or on bodies to which they have been administered. These agents are not particularly limited; however, they should be physiologically acceptable and compatible with the film. Suitable pharmaceutically active agents include, but are not limited to:

A. antimicrobial agents, such as triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA, and the like;

B. non-steroidal anti-inflammatory drugs, such as aspirin, acetaminophen, ibuprofen, ketoprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and the like;

C. anti-tussives, such as benzonatate, caramiphen edisylate, menthol, dextromethorphan hydrobromide, chlophedianol hydrochloride, and the like;

D. decongestants, such as pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine, pseudoephedrine sulfate, and the like;

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like;

F. expectorants, such as guaifenesin, ipecac, potassium iodide, terpin hydrate, and the like;

G. anti-diarrheals, such a loperamide, and the like;

H. H_2-antagonists, such as famotidine, ranitidine, and the like;

I. proton pump inhibitors, such as omeprazole, lansoprazole, and the like;

J. general nonselective CNS depressants, such as aliphatic alcohols, barbiturates and the like;

K. general nonselective CNS stimulants such as caffeine, nicotine, strychnine, picrotoxin, pentylenetetrazol and the like;

L. drugs that selectively modify CNS function, such as phenyhydantoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, diazepam, benzodiazepines, phenacemide, pheneturide, acetazolamide, sulthiame, bromide, and the like;

M. antiparkinsonism drugs such as levodopa, amantadine and the like;

N. narcotic-analgesics such as morphine, heroin, hydromorphone, metopon, oxymorphone, levorphanol, codeine, hydrocodone, xycodone, nalorphine, naloxone, naltrexone and the like;

O. analgesic-antipyretics such as salycilates, phenylbutazone, indomethacin, phenacetin and the like; and

P. psychopharmacological drugs such as chlorpromazine, methotrimeprazine, haloperidol, clozapine, reserpine, imipramine, tranylcypromine, phenelzine, lithium and the like.

The amount of pharmaceutically active agent that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the pharmaceutically active agent. Examples of doses for specific pharmaceutically active agents that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table A.

TABLE A

PHARMACEUTICALLY ACTIVE AGENT	PREFERRED DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrobromide	10-30 mg.
Ketoprofen	12.5-25 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	12.5-25 mg.
Pseudoephedrine Hydrochloride	30 mg.

Ion exchange resins preferred for use in the films of the invention are water-insoluble and consist of a pharmacologically inert organic or inorganic matrix containing covalently bound functional groups that are ionic or capable of being ionized under the appropriate conditions of pH. The organic matrix may be synthetic (e.g., polymers or copolymers of acrylic acid, methacrylic acid, sulfonated styrene, sulfonated divinylbenzene), or partially synthetic (e.g., modified cellulose and dextrans). The inorganic matrix can also be, e.g., silica gel modified by the addition of ionic groups. The covalently bound ionic groups may be strongly acidic (e.g., sulfonic acid), weakly acidic (e.g., carboxylic acid), strongly basic (e.g., quaternary ammonium), weakly basic (e.g., primary amine), or a combination of acidic and basic groups. In general, those types of ion exchangers suitable for use in ion exchange chromatography and for such applications as deionization of water are suitable for use in these

controlled release drug preparations. Such ion exchangers are described by H. F. Walton in "Principles of Ion Exchange" (pp. 312-343). The ion exchange resins useful in the present invention have exchange capacities below about 6 milliequivalents per gram (meq/g) and preferably below about 5.5 meq/g.

The resin is crosslinked with a crosslinking agent selected from difunctional compounds capable of crosslinking polystyrenes; these are commonly known in the art. Preferably, the crosslinking agent is a divinyl or polyvinyl compound. Most preferably the crosslinking agent is divinylbenzene. The resin is crosslinked to an extent of about 3 to about 20%, preferably about 4 to about 16%, more preferably about 6 to about 10%, and most preferably about 8% by weight based on the total resin. The resin is crosslinked with the crosslinking agent by means well known in the art.

The size of the ion exchange resins should preferably fall within the range of about 20 to about 200 micrometers. Particle sizes substantially below the lower limit are difficult to handle in all steps of the processing. Particle sizes substantially above the upper limit, e.g., commercially available ion exchange resins having a spherical shape and diameters up to about 1000 micrometers, are gritty in liquid dosage forms and have a greater tendency to fracture when subjected to drying-hydrating cycles.

Representative resins useful in this invention include AMBERLITE IRP-69 (obtained from Rohm and Haas) and Dow XYS-40010.00 (obtained from The Dow Chemical Company). Both are sulfonated polymers composed of polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H+-form). Their essential difference is in physical form. AMBERLITE IRP-69 comprises irregularly-shaped particles with a size range of 47 to 149 micrometers, produced by milling the parent, large-sized spheres of AMBERLITE IRP-120. The Dow XYS-40010.00 product comprises spherical particles with a size

range of 45 to 150 micrometers. Another useful exchange resin, Dow XYS-40013.00, is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group; its exchange capacity is normally within the range of approximately 3 to 4 meq/g of dry resin.

The most preferred resin is AMBERLITE IRP-69. However, in less preferred embodiments, the taste masking agent need not be an ion exchange resin. In these embodiments, the taste masking agent can be, e.g., magnesium trisilicate. See, e.g., U.S. Patents Nos. 4,650,663 and 4,581,232 to Peters et al. Taste can also be masked by polymers, such as EUDRAGIT E (Rohm and Haas), and/or cellulosics, such as ethylcellulose, and the like.

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt%, preferably about 30 to about 80 wt%, more preferably from about 45 to about 70 wt% of the film and even more preferably from about 60 to about 65 wt% of the film.

Unless specified otherwise, the term "wt%" as used herein with reference to the final product (i.e., the film, as opposed to the formulation used to create it), denotes the percentage of the total dry weight contributed by the subject ingredient. This theoretical value can differ from the experimental

value, because in practice, the film typically retains some of the water and/or ethanol used in preparation.

In embodiments containing relatively high oil content, it is preferable to avoid substantial amounts of humectant in the film (and more preferable to have no humectant in the film), so as to avoid producing an overly moist, self-adhering film. In particular, it is preferred to formulate high oil content films with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Saliva stimulating agents can also be added to the films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506. Saliva stimulating agents include food acids such as citric, lactic, malic, succinic, ascorbic, adipic, fumaric and tartaric acids. Preferred food acids are citric, malic and ascorbic acids. The amount of saliva stimulating agents in the film is from about 0.01 to about 12 wt%, preferably about 1 wt% to about 10 wt%, even more preferably about 2.5 wt% to about 6 wt%.

Preferred plasticizing agents include triacetin in amounts ranging from about 0 to about 20 wt%, preferably about 0 to about 2 wt%. Other suitable plasticizing agents include monoacetin and diacetin.

Preferred cooling agents include monomenthyl succinate, in amounts ranging from about 0.001 to about 2.0 wt%, preferably about 0.2 to about 0.4 wt%. A monomenthyl succinate containing cooling agent is available from Mane, Inc. Other suitable cooling agents include WS3, WS23, Ultracool II and the like.

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The surfactant can be added in amounts ranging from about 0.5 to about 15 wt%, preferably about 1 to about 5 wt% of the film. Other suitable surfactants

include pluronic acid, sodium lauryl sulfate, and the like.

Preferred stabilizing agents include xanthan gum, locust bean gum and carrageenan, in amounts ranging from about 0 to about 10 wt%, preferably about 0.1 to about 2 wt% of the film. Other suitable stabilizing agents include guar gum and the like.

Preferred emulsifying agents include triethanolamine stearate, quaternary ammonium compounds, acacia, gelatin, lecithin, bentonite, veegum, and the like, in amounts ranging from about 0 to about 5 wt%, preferably about 0.01 to about 0.7 wt% of the film.

Preferred thickening agents include methylcellulose, carboxyl methylcellulose, and the like, in amounts ranging from about 0 to about 20 wt%, preferably about 0.01 to about 5 wt%.

Preferred binding agents include starch, in amounts ranging from about 0 to about 10 wt%, preferably about 0.01 to about 2 wt% of the film.

Suitable sweeteners that can be included are those well known in the art, including both natural and artificial sweeteners. Suitable sweeteners include, e.g.:

A. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

B. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin,

and the like;

C. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame) and materials described in U.S. Pat. No. 3,492,131, L- alpha-aspartyl-N-(2,2,4,4--tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenyl-glycine, L-aspartyl-2,5-dihydro- L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

D. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivative of ordinary sugar (sucrose), known, for example, under the product description of sucralose; and

E. protein based sweeteners such as thaumatoccous danielli (Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition when using an easily extractable sweetener. The water-soluble sweeteners described in category A above, are usually used in amounts of about 0.01 to about 10 wt%, and preferably in amounts of about 2 to about 5 wt%. Some of the sweeteners in category A (e.g., glycyrrhizin) can be used in amounts set forth for categories B-E below due to the sweeteners' known sweetening ability. In contrast, the sweeteners described in categories B-E are generally used in amounts of about 0.01 to about 10 wt%, with about 2 to about 8 wt% being preferred and about 3 to about 6 wt% being most preferred. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);

2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useable with amounts of about 2 to about 25 wt% being preferred and amounts from about 8 to about 10 wt% are more preferred.

The compositions of this invention can also contain coloring agents or colorants. The coloring agents are used in amounts effective to produce the desired color. The coloring agents useful in the present invention, include pigments such as titanium dioxide, which may be incorporated in amounts of up to about 5 wt%, and preferably less than about 1 wt%. Colorants can also include natural food colors and dyes suitable for food, drug and cosmetic applications. These colorants are known as FD&C dyes and lakes. The materials acceptable for the foregoing spectrum of use are preferably water-soluble, and include FD&C Blue No. 2, which is the disodium salt of 5,5-indigotindisulfonic acid. Similarly, the dye known as Green No. 3 comprises a triphenylmethane dye and is the monosodium salt of 4-[4-N-ethyl-p-sulfobenzylamino) diphenyl-methylene]-[1-N-ethyl-N-p-sulfonium benzyl)-2,5-cyclo-hexadienimine]. A full recitation of all FD&C and D&C dyes and their corresponding chemical structures may be found in the Kirk-Othmer Encyclopedia of Chemical Technology, Volume 5, Pages 857-884, which text is accordingly incorporated herein by reference.

The films can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil,

canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt% to about 12 wt%, preferably in a range from about 0.5 wt% to about 9 wt%, of the film.

The films can include a preservative in amounts from about 0.001 wt% to about 5 wt%, preferably from about 0.01 wt% to about 1 wt% of the film. Preferred preservatives include sodium benzoate and potassium sorbate. Other suitable preservatives include, but are not limited to, salts of edetate (also known as salts of ethylenediaminetetraacetic acid, or EDTA, such as disodium EDTA) and parabens (e.g., methyl, ethyl, propyl or butyl-hydroxybenzoates, etc.) or sorbic acid. The preservatives listed above are exemplary, but each preservative must be evaluated on an empirical basis, in each formulation, to assure the compatibility and efficacy of the preservative. Methods for evaluating the efficacy of preservatives in pharmaceutical formulations are known to those skilled in the art.

The films can also include a polyethylene oxide compound. The molecular weight of the polyethylene oxide compound ranges from about 50,000 to about 6,000,000. A preferred polyethylene oxide compound is N-10 available from Union Carbide Corporation. The polyethylene oxide compound is added in amounts from about 0.1 wt% to about 5 wt%, preferably from about 0.2 wt% to about 4.0 wt% of the film.

The films can also include propylene glycol. The propylene glycol is added in amounts from about 1 wt% to about 20 wt%, preferably from about 5 wt% to about 15 wt% of the film.

Methods for preparing films according to the invention are capable of encapsulating the oil ingredients within the film-forming matrix and maintaining the integrity of the film, even when the film contains oils in amounts of 10 wt% or more.

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic ingredients and surfactants. In these methods, the final formulation is preferably produced by mixing the film-forming phase with the aqueous phase, then mixing in the organic phase, which includes surfactants, such as Polysorbate 80 and Atmos 300. This mass is mixed until emulsified. In other embodiments, the aqueous and film forming phases are combined into a single phase by dissolving the water soluble ingredients in the water and then adding the gums to hydrate. The organic phase is then added to this single aqueous phase.

The resulting formulation is cast on a suitable substrate and dried to form a film. The film is preferably air-dried or dried under warm air and cut to a desired dimension, packaged and stored. The film can contain from about 0.1% to about 10 wt% moisture, preferably from about 3 % to about 8 wt% moisture, even more preferably from about 4 to about 7 wt% moisture.

The film-forming phase can include pullulan and stabilizing agents such as xanthan gum, locust bean gum and carrageenan. These ingredients are mixed and then hydrated in water for about 30 to about 48 hours to form a gel. The water is preferably heated to a temperature of about 25 to about 45°C to promote hydration. The amount of water is about 40 to 80% of the gel. The resulting hydrated gel is then chilled to a temperature of about 20 to about 30°C for about 1 to about 48 hours. The water is preferably deionized.

In preferred embodiments, the aqueous phase includes water heated to a temperature of about 60 to 90°C, preferably 70 to 80°C, and ingredients such as the pharmaceutically active agent, ion exchange resin (or other masking agent), coloring agent, preservative and sweetener. The water is preferably deionized and the amount of water used is about 5 to about 80 wt% of the final gel

mixture.

The pharmaceutically active agent is sorbed to the ion exchange resin (or other masking agent) without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

Adsorption of the pharmaceutically active agent onto the ion exchange resin particles to form the pharmaceutically active agent/resin complex is a well known technique as shown in U.S. Pat. Nos. 2,990,332 and 4,221,778. In general, the pharmaceutically active agent is mixed with an aqueous suspension of the resin, and in less preferred embodiments, the complex is then washed and dried. Adsorption of pharmaceutically active agent onto the resin may be detected by measuring a change in the pH of the reaction medium, or by measuring a change in concentration of sodium or pharmaceutically active agent.

Binding of pharmaceutically active agent to resin can be accomplished according to four general reactions. In the case of a basic pharmaceutically active agent, these are: (a) resin (Na-form) plus pharmaceutically active agent (salt form); (b) resin (Na-form) plus pharmaceutically active agent (as free base); (c) resin (H-form) plus pharmaceutically active agent (salt form); and (d) resin (H-form) plus pharmaceutically active agent (as free base). All of these reactions except (d) have cationic byproducts, by competing with the cationic pharmaceutically active agent for binding sites on the resin, reduce the amount of pharmaceutically active agent bound at equilibrium. For basic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d).

Four analogous binding reactions can be carried out for binding an acidic pharmaceutically active agent to an anion exchange resin. These are: (a) resin (Cl--form) plus pharmaceutically active agent (salt form); (b) resin (Cl--form) plus pharmaceutically active agent (as free acid); (c) resin

(OH--form) plus pharmaceutically active agent (salt form); and (d) resin (OH--form) plus pharmaceutically active agent (as free acid). All of these reactions except (d) have ionic by-products and the anions generated when the reactions occur compete with the anionic pharmaceutically active agent for binding sites on the resin with the result that reduced levels of pharmaceutically active agent are bound at equilibrium. For acidic pharmaceutically active agents, stoichiometric binding of pharmaceutically active agent to resin is accomplished only through reaction (d). The binding may be performed, for example, as a batch or column process, as is known in the art.

In less preferred embodiments, the adsorption complex, including pharmaceutically active agent and resin, is collected and washed with ethanol and/or water to insure removal of any unadsorbed pharmaceutically active agent. The complexes are usually air-dried in trays at room or elevated temperature.

The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one.

The amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 25 to about 75% by weight of the pharmaceutically active agent/resin adsorption complex (hereinafter referred to as the "pharmaceutically active agent/resin complex" or "complex"). More preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 33 to about 77% by weight of the pharmaceutically active agent/resin complex. Most preferably, the amount of the pharmaceutically active agent adsorbed to the ion exchange resin is in the range from about 40 to about 60% by weight of the pharmaceutically active agent/resin complex.

The amount of pharmaceutically active agent/resin complex in the formulation is adjusted to deliver a predetermined dose of the pharmaceutically active agent over a predetermined period of time.

For example, a preferred antitussive film of the invention is administered at one dose every 12 hours to deliver a pharmaceutically effective amount of dextromethorphan over a period of approximately 12 hours to a patient in need of such administration. A typical adult dose of a film of the invention measuring 1" x 1.25" (2.54 cm x 3.18 cm) weighs about 60 to about 190 mg and contains about 20 to about 130 mg of pharmaceutically active agent/resin complex to deliver about 5 to about 65 mg of pharmaceutically active agent (e.g., dextromethorphan hydrobromide) when the average pharmaceutically active agent:ion exchange resin ratio is about 1:1.

In a particularly preferred embodiment of the invention, pullulan is present in the film in an amount of about 2 to about 6 mg/cm^2, dextromethorphan is present in the film in an amount of about 1.4 to about 3 mg/cm^2, and sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

The antitussive pharmaceutically active agents that are suitable for use in these preparations are acidic, amphoteric or most often basic antitussives. Examples of basic pharmaceutically active agents useful in the present invention include, but are not limited to dextromethorphan, diphenhydramine, caramiphen, carbapentane, ethylmorphine, noscapine and codeine. In addition, the antitussive embodiments of the invention can further comprise additional agents that are therapeutically effective to treat conditions other than coughing. That is, more than one type of pharmaceutically active agent can be included in a film of the invention. For example, in the case of a film containing an antitussive agent, the film can further comprise an antihistamine, sympathomimetic pharmaceutically active agent (nasal decongestant,

bronchodilator), analgesic, antiinflammatory, cough suppressant and/or expectorant. Compounds which are antihistamines, sympathomimetic pharmaceutically active agents (nasal decongestant, bronchodilator), analgesic, antiinflammatory, cough suppressants and/or expectorants are well known to those of skill in the art and need not be discussed in detail herein.

In embodiments, a certain percentage of the films disclosed herein will contain non-coated pharmaceutically active agent/resin complexes. The remaining pharmaceutically active agent/resin complexes are further characterized by the presence of a coating. In the preferred embodiment of the present invention, about 20 to about 80% of the pharmaceutically active agent/resin complexes in the sustained-release compositions are coated, most preferably about 40 to about 60% of the pharmaceutically active agent/resin complexes. The coating is a water-permeable, diffusion barrier coating material. The presence of a coating allows one to selectively modify the dissolution profile as desired of a pharmaceutical composition comprising the pharmaceutically active agent/resin complexes of the present invention.

The coating materials can in general be any of a large number of conventional natural or synthetic film-forming materials used singly, in admixture with each other, and in admixture with plasticizers, pigments, etc. with diffusion barrier properties and with no inherent pharmacological or toxic properties. In general, the major components of the coating should be insoluble in water, and permeable to water and pharmaceutically active agent. However, it might be desirable to incorporate a water-soluble substance, such as methyl cellulose, to alter the permeability of the coating, or to incorporate an acid-insoluble, base-soluble substance to act as an enteric coating. The coating materials may be applied as a suspension in an aqueous fluid or as a solution in organic solvents. Suitable examples of such coating materials are described by R. C. Rowe in Materials used in Pharmaceutical Formulation. (A. T. Florence,

editor), Blackwell Scientific Publications, Oxford, 1-36(1984), incorporated by reference herein. Preferably the water-permeable diffusion barrier is selected from the group consisting of ethyl cellulose, methyl cellulose and mixtures thereof Most preferably, the coating material is SURELEASE, manufactured by Colorcon which is water based ethyl cellulose latex, plasticized with dibutyl sebacate or with vegetable oils. Other non-limiting coating materials included within the scope of the present invention are AQUACOAT, manufactured by FMC Corporation of Philadelphia, which is ethylcellulose pseudolatex; solvent based ethylcellulose; shellac; zein; rosin esters; cellulose acetate; EUDRAGITS, manufactured by Rohm and Haas of Philadelphia, which are acrylic resins; silicone elastomers; poly(vinyl chloride) methyl cellulose; and hydroxypropylmethyl cellulose.

Conventional coating solvents and coating procedures (such as fluid bed coating and spray coating) can be employed to coat the particles. Techniques of fluid bed coating are taught, for example, in U.S. Patents Nos. 3,089,824, 3,117,027, and 3,253,944. The coating is normally applied to the pharmaceutically active agent/resin complex, but alternatively can be applied to the resin before complexing with the pharmaceutically active agent. Non-limiting examples of coating solvents include ethanol, a methylene chloride/acetone mixture, coating emulsions, methyl acetone, tetrahydrofuran, carbonetetrachloride, methyl ethyl ketone, ethylene dichloride, trichloroethylene, hexane, methyl alcohol, isopropyl alcohol, methyl isobutyl ketone, toluene, 2-nitropropane, xylene, isobutyl alcohol, n-butyl acetate.

It is preferred that the coated pharmaceutically active agent/resin complexes are coated in the range from about 40 to about 70% w/w pharmaceutically active agent/resin complex. More preferably, the pharmaceutically active agent/resin complex is coated in the range from about 45 to about 55% w/w pharmaceutically active agent/resin complex. Most

preferably, the pharmaceutically active agent/resin complex is coated about 50% w/w pharmaceutically active agent/resin complex. Variation in the amount of coating and/or the use of coated/uncoated complex mixtures can be employed to selectively modify the dissolution profile as desired.

The average particle sizes of the non-hydrated coated and uncoated pharmaceutically active agent/resin complexes is about 60 to about 200 and about 60 to about 250 micrometers, respectively. More preferably, average particle sizes of the coated pharmaceutically active agent/resin complexes is between about 70 and about 190 micrometers, and most preferably about 70 to about 180 micrometers. More preferably, average particle sizes of the uncoated pharmaceutically active agent/resin complexes is between about 55 and about 160 micrometers, and most preferably about 60 to about 150 micrometers. It is desirable that about 85%, preferably about 95%, and most preferably about 98% of the resin particles have sizes within the ranges set forth above. Adjustments within these ranges can be made to accommodate desired aesthetic qualities of the final formulation product. It is more preferable that the resin dextromethorphan complex have particle sizes within these ranges as well.

In embodiments, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. This method comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, menthol and any other oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a

film. This method hydrates the film-forming ingredients without heating the water, which can reduce energy costs in the manufacturing process and undesirable losses of volatile ingredients to evaporation. Further, mixing the oils in two steps minimizes the amount of flavor lost.

While not wishing to be bound by any theories, it is believed that the film-forming ingredients can be hydrated and mixed without heating due to an ionic effect known as the Donnan equilibrium. Hydrating the film-forming agents in the presence of electrolytes in solution effectively lowers the viscosity of the polymer gel being formed, thus increasing the efficiency of the hydrating process. The water-soluble ingredients of the formulation provide the electrolytes, which are dissolved in the hydration solution prior to addition of the film-forming ingredients. High-shear mixing also accelerates hydration, which delumps the powders, providing greater surface area for water contact. In addition, local heating effects, generated in the shear regions, provide energy for hydration without substantially raising the temperature of the mass.

Examples

The invention will be illustrated in more detail with reference to the following Examples, but it should be understood that the present invention is not deemed to be limited thereto.

Example 1

The ingredients listed in Table 1 were combined to provide a comparative example of an antitussive film in accordance with the following procedure:

A. The water was heated to 50°C. The potassium sorbate and sweeteners were dissolved in the water with mixing. The titanium dioxide was then added with further mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form

Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The glycerin and olive oil were combined in a separate container and then the menthol and monoammonium glycyrrhizinate (MAG) were dissolved therein by heating to 45°C to form Preparation D.

E. Preparation D was added to Preparation C with thorough mixing and then the flavor agents were added with continued mixing to provide Preparation E.

F. Dextromethorphan coated with ethyl cellulose was then added to Preparation E with mixing. The pH was adjusted as necessary to 6.0 using 10% citric acid solution to provide Preparation F (Examples 1-3 only).

Preparation F was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 1

Material	% w/w in batch	g/batch	%w/w*	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (55% DM)		103.6291		27.3000	29.5775	9.3899
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1998	0.0634
Carrageenan	0.3000	3.0000	1.2159	0.7903	0.8563	0.2718
Pullulan	16.0000	160.0000	64.8466	42.1503	45.6666	14.4976
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1713	0.0544
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Aspartame NF	1.4000	14.0000	5.6741	3.6882	3.9958	1.2685
Purified Water	75.3264	753.2640				68.2534
Physcool	0.1000	1.0000	0.4053	0.2634	0.2854	0.0906
Menthol	1.0000	10.0000	4.0529	2.6344	2.8542	0.9061
Citric Acid	0.0710	0.7100	0.2878	0.1870	0.2026	0.0643
Cherry Flavor (Givudan)	0.1500	1.5000	0.6079	0.3952	0.4281	0.1359
Peppermint Flavor	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0285	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Atmos 300	0.3500	3.5000	1.4185	0.9220	0.9990	0.3171
Glycerine	3.0000	30.0000	12.1587	7.9032	8.5625	2.7183
Olive Oil	0.5000	5.0000	2.0265	1.3172	1.4271	0.4531
FD&C green #3	0.0026	0.0260	0.0105	0.0068	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0132	0.6586	0.7135	0.2265
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1103.6291		92.3000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 2

Comparative films having the ingredients listed in Table 2 were prepared in accordance with the method of Example 1.

Table 2

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (53.5% DM)		106.4239		28.0374	30.1356	9.6187
Xanthan Gum	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Locust Bean Gum	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Carrageenan	0.3000	3.0000	1.2159	0.7904	0.8495	0.2711
Pullulan	16.0000	160.0000	64.8493	42.1520	45.3065	14.4610
Potassium Sorbate	0.0600	0.6000	0.2432	0.1581	0.1699	0.0542
Acesulfame Potassium Salt	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Aspartame NF	1.4000	14.0000	5.6743	3.6883	3.9643	1.2653
Purified Water	75.3274	753.2740				68.0819
Physcool	0.1000	1.0000	0.4053	0.2635	0.2832	0.0904
Menthol	1.0000	10.0000	4.0531	2.6345	2.8317	0.9038
Citric Acid (used to adjust pH to 6.0)	0.0700	0.7000	0.2837	0.1844	0.1982	0.0633
Cherry Flavor (Givudan)	0.1500	1.5000	0.6080	0.3952	0.4247	0.1356
Peppermint Flavor	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0405	0.0263	0.0283	0.0090
Polysorbate 80 NF	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Atmos 300	0.3500	3.5000	1.4186	0.9221	0.9911	0.3163
Glycerine	3.0000	30.0000	12.1592	7.9035	8.4950	2.7114
Olive Oil	0.5000	5.0000	2.0265	1.3173	1.4158	0.4519
FD&C Green #3	0.0026	0.0260	0.0105	0.0069	0.0074	0.0024
Titanium Dioxide	0.2500	2.5000	1.0133	0.6586	0.7079	0.2260
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1106.4239		93.0374	100.0000	100.0000
* assuming that all water is evaporated						

The active film was gritty and bitter.

Example 3

Comparative films having the ingredients listed in Table 3 were prepared in accordance with the method of Example 1.

Table 3

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Coated Dextromethorphan (60% DM)		94.7292		25.0000	27.7778	8.6532
Xanthan Gum	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Locust Bean Gum	0.0700	0.7000	0.2842	0.1847	0.2053	0.0639
Carrageenan	0.3000	3.0000	1.2180	0.7917	0.8797	0.2740
Pullulan	16.0000	160.0000	64.9625	42.2256	46.9174	14.6155
Potassium Sorbate	0.0600	0.6000	0.2436	0.1583	0.1759	0.0548
Acesulfame Potassium Salt	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Aspartame NF	1.4000	14.0000	5.6842	3.6947	4.1053	1.2789
Purified Water	75.3704	753.7040				68.8484
Physcool	0.1000	1.0000	0.4060	0.2639	0.2932	0.0913
Menthol	1.0000	10.0000	4.0602	2.6391	2.9323	0.9135
Citric Acid	0.0270	0.2700	0.1096	0.0713	0.0792	0.0247
Cherry Flavor (Givudan)	0.1500	1.5000	0.6090	0.3959	0.4399	0.1370
Peppermint Flavor	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.1000	0.0406	0.0264	0.0293	0.0091
Polysorbate 80 NF	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Atmos 300	0.3500	3.5000	1.4211	0.9237	1.0263	0.3197
Glycerine	3.0000	30.0000	12.1805	7.9173	8.7970	2.7404
Olive Oil	0.5000	5.0000	2.0301	1.3196	1.4662	0.4567
FD&C green #3	0.0026	0.0260	0.0106	0.0069	0.0076	0.0024
Titanium Dioxide	0.2500	2.5000	1.0150	0.6598	0.7331	0.2284
Total w/o active		0.0000	100.0000	65.0000		
Total with active	100.0000	1094.7292		90.0000	100.0000	100.0000
* assuming that all water is evaporated						

The active film was very thin, blue and gritty. Sensations of bitterness and numbness were minimal, but the flavor was not entirely agreeable.

Example 4

Films of the invention having the ingredients listed in Table 4 were prepared in accordance with the method of Example 1, except that Step F comprised adding uncoated dextromethorphan hydrobromide and AMBERLITE resin to Preparation E as separate ingredients.

Table 4

Material	%w/w in batch	g/batch	%w/w* placebo film	mg/dose*	%w/w* active film	% w/w actual batch
Dextromethorphan		17.0326		15.0000	15.7563	5.0951
Amberlite IRP69		17.2597		15.2000	15.9664	5.1630
Xanthan Gum	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Locust Bean Gum	0.0700	0.2100	0.2845	0.1849	0.1943	0.0628
Carrageenan	0.3000	0.9000	1.2194	0.7926	0.8326	0.2692
Pullulan	16.0000	48.0000	65.0338	42.2720	44.4033	14.3587
Potassium Sorbate	0.0600	0.1800	0.2439	0.1585	0.1665	0.0538
Acesulfame Potassium Salt	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Aspartame NF	1.4000	4.2000	5.6905	3.6988	3.8853	1.2564
Purified Water	75.3974	226.1922				67.6630
Physcool	0.1000	0.3000	0.4065	0.2642	0.2775	0.0897
Menthol	1.0000	3.0000	4.0646	2.6420	2.7752	0.8974
Citric Acid	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
Cherry Flavor (Givudan)	0.1500	0.4500	0.6097	0.3963	0.4163	0.1346
Peppermint Flavor	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0300	0.0406	0.0264	0.0278	0.0090
Polysorbate 80 NF	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Atmos 300	0.3500	1.0500	1.4226	0.9247	0.9713	0.3141
Glycerine	3.0000	9.0000	12.1938	7.9260	8.3256	2.6923
Olive Oil	0.5000	1.5000	2.0323	1.3210	1.3876	0.4487
FD&C green #3	0.0026	0.0078	0.0106	0.0069	0.0072	0.0023
Titanium Dioxide	0.2500	0.7500	1.0162	0.6605	0.6938	0.2244
Total w/o active		300.0000	100.0000	65.0000		
Total with active	100.0000	334.2922		95.2000	100.0000	100.0000
* assuming that all water is evaporated						

The active film had a pleasing appearance and taste.

Example 5

The ingredients listed in Table 5 were combined to provide an example of an antitussive film of the invention in accordance with the following procedure:

A. The water was heated to 75°C. Uncoated dextromethorphan hydrobromide was dissolved with mixing in the water, while maintaining the temperature at 75°C. AMBERLITE resin was then mixed into the water with heating for 4 to 5 hours at 70-80°C. Heating was stopped, water lost to evaporation was replaced, and the potassium sorbate and sweeteners were then added to the composition with mixing to form Preparation A.

B. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) were mixed in a separate container to form Preparation B.

C. Preparation B was slowly added to Preparation A with rapid mixing, followed by overnight mixing at a reduced rate to provide Preparation C.

D. The menthol was dissolved with mixing in the alcohol in a separate container. The Physcool was then dissolved with mixing therein. The MAG, Polysorbate 80, Atmos 300 and flavors were then added to the mixture and mixed to enhanced uniformity to form Preparation D.

E. Preparation D, glycerine and mannitol were added to Preparation C with thorough mixing to provide Preparation E.

Preparation E was poured on a mold and cast to form a film of a desired thickness at room temperature. The film was dried under warm air and cut to a desired dimension (dictated by, e.g., dosage and mouthfeel) for taste testing. The film was segmented into 1.5 in^2 (9.7 cm^2) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 70±3 mg.

A placebo film was also prepared in accordance with the foregoing to facilitate evaluation of, e.g., the taste and appearance of the active film.

Table 5

Material	%w/w in batch	g/batch	mg/dose*	%w/w* film	% w/w actual batch
Dextromethorphan HBr		11.4615	15.0000	21.4286	9.2666
Amberlite IRP69		12.2256	16.0000	22.8571	9.8843
Xanthan Gum	0.0600	0.0600	0.0944	0.1348	0.0485
Locust Bean Gum	0.0700	0.0700	0.1101	0.1573	0.0566
Carrageenan	0.3000	0.3000	0.4718	0.6740	0.2425
Pullulan	16.0000	16.0000	25.1613	35.9447	12.9359
Potassium Sorbate	0.0600	0.0600	0.0944	0.1348	0.0485
Acesulfame Potassium Salt	0.5000	0.5000	0.7863	1.1233	0.4042
Aspartame NF	1.4000	1.4000	2.2016	3.1452	1.1319
Purified Water	70.2000	70.2000			56.7561
Alcohol USP	5.0000	5.0000			4.0425
Physcool	0.1000	0.1000	0.1573	0.2247	0.0808
Menthol	1.5000	1.5000	2.3589	3.3698	1.2127
Peppermint Flavor	0.1000	0.1000	0.1573	0.2247	0.0808
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7863	1.1233	0.4042
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0157	0.0225	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5504	0.7863	0.2830
Atmos 300	0.3500	0.3500	0.5504	0.7863	0.2830
Glycerine	1.5000	1.5000	2.3589	3.3698	1.2127
Mannitol USP	2.0000	2.0000	3.1452	4.4931	1.6170
Total w/o active		100.0000	39.0000		

The active film had a pleasing appearance and taste.

Example 6

Films of the invention having the ingredients listed in Table 6 were prepared in accordance with the method of Example 5.

Table 6

Material	%w/w in batch	g/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		11.6538	15.0000	21.4286	9.3919
Amberlite IRP69		12.4308	16.0000	22.8571	10.0180
Xanthan Gum	0.0600	0.0600	0.0925	0.1321	0.0484
Locust Bean Gum	0.0700	0.0700	0.1079	0.1542	0.0564
Carrageenan	0.3000	0.3000	0.4625	0.6606	0.2418
Pullulan	16.0000	16.0000	24.6640	35.2343	12.8944
Potassium Sorbate	0.0600	0.0600	0.0925	0.1321	0.0484
Acesulfame Potassium Salt	0.5000	0.5000	0.7708	1.1011	0.4030
Aspartame NF	1.4000	1.4000	2.1581	3.0830	1.1283
Purified Water	69.7000	69.7000			56.1713
Alcohol USP	5.0000	5.0000			4.0295
Physcool	0.1000	0.1000	0.1542	0.2202	0.0806
Menthol	2.0000	2.0000	3.0830	4.4043	1.6118
Peppermint Flavor	0.1000	0.1000	0.1542	0.2202	0.0806
Raspberry Flavor (Givudan)	0.5000	0.5000	0.7708	1.1011	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0100	0.0154	0.0220	0.0081
Polysorbate 80 NF	0.3500	0.3500	0.5395	0.7708	0.2821
Atmos 300	0.3500	0.3500	0.5395	0.7708	0.2821
Glycerine	1.5000	1.5000	2.3123	3.3032	1.2089
Mannitol USP	2.0000	2.0000	3.0830	4.4043	1.6118
Total w/o active		0.0000	39.0000		
Total with active	100.0000	124.0846	70.0000	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

Example 7

A film of the invention having the ingredients listed in Table 7 were

prepared in accordance with the method of Example 5. The film was segmented into 1" x 1.25" (2.54 cm x 3.18 cm) dosage units, each of which had a thickness of 0.009±0.002 in (0.23±0.05 mm) and a weight of 63.6±3 mg.

Table 7

Material	%w/w in batch	kg/batch	mg/dose*	%w/w*	%w/w
Dextromethorphan HBr		1.3567	15.0000	23.5981	9.3918
Amberlite IRP69		1.4472	16.0000	25.1713	10.0180
Xanthan Gum	0.0600	0.0070	0.0772	0.1215	0.0484
Locust Bean Gum	0.0700	0.0081	0.0901	0.1417	0.0564
Carrageenan	0.3000	0.0349	0.3661	0.6075	0.2418
Pullulan	16.0000	1.8627	20.5941	32.3988	12.8944
Potassium Sorbate	0.0600	0.0070	0.0772	0.1215	0.0484
Acesulfame Potassium Salt	0.5000	0.0582	0.6436	1.0125	0.4030
Aspartame NF	1.4000	0.1630	1.8020	2.8349	1.1283
Purified Water	69.7000	8.1145			56.1714
Alcohol USP	5.0000	0.5821			4.0295
Physcool	0.1000	0.0116	0.1287	0.2025	0.0806
Menthol	2.0000	0.2328	2.5743	4.0498	1.6118
Peppermint Flavor	0.1000	0.0116	0.1287	0.2025	0.0806
Raspberry Flavor (Givudan)	0.5000	0.0582	0.6436	1.0125	0.4030
Mono ammonium glycyrrhizinate (MAG)	0.0100	0.0012	0.0129	0.0202	0.0081
Polysorbate 80 NF	0.3500	0.0407	0.4505	0.7087	0.2821
Atmos 300	0.3500	0.0407	0.4505	0.7087	0.2821
Glycerine	1.5000	0.1746	1.9307	3.0374	1.2089
Mannitol USP	2.0000	0.2328	2.5743	4.0498	1.6118
Total w/o active + resin		11.6420	32.5644		
Total with active + resin	100.0000	14.4459	63.5644	100.0000	100.0000
* assuming that all water and alcohol is evaporated					

The active film had a pleasing appearance and taste.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer, at least one pharmaceutically active agent and at least one taste masking agent.

2. The consumable film according to claim 1, wherein said at least one water soluble polymer is a member selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

3. The consumable film according to claim 2, wherein said at least one water soluble polymer is pullulan.

4. The consumable film according to claim 1, wherein said at least one pharmaceutically active agent is a member selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, antitussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2-antagonists, proton pump inhibitors, central nervous system agents, analgesics and mixtures thereof.

5. The consumable film according to claim 4, wherein the antimicrobial agent is a member selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

6. The consumable film according to claim 4, wherein the non-steroidal anti-inflammatory agent is a member selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

7. The consumable film according to claim 4, wherein the antitussive is a member selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan, chlophedianol, diphenhydramine, salts thereof and mixtures thereof.

8. The consumable film according to claim 4, wherein the decongestant is selected from the group consisting of pseudoephedrine, phenylepherine, phenylpropanolamine, salts thereof and mixtures thereof.

9. The consumable film according to claim 4, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

10. The consumable film according to claim 4, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

11. The consumable film according to claim 4, wherein the anti-diarrheal is loperamide.

12. The consumable film according to claim 4, wherein the H_2-antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

13. The consumable film according to claim 4, wherein the proton pump inhibitor is selected from the group consisting of omeprazole,

lansoprazole, and mixtures thereof.

14. The consumable film according to claim 1, wherein the at least one taste masking agent is an ion exchange resin.

15. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with divinylbenzene.

16. The consumable film according to claim 14, wherein the ion exchange resin is a sulfonated polymer comprising polystyrene cross-linked with 8% of divinylbenzene, with an ion exchange capacity of about 4.5 to 5.5 meq/g of dry resin (H^+-form).

17. The consumable film according to claim 16, wherein the ion exchange resin has irregularly-shaped particles ranging in size from about 47 to about 149 micrometers.

18. The consumable film according to claim 16, wherein the ion exchange resin has spherical particles ranging in size from about 45 to about 150 micrometers.

19. The consumable film according to claim 14, wherein the ion exchange resin is a polymer composed of polystyrene cross-linked with 8% of divinylbenzene and functionalized with a quaternary ammonium group, and wherein an exchange capacity of said ion exchange resin is normally within a range of about 3 to about 4 meq/g of dry ion exchange resin.

20. The consumable film according to claim 1, wherein the at least one taste masking agent is magnesium trisilicate.

21. The consumable film according to claim 1, wherein said at least one water soluble polymer is pullulan, said at least one pharmaceutically active agent is dextromethorphan, and said at least one taste masking agent is a sulfonated polymer ion exchange resin comprising polystyrene cross-linked with divinylbenzene.

22. The consumable film according to claim 21, wherein said pullulan is present in an amount of about 40 to about 80 wt% of said film, said dextromethorphan is present in an amount of about 5 to about 40 wt% of said film, said sulfonated polymer ion exchange resin is present in an amount of about 5 to about 40 wt% of said film, and a ratio of said dextromethorphan to said sulfonated polymer ion exchange resin is 1:3 to 3:1.

23. The consumable film according to claim 22, wherein said pullulan is present in said film in an amount of about 2 to about 6 mg/cm^2, said dextromethorphan is present in said film in an amount of about 1.4 to about 2 mg/cm^2, and said sulfonated polymer ion exchange resin is present in said film in an amount of about 1.4 to about 2 mg/cm^2.

24. The consumable film according to claim 22, further comprising:

about 0.01 to about 5 wt% of at least one stabilizing agent;

about 0.001 to about 0.1 wt% of at least one of at least one coloring agent;

about 0.1 to about 70 wt% of water;

about 0.1 to about 15 wt% of at least one sweetening agent;

about 0.1 to about 15 wt% of at least one flavoring agent;

about 0.1 to about 4 wt% of at least one cooling agent;

about 0.1 to about 5 wt% of at least one surfactant;

about 0.1 to about 12 wt% of a triglyceride;

about 0.001 to about 5 wt% of a preservative;

about 0.1 to about 5 wt% of a polyethylene oxide compound; and

about 1 to about 20 wt% of propylene glycol.

25. A method for preparing the consumable film of claim 1, said method comprising:

dissolving water-soluble ingredients in water to provide an aqueous solution;

mixing at least one water soluble film former and at least one stabilizing agent to provide a film-forming mixture;

combining said film-forming mixture and said aqueous solution to provide a hydrated polymer gel;

mixing oils to form an oil mixture;

adding said oil mixture to said hydrated polymer gel and mixing to provide a uniform gel;

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

26. The method of claim 25, wherein said at least one pharmaceutically active agent and said at least one taste masking agent are incorporated into said aqueous solution or into said uniform gel.

27. The method of claim 25, wherein said at least one taste masking agent is an ion exchange resin, and said at least one pharmaceutically active agent is sorbed to said ion exchange resin without separating ion exchanged pharmaceutically active agent from unexchanged agent and counter ion salts.

INTERNATIONAL SEARCH REPORT

Inter. ›nal Application No
PCT/US 01/02192

A. CLASSIFICATION OF SUBJECT MATTER
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B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

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Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, PAJ, EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	EP 0 225 615 A (CIBA-GEIGY) 16 June 1987 (1987-06-16) claims 1-4,10 page 6, paragraph 2 page 10; example 6	1,2,4,7, 14-19 21-27
X	EP 0 438 147 A (SCLAVO) 24 July 1991 (1991-07-24) claims 1-5,13	1,2, 14-19
P,X Y,P	WO 00 42992 A (LAVIPHARM) 27 July 2000 (2000-07-27) claims 1,11,12,15,17,21,23,40 page 14, line 12 - line 21 page 18; table 1	1-4 21-27

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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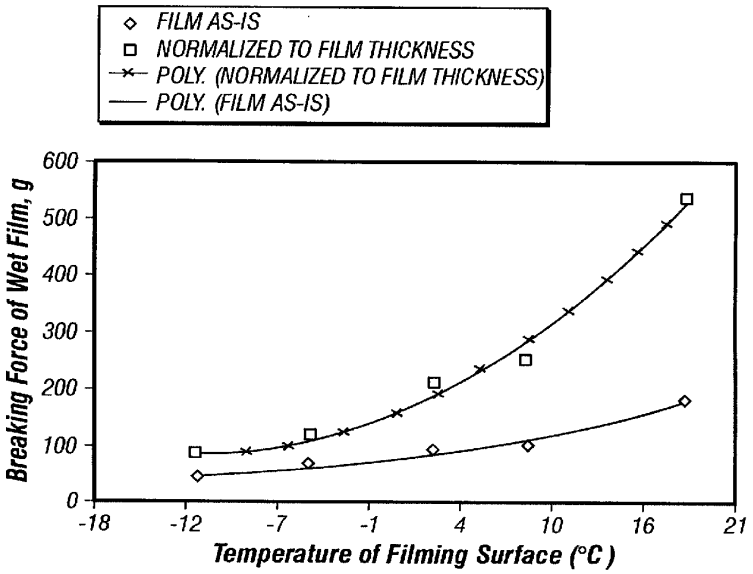
(54) Title: MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

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MODIFIED STARCH AS A REPLACEMENT FOR GELATIN IN SOFT GEL FILMS AND CAPSULES

BACKGROUND OF THE INVENTION

This invention relates to starch compositions useful in forming flexible films. More particularly, it relates to film-forming compositions containing certain modified starches.

Gelatin is a protein that forms thermo-reversible films. Gel masses composed of gelatin and a plasticizer such as glycerin are formulated to be liquid above room temperature, form a film when cast on a cooled surface, and re-melt when exposed to higher temperatures again. This ability to re-tackify enables encapsulation of liquid materials in gelatin soft capsules. Films formed from plasticized gelatin set very quickly and have high wet film strength. They are also very elastic with good clarity. Plasticized gelatin also has a relatively low viscosity, even when used at high solids concentrations. In addition, when gelatin is in the presence of water at room temperature, it swells but does not go into solution until heat is applied.

In the manufacture of soft gel films and capsules, the soft gel composition must possess the properties of good wet and dry film strength, insolubility in cold water, oil, and alcohol, solubility in hot water, temperature and pressure sealability, film clarity, film flexibility, edibility, inertness to drugs or other materials to be encapsulated, and rapid setting from a hot liquid to form a gel. In the manufacture of photographic elements, the soft gel films must possess the qualities of clarity, strength, setting power, flexibility, and non-interaction with other chemicals in the photographic film.

Although gelatin is useful in soft gel applications because of its rapid gelling ability, excellent film forming properties, and ability to impart oxygen impermeability, it has the disadvantages of high cost, limited availability, non-kosher status for food products and, at times, batch property variations. Because of these shortcomings, those industries where the need for gelatin is greatest have long sought means for replacing gelatin.

A useful gelatin replacer must be compatible with common plasticizers and fill materials used in the industry, and must provide properties equivalent to those of the gelatin which it is replacing for a particular application, e.g., film or binding strength in the pharmaceutical industry, phototransmissibility and resistance to abrasion in the photographic industry, and binding strength in the adhesive industry.

SUMMARY OF THE INVENTION

One aspect of the present invention is a film-forming composition that comprises starch material selected from the group consisting of modified starch and waxy starch; gum; and plasticizer. The modified starch or waxy starch has a dextrose equivalent (DE) of less than about 1, and preferably has no measurable DE. This composition can be, but is not required to be, 100% gelatin-free. Thus, the composition can be used as a gelatin replacement, or as an extender in gelatin formulations.

The composition typically will be prepared with water, and have a solids concentration of about 30-70% by weight. The solids in the composition preferably comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum. In certain preferred embodiments of the invention, the weight ratio of gum to starch is from about 0.1:1 to about 1:1, and the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

The starch material preferably comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015. It is also preferred that the starch material has an average molecular weight between about 100,000-2,000,000. In a particularly preferred embodiment, the starch material is selected from the group consisting of ether and ester derivatives of starch, such as hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch. One specific embodiment of the invention comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

The gum preferably is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin. A combination of kappa carrageenan and iota carrageenan, most preferably in a weight ratio of about 1:1, is especially preferred. The plasticizer preferably comprises at least one polyol, such as glycerol, sorbitol, maltitol, or a mixture of one or more of these. The composition of the present invention can optionally also comprise at least one monovalent or divalent cation, such as sodium, potassium, and calcium salts, or mixtures thereof.

Another aspect of the invention is an edible film that comprises the above-described starch-based composition, usually with much of the water removed. Yet another aspect of the invention is a soft gel capsule that comprises a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall. The capsule wall comprises the above-described starch-based composition. In one embodiment of the invention, the film or the capsule wall consists essentially of the combination of starch material, gum, and plasticizer.

The first substance encapsulated by the capsule wall can be any of a variety of materials which have been encapsulated by gelatin in the past. Many such substances are edible, including drugs, vitamins, nutritional supplements, and pre-measured food ingredients such as flavorings. It can also comprise, for example, photographic or dye solutions.

Another aspect of the invention is a method of encapsulating a first substance. This method comprises the steps of: providing a first substance and an edible film as described above; and encapsulating the first substance in the film. Preferably, the film used in this method has been formed on a surface having a temperature of at least about 38°C (100°F).

One object of this invention to provide an economical means for replacing gelatin in compositions utilized in the production of soft gel for food, pharmaceutical, and industrial applications. It is a further object of this invention to provide starch-based materials which are compatible with the existing application equipment used for manufacture of the various products which are primarily comprised of gelatin films.

The starch-based systems of the present invention, when incorporated as a replacement for gelatin in aqueous solutions, display properties superior to those of their parent base starch. More precisely, modified starches that have been chemically modified with monoreactive moieties to a degree of substitution of at least 0.015 DS, and degraded to molecular weights between 100,000 and 2,000,000, or, alternatively, waxy starches, when combined with gum and plasticizing agents, are a highly functional replacement for gelatin in soft gel film forming applications. The presence of gum increases the rate of film formation and enhances film strength.

In compositions of the present invention, the starch and gum preferably are mixed with plasticizers at ratios ranging from about 1 part starch and gum to about 0.8-3 parts plasticizer. The total solids in the composition preferably range from about 30 to 70% weight. Edible films are prepared by blending together the starch, gum, plasticizer, and water, and heating the mixture to a temperature and for a time sufficient to gelatinize the starch fully, (e.g., 80-100 °C for 10-60 min). A vacuum can be used either during or after cooking to remove entrained air and improve film properties. Additional materials may be added to the mixture of starch and plasticizer in order to impart improved functionality. Furthermore, properties of this system can be modified by the inclusion of various mono and divalent cations, including but not limited to sodium, potassium, and calcium. The mixture is then sheeted, while hot, to form a thin film. This film can be formed into soft gel capsules, encapsulating pharmaceutical, nutritional, photographic, or other materials, using well-known techniques.

The modified starch-based compositions of the present invention provide an acceptable balance of critical variables including mass viscosity and pot life, film rate, wet film strength, dry film strength and flexibility, and thermo-reversibility.

In one embodiment of the invention, wet film strength is significantly improved by increasing the temperature of the surface on which the film is formed. It is preferred in the present invention to use film-forming surface temperatures of about 38°C (100°F) or greater. Commercial capsule filming drum temperatures are often set around 10°C (50°F) for gelatin filming, but can easily be adjusted to 38-43°C (100-110°F). Breaking strengths can be increased by as much as 500% by increasing surface temperature from 12-66°C (53°F to 150°F). Films cast at 41°C (105°F) can have as much as twice the breaking strength films cast on 12°C (53°F) surfaces.

In one particularly preferred embodiment, the gum component of the composition consists essentially of 50% kappa carrageenan and 50% iota carrageenan. This combination can increase film strength by as much as 50% over films formed with 100% kappa carrageenan as the gum component, increase film elasticity, reduce the viscosity of the hot mass, lower the minimum temperature at which the gelled mass can be handled in liquid form, and lower the gel-setting temperature of the mass. This composition also broadens the temperature range over which the mass gels, which can improve the ease of film sealing.

The present invention has a number of benefits. One advantage of the invention is that it is a simple, cost-effective, dependable, intrinsically safe, Kosher, and efficient means for replacing the gelatin used in soft gel capsule compositions.

Another advantage of the invention is that the preparation of the starch-based compositions can be carried out by ordinary means with conventional manufacturing apparatus. The resulting compositions can be utilized in any commercial process requiring gelatin and to which conventional coating and drying methods are adaptable. Examples of end-product uses for the compositions of the present invention include encapsulated bath beads, paint balls, and pharmaceuticals. Therefore, the present invention provides a novel, efficient means for replacing gelatin in these and other applications.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph showing the effect of the temperature of the surface on which a film is formed on the strength of that film.

Figure 2 is a graph showing the effect of temperature on flow and gelation for compositions containing different types of carrageenan.

Figure 3 is a graph showing the effect of mass solids percentage on the flowability of compositions containing different types of carrageenan.

DETAILED DESCRIPTION OF SPECIFIC EMBODIMENTS

Examples of modified starches that can be used in the present invention include non-retrograding starches derived by chemical modification of starch from any plant source, including corn, waxy maize, potato, sweet potato, wheat, rice, sago, tapioca, sorghum, high amylose corn, and the like. The particular starch chosen will depend on its performance, availability, and cost. The starch should have a DE less than about 1, and preferably has no measurable DE (using the Lane-Eynon method). Among the useful modified starches are the common ether and ester derivatives of starch, including but not limited to hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch derivatives. Also included among the modified starches suitable for use in the practice of this invention are the thermally converted, fluidity or thin boiling type products derived from the aforementioned types of chemically modified starches. Such materials may be of lower molecular weight, prepared by heating the modified starch alone or by subjecting the starch to a hydrolytic acid and/or heat treatment, or by any other known method designed for the thermal conversion of the starch, such as enzymic heat treatment.

Preferred modified starches are the hydroxypropyl derivatives of potato starch having a degree of substitution from 0.015-0.30 ds and a molecular weight of from 100,000 to 2,000,000. In the case of waxy starches of corn, potato, etc., the branches of the amylopectin replace the function of the ether or ester substituents; these starches are functional in the present invention without additional chemical modification, although their properties are not impaired by additional modification, and are enhanced by molecular weight reduction.

Suitable plasticizers include, but are not limited to, glycerol, sorbitol, and maltitol. Suitable hydrocolloid gums include carrageenan, locust bean gum, xanthan gum, gellan gum, agar, alginates, guar gum, gum arabic, and pectin.

The properties of the composition can be enhanced by the addition of certain cations, including but not limited to sodium, potassium, and calcium. The presence of these cations, in combination with certain gums, generally enhances viscoelastic properties and gel strength.

A variety of optional ingredients may be incorporated into the starch compositions of this invention, before, during, or after cooking the starch. Among the suitable additives which may be utilized are preservatives, colorants, flavoring agents, hardeners, antifoggers, sensitizers, and spreading agents. The inclusion of such additives has no adverse effect upon the properties exhibited by the novel starch-based compositions of the present invention.

A composition of the present invention is formed by combining the dry solids (i.e., the modified starch or waxy starch, gum, and plasticizer, plus any other additives), slurrying in water, and heating at a temperature and for a time sufficient to gelatinize the starch. Optionally, this can take place under a vacuum. Films can be formed from these starch-based compositions by any conventional method designed to solubilize and deposit a continuous coating or layer of the solution onto a substrate or mold of any form. Among the suitable coating techniques are spraying, dipping, air knife, trailing blade, reverse and direct roll coaters, etc. A film, such as an overcoating or capsule shell, may then be formed by drying the coated solution to a desired moisture content, using any means suitable for the particular purpose. Suitable conventional means include warm or cold air impingement, low humidity chamber or oven drying, etc. For example, in the pharmaceutical industry, soft gel capsules are prepared by casting a film of the gelatin solution and then continuously passing two ribbons of the film between two opposing rollers, each of which is equipped with an internal vacuum that draws in the film through half capsule wells engraved in its surface. The capsule contents are deposited between the shell halves as they are formed and sealed. The process is continuous, ending with the filled capsules being automatically conveyed to and through a drying unit that partially dries the capsule. Drying is completed in warm air tunnels.

The films of the present invention can be re-melted, and two or more of these re-melted films can be joined to form a seal.

The invention is particularly efficacious in the soft gel capsule manufacturing process that calls for film-forming materials, but it is not limited thereto. The characteristics exhibited by the present, novel starch formulations, particularly their ability to serve as a total replacement for gelatin, permit them to be used in a wide range of applications.

Although the emphasis has been placed on describing this invention in connection with film-forming gelatin-free compositions, compositions of the present invention can also be utilized as extenders in gelatin compositions such as creams, emulsions, binders, adhesives, etc.

Further compositions of the present invention can be used in the replacement of gelatin in hard shell capsule manufacturing.

EXAMPLES

The invention will be further illustrated by, but is not intended to be limited to, the following examples.

Compositions were prepared containing the component amounts given in Examples 1-7 on a dry solids basis. Starch molecular weights were measured by gel permeation chromatography and weight averaged. In Examples 1-7, the starch, plasticizer, and gum, if used, were mixed with sufficient deionized water (except where indicated) to give a total slurry mass of 35 g. The components were mixed together in the cup of a Rapid Visco Analyzer (Model RVA-4D, Foss Food Technology, Eden Prairie, MN) (hereafter referred to as "RVA"), and heated, using 160 rpm stirring, to 98°C over 4.5 minutes. The mixture was held at 98°C, with continued stirring, for 6.5 minutes, then transferred to a chilled surface and drawn into a film of 0.5 mm thickness for film testing. A second paste of the same composition was cooked in the same way and then transferred into a pre-heated glass jar, tightly capped, and placed into an oven for pot life evaluations.

In particular, in Examples 1-7, the film samples were prepared by casting a layer of the test solution at about 82°C (180°F) onto a Teflon-coated piece of glass (approximately 22.9 x 33 cm (9 in x 13 in)). The bottom of the glass was in contact with circulating cold water so that the surface temperature of the glass was 52°C. The film was formed by pouring the hot paste onto the Teflon surface and then quickly drawing the paste across the glass using a Bird Applicator or similar device, the gap width of which could be adjusted to control film thickness. Wet film thicknesses were typically 0.5-0.8 mm. The films were cast, dried, and aged in a room controlled to 21°C (70°F) and 25-30% relative humidity.

The viscosity of the starch mixture was measured by the RVA instrument, which records viscosity throughout the cook.

Pot life was evaluated by transferring the hot paste into preheated glass jars with screw lids, and placing these in a 82°C (180°F) oven. The fluidity of the mass was evaluated after 2 hours by tipping the jars upside down and assigning a flow rating of 0-5. A mass that flowed with the ease of water was given a rating of 5; a mass which did not flow at all was given a rating of 0. The oven temperature was then lowered by 10°C and the samples allowed to equilibrate for 2 hours, and then their flow properties re-assessed. The oven was lowered in 5.6°C (10 °F) increments until all samples had a flow rating of zero – that is, they had all gelled.

Thermo-reversibility was assessed by reheating the pot life samples, described above, in 5.6°C (10 °F) increments, allowing them to equilibrate at each temperature, and then assigning a flow rating using the same criteria as for pot life.

The films were evaluated for rate of filming using a Gardco Electronic Multicycle Circular Drying Time Recorder, and following test method procedure ASTM D 5895. The recorder was placed above the wet film, and a stylus was lowered onto the surface of the film and allowed to rotate for a defined time of 10 minutes. Three points were determined from this test: tack free, dry hard, and dry through. Tack free is defined as the point in the path made by the stylus on the film where the continuous track ends and a discontinuous track or tear begins. Dry hard is the point in the path where the stylus no longer tears the film, and only leaves a visible trace. Dry through is reached when the stylus no longer leaves any visible track on the film.

The tensile strength of the wet film was measured using a Stable Microsystems TA-XT2 Texture Analyzer. To do this, 1.3 cm x 20.3 cm (0.5 in x 8 in) strips were cut from the wet film 5 minutes after it was cast and these were loaded onto the Texture Analyzer. The tensile test was started 15 minutes after the film was cast.

Film appearance (color and clarity) was evaluated on the basis of visual observation.

Example 1

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special (obtained from SPI Polyols, New Castle, Delaware)

Example 2

8.4 g potato starch, substituted with 0.5% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

Example 3

8.4 g potato starch, substituted with 3.0% hydroxypropyl groups and of 600,000 molecular weight

11.8 g Sorbitol Special

0.5 mm thickness.

Example 4

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g gellan

9.7 g sorbitol

0.5 mm thickness.

Example 5

5.2 g waxy corn starch of 800,000 molecular weight

0.75 g kappa carrageenan

9.7 g sorbitol

Example 6

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g glycerine

Example 7

5.2 g potato starch, substituted with 3 wt % hydroxypropyl groups and of 600,000 molecular weight

0.75 g kappa carrageenan

9.7 g Sorbitol Special

Sufficient 1% NaCl to bring to 35 g total mass.

The physical properties of the hot starch/plasticizer pastes for Examples 1-7, and the resulting films, are listed below in Table 1.

Table 1

Example number	Peak viscosity during cook, cps	Hot paste final visc, cps, 98°C	Time until tack free, sec	Time until dry hard, sec	Wet film tensile strength, g force	Pot life rating @ 82°C (180°F)	Minimum flowable temp, °C	Re-softening temp, °C
1	18000	1700	<5	<10	75	3.5	71	66
2	14000	2500	65	100	*			
3	13000	1150	4020	5700	*			
4		2300	<5	<10	108	0.5	>82	>82
5	13000	2400	<5	<10	65	3.0	77	66
6	16000	1500	<5	<10	50	4.0	71	66
7	11000	1300	<5	<10	75	3.5	77	66

* Too weak to test

Example 8

A formulation was prepared having the following composition (on an as-is basis):

16% starch which had been acid-thinned to approximately 600,000 mol wt and substituted with about 4 wt % hydroxypropyl groups (approx. 10% moisture).

2.3% kappa carrageenan (approx. 9% moisture)

26% Sorbitol Special (24% moisture)

6.7% glycerine (1% moisture)

49% added water

When the moisture in the components is taken into account, the total solids of the composition was 44%. The starch to carrageenan ratio was 6.75/1, and the ratio of plasticizer to thickener (starch plus carrageenan) was 1.6/1. The plasticizer was composed of 75% Sorbitol Special and 25% glycerine. The components were mixed together and then heated to 98°C for 15 minutes (or to 92°C for 30 minutes), then poured hot onto a surface and drawn down into a film.

To control the temperature of the surface onto which films were cast, a stream of water was passed underneath and in contact with that surface. In this experiment, the water stream heated water, rather than chilled water as in the previous examples. The surface temperature was controlled by adjusting the thermostat in the water reservoir – a conventional re-circulating water bath.

To determine "minimum flow temperature" and "gel temperature", masses were cooked in an RVA, then transferred to preheated glass vials and placed in a 82°C (180°F) oven. After 2 hours equilibration, the vials were tipped and the flow of the mass observed, and a ranking assigned and recorded. The oven temperature was then reduced by 5.6°C (10°F) and the samples allowed to equilibrate for an additional 2 hours. The "minimum flow temperature" was defined as the lowest temperature at which the mass would easily flow in the vial. It was viscous but "pourable". The "gel temperature" was the highest temperature at which the mass did not flow at all. Since the samples were evaluated in 5.6°C (10°F) increments, the temperature assignments are approximate.

The kappa carrageenan used for this experiment was SKW Satiagel RPT 8/60 Kappa Carrageenan. The iota carrageenan used was FMC SD 389 PF Iota Carrageenan.

During conventional production of gelatin soft-gel capsules, the hot gelatin mass is cast onto a cooled drum (10-13°C; 50-55°F). In this experiment, the surface onto which the mass was cast was heated by the circulating water stream, in order to slow the rate of cooling of the

composition. Figure 1 shows the variation in wet strength of the films formed as the surface temperature varied.

Increasing the temperature of the filming surface dramatically increased wet film strength. (Wet film strength is the important strength parameter since the film must have sufficient integrity within 1-4 minutes of casting to survive an open draw and other rigors of capsule production.) At higher temperatures, the film thicknesses were lower (probably due to flow on the heated surface). When the film strengths were normalized to film thickness (g force per mm thickness), the temperature effect was especially dramatic – increasing 5 fold as the surface temperature increased from 12-66°C (53°F to 150°F). The "as-is" film strength, uncorrected for film thickness, increased 4 fold.

Film rates were not quantified, but all conditions generated films which could be lifted and handled in under a minute.

Without being bound by theory, it is possible that the higher film strength observed when the surface temperature was higher is due to larger, greater numbers and/or more perfect helices. When the films cool slowly, they have time and mobility near the gelation temperature to form larger and/or more perfect helices. A higher percentage of the carrageenan may be involved in helices compared to material that is quench-cooled.

Example 9

Experiments were performed using compositions like that of Example 8, but in which the carrageenan content was reduced by 25% and the total mass solids percentage was increased. These compositions had a mass viscosity and wet film strength similar to that exhibited by the formulation of Example 8. The composition and properties of the two soft gels are compared in Table 2 below. The two gel masses have similar viscosity/temperature profiles, and gel at similar temperatures. (As mentioned above, a flow rating of 5 is similar to water. A rating of zero indicates that the sample is gelled and there is no flow. A rating of at least 3 is preferred for handing on commercial equipment.)

Table 2

mass solids, %	% carrageenan	% starch	Flow rating 82°C	Flow rating 77°C	Flow rating 72°C	Flow rating 66°C	Breaking strength, g 12°C filming	Breaking strength, g 41°C filming
44	4.1	37	4.5	4.0	2.0	0.0	57	180
48	5.2	42	4.0	3.0	2.0	0.0	---	78

A 25% reduction in carrageenan makes the composition significantly less costly. Increased mass solids percentage reduces shrinkage and drying costs.

Example 10

Starch-based compositions were prepared containing the same ingredients as in Example 8, except iota carrageenan was used as a complete replacement for kappa carrageenan. However, films formed from such compositions had a slow film formation rate. In addition, the films formed were soft, weak, and very elastic.

Tests were then performed using a composition like that of Example 8, except that it included a combination of kappa and iota carrageenan, rather than only kappa carrageenan. This change resulted in stronger films (higher yield stress) than either of the two types of carrageenan alone. The strongest films comprised a 50/50 (weight) combination of the two. As much as 50% increase in film strength was measured with the 50/50 blend of kappa/iota compared with the kappa-only films.

The temperature at which the kappa-only gel mass became a rigid gel was high - about 160°F for the composition of Example 8 at 44% solids. The mass viscosity builds rapidly as its temperature is dropped below 82°C (180°F). This could be a problem in manufacturing operations, because the hot mass could set up in a location in manufacturing equipment that is inadvertently underheated. Further, even higher temperatures (88°C plus) are needed to re-soften the kappa-only gel for capsule sealing. Moreover, kappa carrageenan has a very sharp liquid-gel transition, whereas iota's transition is rather broad.

Because the strength of films formed from kappa/iota blends were not a mathematical combination of the two individual carrageenans, and a 50/50 combination of the two gave the strongest films, a mixed gel structure was strongly implied. Carrageenan gels by coiling portions of its carbohydrate backbone into helixes with portions of another carrageenan molecule. If the gel is composed of helixes containing one strand of kappa carrageenan and one strand of iota carrageenan, predicting the softening temperature is not straightforward.

We therefore prepared gel masses composed of either kappa carrageenan, or a 50/50 blend of kappa and iota. All other aspects of the formula were held constant (see Example 8 for the formulation details). A series of gel masses with varying total solids were prepared for each carrageenan composition. The effects on gel temperature are illustrated in Table 3 below. ("Minimum flow" and "gel temperature" are as defined above.)

Table 3

Effect of carrageenan on mass flow properties and gel temperature

% ds	approx min. flow temp, deg C		approx gel temp, deg C	
	kappa	kappa/iota	kappa	kappa/iota
42	71	66	66	60
44	74	71	71	66
45	77	71	71	66
46	82	77	71	66
47	85	77	71	66

It can be seen that replacing half of the kappa carrageenan with iota decreased the temperature at which the mass will flow, and decreased its gel temperature, by about 5.6°C (10°F) for each of the solids levels tested.

At 82°C (180°F) the two formulations had similar flow properties, but the kappa-only samples thickened rapidly with drop in temperature. Figure 2 illustrates the effect. Lower gel temperature, and more gradual gelation, should make the films made from kappa/iota mixtures easier to handle and easier to seal.

Table 3 above illustrates the importance of solids control during handling of these formulations. Figure 3 illustrates the rapid decrease in mass flowability at 77°C (170°F) as mass solids increases. The effect is especially pronounced for the kappa-only formulation. Blending iota carrageenan with kappa allows for higher solids while maintaining manageable viscosity.

Example 11

Two films that comprised the same ingredients as Example 10 were dipped in mineral oil and then were re-melted and sealed together. During capsule production, gelatin films are typically coated with oil before they are sealed. Without being bound by theory, it is believed that in the absence of the oil coating, evaporative cooling makes it difficult to seal the films (the rapid evaporation cools the films below their gel point by the time the two surfaces came together). The mineral oil appeared to suppress evaporation and the starch-based films could be readily sealed. Both films made with kappa carrageenan and with kappa/iota blends sealed readily using this technique.

The preceding description of specific embodiments of the present invention is not intended to be a complete list of every possible embodiment of the invention. Persons skilled

in this field will recognize that modifications can be made to the specific embodiments described here that would be within the scope of the present invention.

WHAT IS CLAIMED IS:

1. A film-forming composition, comprising:
starch material having a dextrose equivalent less than about 1 and selected from the group consisting of modified starch and waxy starch;
gum; and
plasticizer.

2. The composition of claim 1, wherein the composition is gelatin-free.

3. The composition of claim 1, further comprising water.

4. The composition of claim 3, wherein the composition comprises 30-70% by weight dry solids.

5. The composition of claim 4, wherein the dry solids in the composition comprise 25-75% starch material, 25-75% plasticizer, and 0.1-15% gum.

6. The composition of claim 1, wherein the weight ratio of gum to starch is from about 0.1:1 to about 1:1.

7. The composition of claim 1, wherein the weight ratio of starch and gum to plasticizer is from about 1:0.8 to about 1:3.

8. The composition of claim 1, wherein the starch material comprises starch which has been chemically modified with a monoreactive moiety to a degree of substitution of least about 0.015.

9. The composition of claim 8, wherein the starch material has an average molecular weight of about 100,000-2,000,000.

10. The composition of claim 9, wherein the starch material is selected from the group consisting of ether and ester derivatives of starch.

11. The composition of claim 10, wherein the starch material is selected from the group consisting of hydroxypropyl, hydroxyethyl, succinate, and octenyl succinate starch.

12. The composition of claim 1, wherein the starch material comprises hydroxypropylated potato starch having a degree of substitution of about 0.015-0.30 and a molecular weight of about 100,000-2,000,000.

13. The composition of claim 1, wherein the gum is selected from the group consisting of carrageenan, locust bean, xanthan, gellan, agar, alginates, guar, gum arabic, and pectin.

14. The composition of claim 13, wherein the gum comprises a combination of kappa carrageenan and iota carrageenan.

15. The composition of claim 14, wherein the weight ratio of kappa carrageenan to iota carrageenan is about 1:1.

16. The composition of claim 1, wherein the plasticizer comprises at least one polyol.

17. The composition of claim 16, wherein the plasticizer is selected from the group consisting of glycerol, sorbitol, maltitol, and mixtures thereof.

18. The composition of claim 1, further comprising at least one monovalent or divalent cation.

19. The composition of claim 18, wherein the cation is selected from the group consisting of sodium, potassium, and calcium, and mixtures thereof.

20. The composition of claim 1, wherein:
the starch material is selected from the group consisting of (a) ether and ester derivatives of starch having a molecular weight of about 100,000-2,000,000 and a degree of substitution of about 0.015-0.30;
the gum comprises a combination of kappa carrageenan and iota carrageenan; and
the plasticizer comprises at least one polyol.

21. An edible film comprising the composition of any of claims 1-20.

22. A soft gel capsule comprising a sealed capsule wall and a first substance that is encapsulated by the sealed capsule wall;
wherein the capsule wall comprises a composition according to any of claims 1-20.

23. The capsule of claim 22, wherein the capsule wall consists essentially of a composition according to any of claims 1-20.

24. The capsule of claim 22, wherein the first substance is edible.

25. The capsule of claim 21, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

26. A method of encapsulating a first substance, comprising the steps of:
providing a first substance and an edible film that comprises a composition according to any of claims 1-20; and
encapsulating the first substance in the film.

27. The method of claim 26, wherein the first substance is selected from the group consisting of drugs, vitamins, nutritional supplements, and pre-measured food additives.

28. The method of claim 26, wherein the film is formed at a temperature of at least about 38°C.

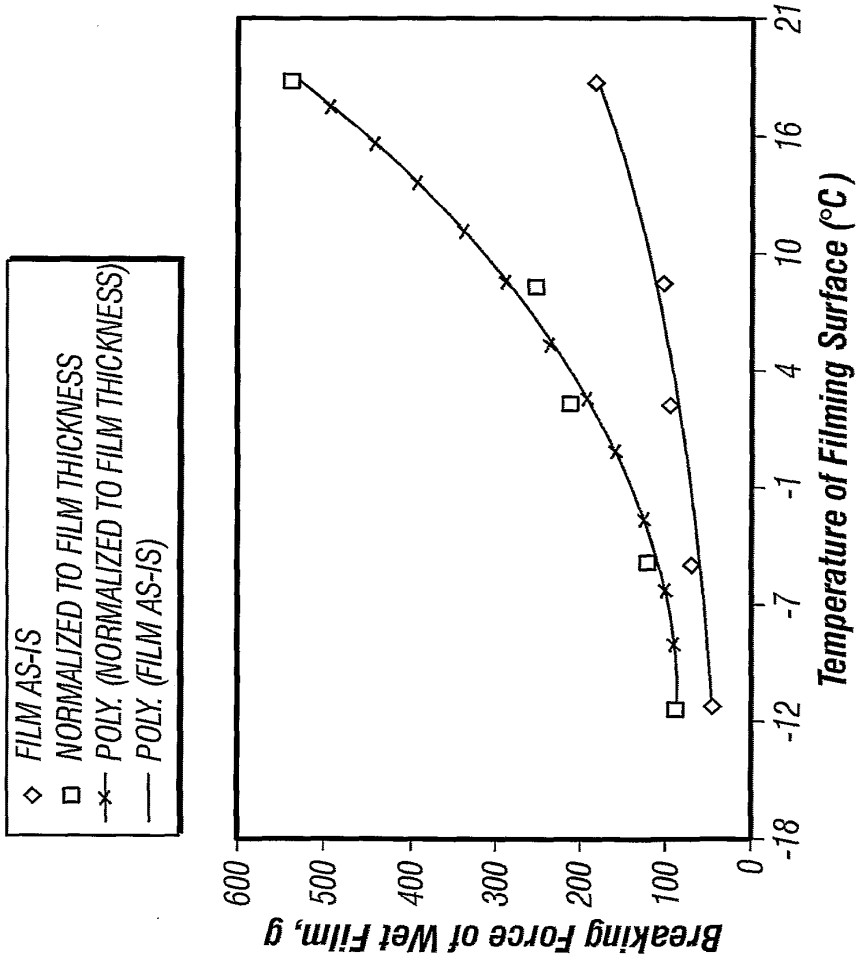

FIG. 1

2/2

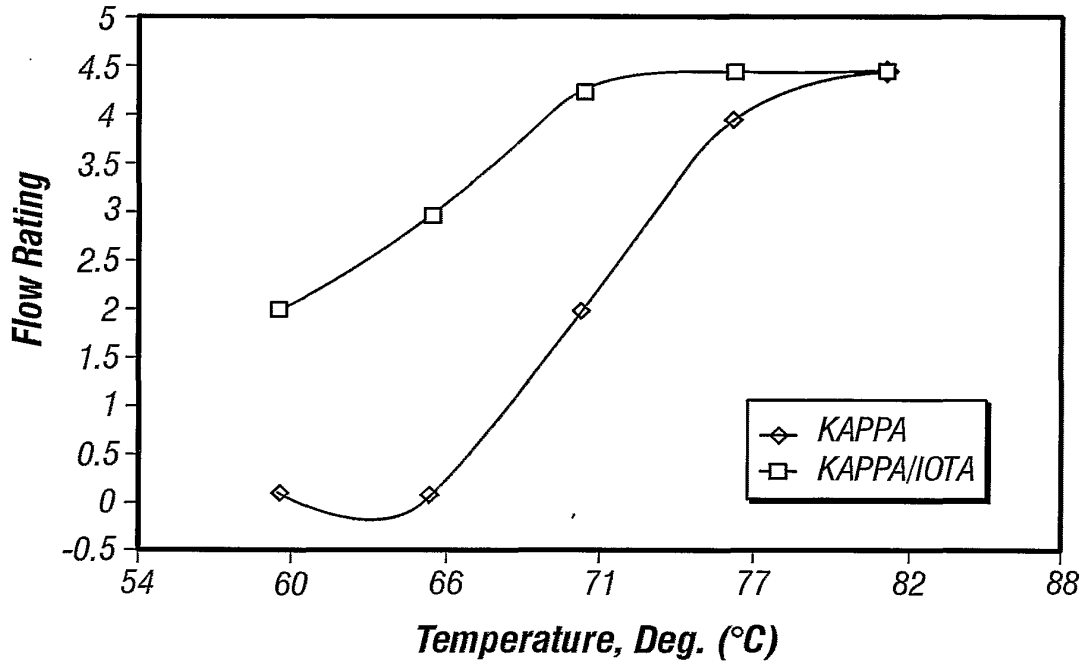

FIG. 2

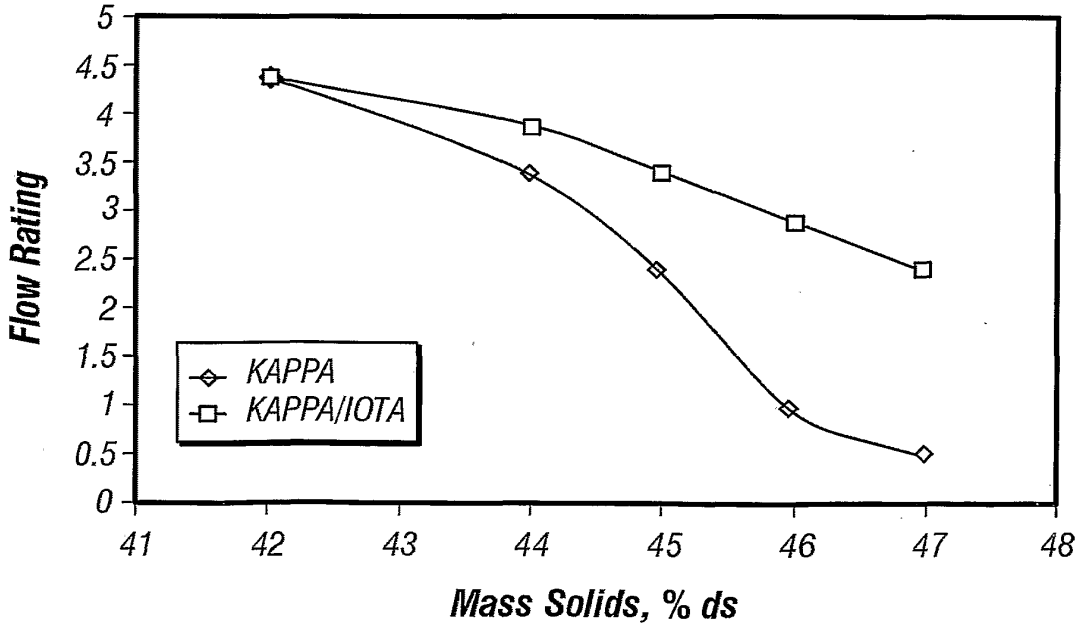

FIG. 3

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(54) Title: ORAL AND DENTAL HYGIENE PREPARATION

(54) Bezeichnung: MUND- UND ZAHNPFLEGEMITTEL

(57) Abstract

An oral and dental hygiene preparation consists of tensides, polishing agents, flavourings and other usual additives, incorporated in a binder or mixture of binders in the form of water-soluble or water-dilatable, physiologically acceptable foil-forming substances. The mixture is processed to a foil, which is predivided into dosage units.

(57) Zusammenfassung

Ein Mund- und Zahnpflegemittel besteht aus Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen welche in ein Bindemittel oder eine Bindemittelmischung aus wasserlöslichen oder -quellenbaren, physiologisch unbedenklichen Folienbildnern eingearbeitet sind. Die Mischung ist zu einer Folie verarbeitet, welche in Dosiseinheiten vorzerteilt ist.

LEDIGLICH ZUR INFORMATION

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Mund- und Zahnpflegemittel

Zahnpflegemittel werden seit vielen Jahren als Pasten, sogenannte Zahnpasten hergestellt. Dabei ist der wesentliche Ausgangsstoff eine Schlämmkreide, die mit Wasser, Glycerin, waschaktiven Stoffen und Verdickungsmitteln zu einer Paste verarbeitet und in Tuben oder Spendern abgefüllt wird. Die Zahnpasta hat den Markt erobert, während andere Zahnpflegemittel wie Tropfen, Zahnseifen und -pulver oder Granulate kaum noch eine Rolle spielen. Mit den Mitteln soll der bakterielle Zahnbelag entfernt, Kariesprophylaxe betrieben sowie die Reinigung der Zähne schonend und durch die Bürstenbehandlung wesentlich unterstützt durchgeführt und der Mundraum gründlich gereinigt und angenehm erfrischt werden.

In neuerer Zeit hat sich das Bild der Zahnpasten nicht wesentlich verändert, obwohl die Rezepturen in vielerlei Hinsicht abgewandelt wurden. Die Verwendung einer recht groben Kreideform zum mechanischen Reinigen der Zähne wich mehr und mehr modernen, feineren Poliermitteln auf Basis von Aluminiumoxid oder Siliciumdioxid (Kieselgele). Neben Tensiden finden strukturbildende Komponenten und ausgefeilte Geschmackskorrigentien Verwendung. Oft werden Wirkstoffe wie insbesondere verschiedene Fluorderivate oder Mineralsalze zugefügt. Das Volumen konnte teilweise

reduziert werden; sicherlich hat die Einführung und allgemeine Verwendung elektrischer Zahnbürsten hierbei einen starken Einfluß gehabt.

Die Handhabung von Zahnpasten ist jedoch mit einer Reihe von Nachteilen verbunden. Weil die Dosierung aus einfachen Tuben Schwierigkeiten bereitet, hat man in neuerer Zeit Zahnpastaspender entwickelt, welche jeweils eine vorbestimmte Menge Zahnpasta abgeben. Diese Spender sind jedoch verhältnismäßig groß und daher zur Mitnahme auf Reisen wenig geeignet. Tuben sind druckempfindlich und daher auf Reisen ebenfalls nicht ideal. Sowohl in Spendern als auch in Tuben kann Zahnpasta bei längeren Gebrauchsunterbrechungen austrocknen, so daß die angebrauchten Behälter dann weggeworfen werden müssen. Ferner lassen sich sowohl Tuben als auch Spender nicht vollständig entleeren. Nach Verbrauch bleiben die aus Metall oder Plastik hergestellten Behälter zurück und verursachen Umweltprobleme.

Der Erfindung liegt demgegenüber die Aufgabe zugrunde, eine neue Verabreichungs- und Dosierungsform für Mund- und Zahnpflegemittel zu entwickeln, welche die vorstehend genannten Nachteile nicht aufweist. Insbesondere soll eine genaue Dosierung für die einzelne Zahnreinigung ermöglicht und sichergestellt werden, daß das Mittel vollständig aufgebraucht werden kann, ohne daß Reste in der Packung zurückbleiben.

Das erfindungsgemäße Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen ist dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittelmischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in

Dosiseinheiten vorzerteilt ist.

Als Bestandteile des Mund- und Zahnpflegemittels kommen die Komponenten in Frage, welche üblicherweise zur Herstellung von Zahnpasten Verwendung finden, wobei natürliche Rohstoffe besonders bevorzugt sind. Wichtig ist darüber hinaus, daß alle Bestandteile völlig ungiftig und physiologisch unbedenklich sind, was selbstverständlich auch für die verwendeten Folienbildner gilt. Als wesentliche Bestandteile von Zahnpflegemitteln sind zu nennen:

- Schleifmittel wie Kreide (Calciumcarbonat), Calcium- und Natriumphosphate, Aluminiumoxid oder Siliciumdioxid, insbesondere Kieselgele
- Tenside (Schaummittel) wie Natriumlaurylsulfat, Natriumlaurylsulfoacetat, Sarcoside, Monoglyceridsulfate und andere
- Aromastoffe wie Pfefferminzöl, Krauseminzöl, Anisöl, Zimtöl, Nelkenöl, Menthol und ähnliche
- Süßstoffe wie Saccharin, Cyclamat, Aspartam und ähnliche.

Die in Zahnpasten üblicherweise enthaltenen flüssigen Komponenten wie Glycerin, Propylenglykol oder Sorbitsirup müssen den erfindungsgemäßen Mitteln in Folienform nicht in den üblichen Mengen zugesetzt werden, da hier die für Tuben oder Spender erforderliche Plastizität keine Rolle spielt. Weitere übliche Zusätze wie Fluorverbindungen, Mittel gegen Zahnsteinbildung, antibakterielle Wirkstoffe und ähnliche, wie sie in Mund- und Zahnpflegemitteln üblicherweise Verwendung finden, können auch erfindungsgemäß eingesetzt werden.

Als wasserlösliche bzw. -quellbare Folienbildner eignen sich vor allem Stärken, Gelatinen, Glycerin und/oder Sorbit sowie ferner natürliche oder synthetische Harze und

Gumme. Folgende Rahmenrezeptur hat sich bewährt:

Gelatine	8 - 10 g
Stärke	3 - 8 g
Glycerin	1 - 2 g
Wasser	30 - 50 g.

In dieser Grundmasse werden die Bestandteile des Mund- und Zahnpflegemittels gelöst bzw. dispergiert, um eine gleichmäßige Verteilung der Stoffe zu erreichen. Die so erhaltene Mischung kann erfindungsgemäß in verschiedener Weise zu einem folienförmigen Mund- und Zahnpflegemittel verarbeitet werden:

a) Es ist einmal möglich, die Masse direkt zu einer Folie zu verarbeiten, welche im allgemeinen eine Dicke zwischen 0,1 und etwa 3 mm aufweist. Durch Sollbruchstellen mittels Stanzung oder Perforierung kann diese Folie in Dosiseinheiten vorzerteilt werden, wobei die Streifenbreite und -länge vorzugsweise etwa der Zahnbürstengröße, d.h. der von den freien Borstenenden gebildeten Fläche des Borstenblocks oder der Längsquerschnittfläche des Borstenblocks in der Borstenebene entsprechen sollte.

b) Alternativ kann die Masse auf eine Trägerfolie aufgebracht werden, deren Zusammensetzung derjenigen des Bindemittels der Masse entspricht, wie dies in der EP-OS 219 762 im einzelnen offenbart ist. Auch die auf diese Weise erhaltenen Folien können wie oben angegeben vorzerteilt werden.

c) Es ist ferner möglich, die Masse auf eine Releasefolie oder ein Releasepapier aufzubringen, wie dies aus der DE-PS 36 30 603 bekannt ist. In diesem Fall wird die Beschichtung in einzelne Abschnitte der oben

angegebenen Größe vorzerteilt, welche sich ähnlich wie Haftetiketten von der Trägerfolie vor Gebrauch abziehen lassen.

In allen Fällen erhält man eine Darreichungs- und Dosierungsform, deren Anwendung besonders leicht ist, da die jeweils zu verwendende Menge gleichmäßig vorgegeben ist. Eine Dosis wird in Form eines Folienabschnittes abgetrennt bzw. abgezogen und auf die angefeuchtete Zahnbürste bzw. zwischen die Borsten gelegt, wo sie durch die Feuchtigkeitsberührung haftet und anquillt. Durch das Einführen in die Mundhöhle und in Verbindung mit dem Speichel und der intensiven Zahnbürstenbewegung wird der Streifen an- und aufgelöst, so daß die Inhaltsstoffe zur vollen Wirkung gelangen. Nach der Anwendung und der anschließenden Mundspülung mit Wasser verbleiben keinerlei Rückstände im Mund.

Gewünschtenfalls können die Folien in unterschiedlicher Weise bedruckt, geprägt oder gestanzt werden, wobei beispielsweise für Kinder auch bildliche Darstellungen möglich sind. Es entfällt das Öffnen und Schließen von Tubenverschlüssen, es wird keine Zahnpasta vergeudet und die erfindungsgemäße Darreichungsform läßt sich auch besondes gut auf Reisen einsetzen, da sie leicht ist, ein Auslaufen nicht befürchtet werden muß und sie äußerst wenig Platz beansprucht. Die Verpackung ist umweltfreundlich in Pappschachteln ohne Verwendung von Metallen oder Kunststoff möglich.

Die Mittel der Erfindung eignen sich nicht nur zur Zahnpflege im Mund, sondern bei geeigneter Zusammensetzung auch zur Reinigung und Pflege von künstlichen Zähnen und Gebissen. Für diesen letzteren Einsatzzweck ist eine Mehrfachbeschichtung besonders günstig, bei der sich in einer Schicht die reinigenden, desinfizierenden und sauren

Komponenten befinden, während sich, ggf. getrennt durch eine ebenfalls wasserlösliche Sperrschicht, in einer zweiten Schicht die CO_2 bzw. O_2 abgebenden Substanzen enthalten sind.

Beispiel

Ein erfindungsgemäßes Zahnpflegemittel hat folgende Zusammensetzung:

Amylogum	57,0 g
Honig	25,0 g
Zitronensäure	2,0 g
Titandioxid	1,0 g
Aroma	1,0 g
Siliciumdioxid	3,0 g
Ca-Hydrog-phos.	10,0 g
Na-Laurylsulfat	1,0 g

Mit der erforderlichen Menge Wasser wird ein Brei hergestellt, der zu einer Folie verarbeitet wird, die ca. 0,5 mm dick ist. Durch Perforation wird die Folie in Abschnitte von 8 x 35 mm unterteilt.

Gegebenenfalls kann die Masse auch als Beschichtung auf ein Releasepapier als Träger aufgebracht und durch Stanzung in Abschnitte der angegebenen Größe vorzerteilt werden.

Patentansprüche

1. Mund- und Zahnpflegemittel auf Basis von Tensiden, Poliermitteln, Aromastoffen sowie weiteren üblichen Zusatzstoffen, dadurch gekennzeichnet, daß die Wirk- und Zusatzstoffe in ein Bindemittel oder eine Bindemittel-Mischung eingearbeitet sind, welche aus wasserlöslichen oder -quellbaren, physiologisch unbedenklichen Folienbildnern bestehen, und daß diese Mischung zu einer Folie verarbeitet ist, wobei die so gebildete Folie in Dosiseinheiten vorzerteilt ist.

2. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Stärken, Gelatinen, Glycerin und/oder Sorbitol oder natürliche und/oder synthetische Harze und Gumme enthält.

3. Mund- und Zahnpflegemittel gemäß Anspruch 1, dadurch gekennzeichnet, daß es als Folienbildner Amylogum enthält.

4. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 3, dadurch gekennzeichnet, daß es als Folienbildner eine Mischung aus 8 bis 10 Gewichtsteilen Gelatine, 4 bis 8 Gewichtsteilen Stärke und 1 bis 2 Gewichtsteilen Glycerin enthält.

5. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß es aus einer Trägerfolie aus dem Bindemittel oder der Bindemittel-Mischung besteht, auf welche eine Schicht aufgebracht ist, welche die Bestandteile des Pflegemittels zusammen mit Bindemittel oder der Bindemittel-Mischung enthält, wobei das Bindemittel oder die Bindemittel-Mischung in der Trägerfolie und in der Beschichtung im wesentlichen die gleiche qualitative

Zusammensetzung aufweisen.

6. Mund- und Zahnpflegemittel nach den Ansprüchen 1 bis 4, dadurch gekennzeichnet, daß eine Beschichtung aus den Bestandteilen des Pflegemittels und dem Bindemittel oder der Bindemittel-Mischung auf eine Trägerfolie in Form eines Trennpapiers, eines Trennfilms oder einer Trennfolie aufgebracht ist, wobei die Beschichtung nach Vorzerteilung in Dosiseinheiten von dem Trägermaterial dosisweise abziehbar ist.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 90/01936

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.[5] A61K 7/16

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
Int.Cl.[5]	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category * [10]	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29 April 1987 see the whole document (cited in the application)	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12 August 1987 see claims 1,2,4,8	1,2,5,6
A	EP, A, 0259749 (DESITIN ARZNEIMITTEL GmbH) 16 March 1988 see the whole document (cited in the application)	1,2,5,6
A	GB, A, 2163348 (DENTAB UK LTD) 26 February 1986 see claims 1,4,9,14	1
A	GB, A, 1476057 (UNICLIFFE LTD) 10 June 1977 see pages 1-3	1,3

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 March 1991 (15.03.91)	11 April 1991 (11.04.91)
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	

Form PCT/ISA/210 (second sheet) (January 1985)

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9001936 SA 41110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/04/91
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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	1275046	09-10-90
		WO-A-	8702241	23-04-87
		EP-A-	0283474	28-09-88
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		US-A-	4849246	18-07-89
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		US-A-	4765984	23-08-88
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		AU-A-	6712887	23-07-87
		AU-B-	598512	28-06-90
		AU-A-	6790387	23-07-87
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		CH-A-	676082	14-12-90
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		US-A-	4925670	15-05-90
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EPO FORM P0479

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

EP 9001936
SA 41110

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 03/04/91 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A- 1476057	10-06-77	None	

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

INTERNATIONALER RECHERCHENBERICHT

Internationales Aktenzeichen PCT/EP 90/01936

I. KLASSIFIKATION DES ANMELDUNGSGEGENSTANDS (bei mehreren Klassifikationssymbolen sind alle anzugeben)[6]

Nach der Internationalen Patentklassifikation (IPC) oder nach der nationalen Klassifikation und der IPC

Int.Cl[5] A 61 K 7/16

II. RECHERCHIERTE SACHGEBIETE

Recherchierter Mindestprüfstoff[7]

Klassifikationssystem	Klassifikationssymbole
Int.Cl.[5]	A 61 K

Recherchierte nicht zum Mindestprüfstoff gehörende Veröffentlichungen, soweit diese unter die recherchierten Sachgebiete fallen[8]

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN[9]

Art*	Kennzeichnung der Veröffentlichung[11], soweit erforderlich unter Angabe der maßgeblichen Teile[12]	Betr. Anspruch Nr.[13]
A	EP, A, 0219762 (DESITIN ARZNEIMITTEL GmbH) 29. April 1987 siehe das ganze Dokument in der Anmeldung erwähnt	1,2,5,6
A	GB, A, 2186190 (COLGATE-PALMOLIVE COMPANY) 12. August 1987 siehe Patentansprüche 1,2,4,8	1,2,5,6
A	EP, A, 0259749 (DESITIN ARZNEIMITTEL GmbH) 16. März 1988 siehe das ganze Dokument in der Anmeldung erwähnt	1,2,5,6
A	GB, A, 2163348 (DENTAB UK LTD) 26. Februar 1986 siehe Patentansprüche 1,4,9,14 ./.	1

* Besondere Kategorien von angegebenen Veröffentlichungen[10]:

"A" Veröffentlichung, die den allgemeinen Stand der Technik definiert, aber nicht als besonders bedeutsam anzusehen ist

"E" älteres Dokument, das jedoch erst am oder nach dem internationalen Anmeldedatum veröffentlicht worden ist

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"&" Veröffentlichung, die Mitglied derselben Patentfamilie ist

IV. BESCHEINIGUNG

Datum des Abschlusses der internationalen Recherche	Absendedatum des internationalen Recherchenberichts
15. März 1991	11 APR 1991
Internationale Recherchenbehörde	**Unterschrift des bevollmächtigten Bediensteten**
Europäisches Patentamt	Mme N. KUIPER

Formblatt PCT/ISA/210 (Blatt 2) (Januar 1985)

III. EINSCHLÄGIGE VERÖFFENTLICHUNGEN (Fortsetzung von Blatt 2)

Art *	Kennzeichnung der Veröffentlichung, soweit erforderlich unter Angabe der maßgeblichen Teile	Betr. Anspruch Nr.
A	GB, A, 1476057 (UNICLIFFE LTD) 10. Juni 1977 siehe Seiten 1-3	1,3

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie		Datum der Veröffentlichung
EP-A- 0219762	29-04-87	AU-A-	6541786	05-05-87
		CA-A-	1275046	09-10-90
		WO-A-	8702241	23-04-87
		EP-A-	0283474	28-09-88
		JP-T-	63501794	21-07-88
		US-A-	4849246	18-07-89
GB-A- 2186190	12-08-87	US-A-	4705680	10-11-87
		US-A-	4765984	23-08-88
		AT-B-	390370	25-04-90
		AT-B-	389812	12-02-90
		AU-B-	598220	21-06-90
		AU-A-	6712887	23-07-87
		AU-B-	598512	28-06-90
		AU-A-	6790387	23-07-87
		BE-A-	1000635	28-02-89
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		JP-A-	63077816	08-04-88
		US-A-	4925670	15-05-90
GB-A- 2163348	26-02-86	US-A-	4753792	28-06-88

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

ANHANG ZUM INTERNATIONALEN RECHERCHENBERICHT ÜBER DIE INTERNATIONALE PATENTANMELDUNG NR.

EP 9001936
SA 41110

In diesem Anhang sind die Mitglieder der Patentfamilien der im obengenannten internationalen Recherchenbericht angeführten Patentdokumente angegeben.
Die Angaben über die Familienmitglieder entsprechen dem Stand der Datei des Europäischen Patentamts am 03/04/91
Diese Angaben dienen nur zur Unterrichtung und erfolgen ohne Gewähr.

Im Recherchenbericht angeführtes Patentdokument	Datum der Veröffentlichung	Mitglied(er) der Patentfamilie	Datum der Veröffentlichung
GB-A- 1476057	10-06-77	Keine	

EPO FORM P0473

Für nähere Einzelheiten zu diesem Anhang : siehe Amtsblatt des Europäischen Patentamts, Nr.12/82

Electronic Acknowledgement Receipt

EFS ID:	2782331
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Andrew Henry Berks/Barbara Thomas
Filer Authorized By:	Andrew Henry Berks
Attorney Docket Number:	1199-4B CIP
Receipt Date:	29-JAN-2008
Filing Date:	10-JUL-2007
Time Stamp:	14:59:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	1199-4B_CIP_IDS1.pdf	11376291 f2bb4a09e403b56f893fa1ab4e0c0fe7f0e804ee	no	10
Warnings:					
Information:					

2	Foreign Reference	DE2432925A1.pdf	799270 9dc715572e4fa76e845f32e64d9f5281f67a7e59	no	24
Warnings:					
Information:					
3	Foreign Reference	DE2449865A1.pdf	809661 6fa02ec176602526dd4b918c9da3728ae488c535	no	19
Warnings:					
Information:					
4	Foreign Reference	DE3630603A1.pdf	398087 e2eb835fe543d71b7a21304f34b99982791dd5d3	no	6
Warnings:					
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5	Foreign Reference	EP00200508B1.pdf	1585276 60e3e1b4f14ed765e1d3b31fd86530fdc19c7410	no	26
Warnings:					
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6	Foreign Reference	EP00219762B1.pdf	688933 2f08a9656e31eb2b468805dc0dd21277ea21d81c	no	7
Warnings:					
Information:					
7	Foreign Reference	EP00250187B1.pdf	785940 a4ba927f878c75d741d081e242536ebc2c11d40a	no	16
Warnings:					
Information:					
8	Foreign Reference	EP00259749B1.pdf	582578 1435c3df3e56248916c0ada0fa77358c1b659ebf	no	8
Warnings:					
Information:					
9	Foreign Reference	EP00273069B1.pdf	948001 ee9a9552c886214f5400e93ba3fb335da5b3e00e	no	14
Warnings:					
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10	Foreign Reference	EP00381194B1.pdf	667475 4d76b9e8d3dfe71fd521414bc57f5223625d14d5	no	9
Warnings:					
Information:					

11	Foreign Reference	EP00452446B1.pdf	292708 7484181723f744248422e344ddd91d29ee832d98	no	5
Warnings:					
Information:					
12	Foreign Reference	EP00514691A2.pdf	401423 ab6a5d4bb029961ff743573cdea808e5cd2e776e	no	6
Warnings:					
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13	Foreign Reference	EP01110546A1.pdf	258701 89be4f073ba87b8a60de50db9104a365e798d797	no	15
Warnings:					
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14	Foreign Reference	WO00018365A2.pdf	2000559 72d873af5261f8f270862205113d9ac4294850c2	no	54
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15	Foreign Reference	WO00042992A2.pdf	1666727 67e6cf45106e3a2c260d0898da2b4e044be5371e	no	44
Warnings:					
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16	Foreign Reference	WO00170194A1.pdf	1700341 fed801bd8631b35546050b039283c5dfa5b853ee	no	41
Warnings:					
Information:					
17	Foreign Reference	WO00191721A2.pdf	1004879 9eae9da5b736c32af0a45ce1c350f2b0616efd37	no	21
Warnings:					
Information:					
18	Foreign Reference	WO09105540A1.pdf	621036 faec2e482b09769eedcdeb79f7a4e73bae32cfe2	no	17
Warnings:					
Information:					
		Total Files Size (in bytes):	26587886		

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/08a (05-07)
Approved for use through 11/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
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	2	4593053		1986-06-03	Jevne	
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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(57) Abstract

A composition for topical application comprising a therapeutically effective amount of a pharmaceutical agent(s), a flexible, finite, pharmaceutically acceptable, adhesive, and a solvent for the pharmaceutical agent(s) in the adhesive and a method of administering the pharmaceutical agent to a mammal are disclosed.

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COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation-in-part of U.S. Patent Application Serial Number 07/661,827 filed February 27, 1991, and U.S. Serial Number 07/813,196 filed December 23, 1991, both of which applications are hereby incorporated by reference.

Field of the Invention

The present invention relates to compositions and methods for the topical administration of pharmaceutically active agents, namely those having a pharmacological or cosmetic effect, to a mammal in need thereof. The present invention is especially useful with local anesthetic agents for topical administration. In addition, the invention relates to a method for the topical administration of a pharmaceutical agent, especially an anesthetic agent or a combination of anesthetic agents, to prevent or ameliorate a disease or other medical or cosmetic condition, especially pain.

There is no limitation on the type of pharmaceutical agent that can be used in the present invention, provided that the agent can be absorbed percutaneously. Thus, the pharmaceutical agents can be drugs that can be topically applied for local effects and those which can be topically applied for systemic effects.

Background of the Invention

Anesthetic agents are pharmacologically active agents that block nerve conduction when applied in therapeutically effective amounts. They can be used for local or systemic effects. Anesthetic agents

have been used extensively in the medical field to obtain topical anesthesia. Topical administration or application means the direct contact of the anesthetic with tissue to be anesthetized, such as skin or membrane, particularly the oral or buccal mucosa. Previous methods of applying topical anesthetic agents to the skin or mucosa have used "nonfinite" or semi-liquid carriers or spreading substances such as creams, gels or ointments, or "finite" carriers, non-spreading substances which retain their form, e.g. patches, dressings and bandages. The finite carriers are flexible in the sense that they can bend to conform to the configuration of the skin or mucosa where they are applied.

Local anesthetics generally are esters or amides of benzoic acid derivatives, administered either as the free base or the acid-addition salt. Free bases tend to be irritating at high concentrations. Acid-addition salts have low skin permeability.

To be effective, a topical, local anesthetic should contain sufficient concentration of the active agent to produce an anesthetic effect, it should penetrate intact skin or mucosa sufficiently to deliver a therapeutic dose, and it should exhibit rapid onset of anesthetic action and have a prolonged anesthetic effect. In achieving the foregoing, it is often desirable to have the anesthetic agent present in a high concentration in the dosage form to effect a rapid onset and, additionally or alternatively, in excess of the amount that can be immediately absorbed through the dermis at the site of application, so as to prolong the duration or effect of anesthesia. On the other hand, the presence of the anesthetic agent in crystalline form may irritate sensitive tissues such as mucosal tissues. This is particularly true

with regard to lidocaine. The usefulness of topical anesthetics has been limited by the concentration of drug achievable in the dosage form. The same considerations also apply generally to other pharmaceutically active agents.

Anesthetic agents have been used in nonfinite form. United States Patent No. 4,894,232 to Reül, et al. discloses a base for mucosal or denture adhesive pastes and a process for the preparation thereof. A lidocaine salt is named as suitable for this paste.

Finite local anesthetic compositions are reported in the literature. Some compositions are solvent free. For instance, Swedish Patent Publication No. 352,239 published December 27, 1972 in the name of S.G. Davis et al., assigned to Astra Pharmaceutical Products, Inc., and based on Swedish patent application No. 17744/70 filed December 30, 1970, discloses a local anesthetic film containing up to 50% lidocaine in crystallized, microdispersed form. In its final form, this composition lacks a solvent for the anesthetic agent. The preparation is prepared by adding a solution of lidocaine in an organic solvent or an acid addition salt in water, under heat and agitation, to a solution or suspension of a film-forming material, namely carboxymethyl cellulose, polyvinyl alcohol, or a mixture of polyvinyl alcohol and polyvinyl pyrrolidone in water, followed by heating to remove any solvent present.

United States Patent No. 4,900,552 of Sanvordeker et al., disclose a trilaminate film suitable for prolonged and sustained delivery of an active ingredient in a buccal cavity. Specifically a hydratable mucoadhesive base layer, a non-adhesive reservoir layer containing the drug and a water-impermeable carrier film sandwiched between and bonded

to the base layer and the reservoir layer form the trilaminate film.

Some finite anesthetic compositions contain polyhydric alcohol solvents. United States Patent Nos. 4,572,832 and 4,695,465 to Kigasawa and 3,249,109 to Maeth all describe the use of water soluble protein based systems which incorporate anesthetics, and which also contain a tackifier and a polyhydric alcohol.

Some finite anesthetic agent compositions have a separate adhesive. United States Patent No. 3,814,095 to Lubens describes an absorbent pad for topical application of an anesthetic agent having a peripheral adhesive.

Glycerol (glycerin) has been used as a plasticizer for karaya gum. United States Patent Nos. 4,307,717 and 4,675,009 to Hymes et. al., describe a drug in a solid phase formed of a synthetic polymer and/or a long chain natural or synthetic polysaccharide or a combination thereof and a liquid phase of water or an alcohol or a combination thereof. The amount of drug in the preparation (excluding solvent or carrier) is low. The cross-linked polysaccharide plasticized with water and/or a polyhydric alcohol is said to be not self-adhering. The formulations do not include both a solvent for the drug and a plasticizer for the polysaccharide.

It is also known to combine two local anesthetic free bases with different melting points. By mixing the two anesthetic bases, an eutectic mixture has been reported that is liquid at room temperature, making it possible to attain higher concentrations of the active bases. United States Patent No. 4,888,354 to Chang relates to a combination of the free base and an acid addition salt or a variety of drugs, typically in a liquid carrier, to increase skin penetration rates. Anesthetics, along

with a list of other suitable drugs are mentioned. This reference specifically teaches that base and acid-addition forms of the same drug be used in carrier.

United States Patent No. 2,352,691 to Curtis teaches the use of salicylate salts of alkamine esters of aminobenzoic acid to enhance the water solubility of anesthetic agents. In one example, this reference discloses a solution of procaine acetyl salicylate containing insoluble anesthetics such as benzocaine, butesin, orthoform, or their salts, in certain glycols, which are combined with a volatile solvent, and then used to saturate gauze bandages or other suitable fabrics.

United States Patent No. 2,142,537 to Tisza describes an ointment containing isoamylhydrocupreine in combination with a quick acting local anesthetic to overcome the undesirable irritation caused by the prolonged acting anesthetic isoamylhydrocupreine or its salts. The preparation of Tisza combines short and long acting anesthetic agents.

United States Patent No. 2,277,038 to Curtis relates to preparations containing a mixture of two or more anesthetic agent salts having different pH values in solution, whereby the pH value of the combined mixture in solution may be adjusted to obtain a higher degree of stability of the solution, and at relatively higher pH, a more rapid onset of anesthetic action. The anesthetic agents in Curtis are not in highly dispersed form and are used in a liquid-soaked fabric.

Commonly, prolongation of anesthesia with topical anesthetics has been achieved by the addition of vasoconstrictors, such as the catecholamine, epinephrine, which caused constriction of blood vessels. Since catecolamines are not particularly effective when applied topically, such a prolongation

is of minimal usefulness for topical anesthetics. The primary drawbacks of this approach are the potential adverse side effects of catecolamines, and the prolongation itself.

Although many local anesthetic compositions have been proposed, it has been discovered that the incorporation of one or more anesthetic agents in a solvent for the anesthetic agent or agents into a flexible, finite, pharmaceutically acceptable carrier, permits an exceptionally high loading of anesthetic agent in the carrier, permitting more rapid delivery of the anesthetic agent to the dermal membrane and a greater extent of anesthesia without crystallization of the anesthetic agent or agents which can limit absorption by the skin and which can cause irritation of the skin or other dermal membrane.

It has also surprisingly been found that concentrations of substantially dissolved anesthetic agent as high as 50% by weight of the total composition can be achieved in a system in which the adhesion of the adhesive is not hindered. Prolongation of anesthesia can thus be achieved by increasing the amount of time the composition is applied, without detrimental irritation.

The compositions of the present invention are in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate the dermis, for example, intact skin or a mucous membrane. Moreover, the anesthetic action is highly localized. Because the drug is substantially microdispersed in the carrier, it is more readily available for permeation into the skin or dermal membrane.

It still further has surprisingly been found that the use of two different local anesthetic agents, the first in base form and the second in acid-addition

salt form, in a finite, flexible, adhesive, pharmaceutically acceptable carrier, including a solvent for the anesthetic agents, permits the attainment of anesthetic agent concentrations in the final product of up to 50% by weight in microdispersed form, without crystallization of the anesthetic agents which can cause irritation of the skin or other dermal membrane.

Thus, in one embodiment, the present invention is in convenient form for topical application of the anesthetic agents, thereby enabling such anesthetics to penetrate intact skin or mucous membranes and have a highly localized effect. Furthermore, the combination of the salt and base forms, advantageously results in rapid onset of anesthetic action with prolonged anesthetic effect.

Summary of the Invention

The invention relates to a flexible, finite bioadhesive composition, for topical application comprising:

a therapeutically effective amount of at least one local anesthetic or other pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the anesthetic or other pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent based on the weight of the whole composition of a plasticizer for the bioadhesive;

in admixture with the anesthetic agent or other pharmaceutically active agent in the solvent, a flexible, finite, pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20

to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention is comprised of two anesthetic agents, that is:

a therapeutically effective amount of a first local anesthetic agent in base form;

a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form;

a solvent for the first and second local anesthetic agents, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition; and

in an admixture with the anesthetic agents and the solvent, a pharmaceutically acceptable adhesive, preferably a bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the anesthetic agents preferably are in non-crystallized form in the composition.

The compositions of the invention may be further include a backing material which conforms to the size and shape of a single dosage of the composition.

The present invention further relates to a method of administering one or more pharmaceutically active agents in a bioadhesive to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures; a pharmaceutically acceptable solvent for the pharmaceutically active agent, preferably in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive; and in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is substantially free of water, is substantially water insoluble and is self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

The invention further relates to a method of administering two local anesthetic agents to a subject comprising the steps of:

providing a composition comprising a therapeutically effective amount of a first local anesthetic agent in base form; a therapeutically effective amount of a different, second local anesthetic agent in acid-addition salt form; a pharmaceutically acceptable solvent for the anesthetic preferably in an amount which ranges from about 50 to about 70 weight percent based on the weight of the whole composition, said solvent preferably including about 5 to about 50 weight percent of a plasticizer for the bioadhesive carrier; and in admixture with the

pharmaceutically active agent in the solvent, a pharmaceutically acceptable preferably polysaccharide bioadhesive, preferably in an amount from about 20 to about 50 weight percent based on the weight of the whole composition; wherein said composition is preferably substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is in non-crystallized form in the composition; and

contacting an area of skin or mucous membrane with the composition thereby administering the local anesthetic agent.

The compositions of this invention permit a far higher loading of drug than conventional dosage forms. This loading in the case of anesthetic agents can result in an extent (depth) of anesthesia which numbs the teeth when applied buccally, not a typical result for a topical anesthetic cream or ointment.

Detailed Description of the Invention

This invention provides a composition which adheres to an area of the skin or mucosa, and permits delivery at elevated levels of pharmaceutical agent or a combination of agents to produce a local or systemic effect over a prolonged period of time.

In accordance with one embodiment of the present invention, a local anesthetic in solution with a solvent for the anesthetic, containing a plasticizer for the adhesive, is in admixture with a pharmaceutically acceptable adhesive, which is preferably a bioadhesive, and more preferably a polysaccharide bioadhesive, is provided in a finite, flexible form for topical application to the skin or dermal membrane of a mammal.

In accordance with a further embodiment of the present invention, a combination of local anesthetic agents, a solvent for the anesthetic agents

and a flexible, preferably adhesive pharmaceutically acceptable adhesive carrier is provided for topical application to the skin or mucosa of a mammal.

The anesthetic agents of this invention are those known, or of a type known, in the art. The local anesthetic bases encompassed by this invention are weak organic bases which are lipophilic in nature and thus poorly soluble in water. However, these bases will react with organic or inorganic acids to form acidic, water soluble acid-addition salts.

The base form and the salt form of the anesthetic agent incorporated in the combination composition of this invention must be different anesthetic agents, to achieve maximum duration of the anesthetic effect. By the term "different" is meant that the salt form in any combination is not a salt of the base form used in the given combination.

Local anesthetic agents suitable for use in the practice of this invention include amides and esters. Examples of the amides are lidocaine, prilocaine, mepivacaine, bupivacaine, dibucaine and etidocaine. Esters include procaine, tetracaine, propoxycaine, chloroprocaine, benzocaine, butamben picrate, cocaine, hexylcaine, piperocaine, oxyprocaine and proparacaine. Other suitable local anesthetics for use in the practice of this invention include cyclomethycaine, dimethisoquin, ketocaine, diperodon, dyclonine and pramoxine, all typically administered in the form of the acid addition hydro-chloride or sulfate salts.

The acid-addition salts of the present invention are any non-toxic, pharmaceutically acceptable organic or inorganic salts. Typical inorganic salts are the hydrogen halides, especially the hydrochlorides, carbonates, borates, phosphates, sulfates, hydrogen sulfates, hydrobromides, nitrates,

sulfides, and arsenates. Typical organic salts are salts of mono- and polycarboxylic acids such as the citrate, tartrate, malate, cinnamate, oxalate, formate, succinate and phthalates.

The solvents for the anesthetic agents or other drugs are non-toxic, pharmaceutically acceptable substances, preferably liquids, which do not substantially negatively affect the adhesion properties of the system and in which the anesthetic agents or other drugs in the amounts employed are fully soluble. Preferably, the solvent is or is primarily a polyhydric alcohol or combination of polyhydric alcohols, particularly when the adhesive is a gum. The term polyhydric alcohol means any organic polyol. Other suitable solvents include carboxlyic acids and their derivatives and analogs such as fatty acids such as oleic acid, linoleic acid, capric acid and the like, as well as fatty esters or alcohols and ketones such as polyvinylpyrrolidone. Further suitable solvents include other non-toxic, non-volatile solvents commonly used in dermal or transdermal compositions for dissolving like compounds. As apparent to one skilled in the art what is a suitable solvent varies with the solubility of the drug in question.

The above mentioned polyhydric alcohols may include those having 2 to 6 alcoholic hydroxyl groups. Such polyhydric alcohols include glycols, triols and polyols having 4 to 6 alcoholic hydroxyl groups. Typical of said glycols are glycols containing 2 to 6 carbon atoms, e.g. ethylene glycol, propylene glycol, butylene glycol, polyethylene glycol (average molecular weight about 200 - 8,000, preferably about 200 to 6,000), dipropylene glycol, hexylene glycol, polyoxyethylene, polypropylene glycol, sorbitol, and the like. Examples of said triols include glycerin,

trimethylolpropane. Said polyols are exemplified by cycloalkanepolyols such as polyols derived from monosaccharides such as sorbitol (sorbit). These polyhydric alcohols may be used either singly or in combination (preferably, of two or three). Thus, for example, glycerin alone or a mixture of glycerin and butylene glycol is employed. In general, when an anesthetic agent, especially an anesthetic base is used, there are limits to the amounts of lipophilic polyhydric alcohols containing more than two alcoholic hydroxyl groups that can be present in the solvent and yet not result in precipitation of the drug as crystals.

Among those polyhydric alcohols, those which satisfy the requirements relevant to the adjustment and maintenance of softness of the external drug of the invention, the compatibility or co-dispersibility with the other components, and provide a proper consistency of the composition, may be freely used. Those which are low in volatility and plastic, are generally preferred and, in this regard, dipropylene glycol, glycerin, propylene glycol, butylene glycol, and sorbitol are appropriate solvents, according to the invention. Since solvent is to remain, at least in part, in the composition, the solvent should include components that do not substantially volatilize under the drying conditions used in preparing the composition. In other words, the solvent for the drug should be non-volatile.

Solvent selection for a single anesthetic agent or a combination of anesthetic agents in either the free base form or in the acid-addition salt form, depends on the form of the anesthetic agent, namely whether it is in free base form or acid-addition salt form. Solvents for the salt form of anesthetic agent are polar organic solvents. Polar organic solvents

are preferably polyhydric alcohols, as discussed above. Various other solvents suitable for either the base or acid-addition form of the anesthetic agent are those solvents known to dissolve either or both of these two types of forms including cyclic ketones such as 2-pyrrolidone; N-(2-hydroxyethyl) pyrrolidone, N-methylpyrrolidone, 1-dodecylazacycloheptan-2-one and other n-substituted alkyl-azacycloalkyl-2-ones (azones) dimethylformadide, and dimethylsulfoxide.

Other suitable solvents for the free base form of the anesthetic agent are cell envelope disordering compounds known to be useful in topical pharmaceutical preparation, which compounds are thought to assist in skin penetration by disordering the lipid structure of the stratum corneum cell-envelopes. Some of these compounds are generally encompassed by the formula:

R-X

wherein R is a straight-chain alkyl of about 7 to 16 carbon atoms, a non-terminal alkenyl of about 7 to 22 carbon atoms, or a branched-chain alkyl of from about 13 to 22 carbon atoms, and X is -OH, -$COOCH_3$, -$COOC_2H_5$, -$OCOCH_3$, -$SOCH_3$, -$P(CH_3)_2O$, -$COOCH_2H_4OC_2H_4OH$, -$COOCH(CHOH)_4CH_2OH$, -$COOCH_2CHOHCH3$, -$COOCH_2CH(OR")CH_2OR"$. -$(OCH_2CH_2)_mOH$, -COOR', or -$CONR'_2$ where R; is -H, -CH_3, -C_2H_5, -C_3H_7 OR -C_2H_4OH; R" is -H, or a non-terminal alkenyl of about 7 to 22 carbon atoms; and m is a positive integer from 2 to 6; provided that when R" is an alkenyl and X is -OH or -COOH, at least one double bond is in the cis-configuration.

Although the exact amount of the polyhydric alcohol or alcohols in the composition depends on the nature of other components, and therefore cannot be stated in specific terms, the proportion may range

from about 5 to about 70 weight percent based on the whole composition.

The solvent includes from about 5% to about 50% and more preferably about 10% to about 30% of a polyhydric alcohol known to plasticize the bioadhesive carrier. A particularly useful plasticizer is glycerine.

The high concentrations of microdispersed drug, for example anesthetic agent, of this invention are achieved typically by mixing the anesthetic agents with the solvent, preferably at an elevated temperature, for example about 70° to 100°C, to obtain a mixture, preferably a solution, of the anesthetic agents which is then added to the pharmaceutically acceptable adhesive.

Preferably the anesthetic agent is substantially dissolved in the solvent so that when mixed with the adhesive, the anesthetic is microdispersed in the composition. The term "microdispersed" is intended to mean that in the solvent, and subsequently in the carrier, there is an intimate dispersion of the anesthetic agent at the molecular or ionic level, such that crystals of the anesthetic agent cannot be detected using a microscope having a magnification of roughly 25X. As such, the pharmaceutically active agent is in "non-crystallized" form when in the compositions of the present invention.

It has been discovered that high concentrations of a combination of microdispersed anesthetic agents, namely up to 50% by weight of the finite, flexible composition, require the use of a solvent as herein described. Omission of the solvent in the procedure of Example 1 below yields a product filled with crystals or crystalline mass.

In particularly preferred embodiments of this invention, the free base local anesthetic agent is selected from the group comprising lidocaine, procaine, propoxycaine, mepivacaine, prilocaine, dyclonine, pramoxine, benzocaine and chloroprocaine. The salt form is preferably one selected from the group comprising prilocaine, tetracaine, bupivacaine, dyclonine, dibucaine, etidocaine and lidocaine salts. The aforementioned bases and salts can be used alone or in combination with other anesthetic bases and salts as needed to achieve therapeutically affective levels when administered transdermally.

The term "therapeutically effective amount" is intended to mean the amount of drug as a minimizer sufficient to produce a therapeutic effect, for example, an anesthetic effect when applied topically. These amounts are known in the art or may be determined by methods known in the art, and typically range from about 1 to 20,000 mg per human adult and preferably about 10 to 10,000 mg and most preferably range from about 20 to 5,000 mg of the anesthetic agent per application, depending upon the anesthetic agents chosen, and whether the skin or mucous membrane is the site of action. The only upper limit on the amount of anesthetic in the composition is that the preparation is substantially free of crystals of anesthetic agent or other drug and the amount of solvent used is not sufficient to undesirably affect the adhesive properties of the whole composition. Thus, the single ingredient anesthetic agent contains as a minimizer a therapeutically effective amount of anesthetic agent within the foregoing range.

The concentration as well as the quantity of anesthetic per square centimeter can be varied independently in order to achieve the desired effect. Higher concentrations of anesthetic base contained in

a dosage form of decreased thickness will result in a anesthetic with fast onset and short duration. High concentrations of the anesthetic base contained in a dosage form of increased thickness (higher mg of anesthetic per square centimeter) will result in potent anesthesia with fast onset and long duration. Low concentrations of the anesthetic base in a dosage form of decreased thickness will result in mild anesthesia with longer onset and short duration. Low concentrations of the anesthetic base contained in a dosage form of increased thickness will have mild anesthesia with longer onset and longer duration. As shown in the above explanation, the ability to vary the concentration of anesthetic from very low (about 1%) to high (40% or higher) of the total composition, when combined with the ability to coat thin (about 0.001 inches) or thick (about 0.500 or more inches) enables the practitioner of the invention to vary the dosage of the system as needed for particular anatomical sites of interest.

As a general rule, in the case of mucosal application, the anesthetic drug selected, the concentration and thickness and the duration of the application is determined based upon the anesthetic's ability to penetrate the mucosa and to be at peak effectiveness within about 2 to 30 minutes. The duration of the effect of the anesthetic on the oral mucosa should range between about 2 to 240 minutes, depending on the anesthetic agent selected, the concentration of the anesthetic and the thickness of application. Longer or shorter durations can also be selected dependent on need, as will be apparent to one skilled in the art.

The ratio of the free base form to the salt form in the alternate composition of this invention will depend on several factors, namely: (1) the

identity of the salt and base used; (2) the desired duration of action; and (3) the desired rapidity of anesthetic effect. As a general rule in the case of mucosal application, the ratios of base to salt are such that the free base form preferably should penetrate the mucosa and be at its peak effectiveness within about a 2 to 30 minute period, whereas, the salt form should preferably penetrate the mucosa and be at its peak effectiveness within a period of about 10 to 75 minutes. The duration of the effect of these on the oral mucosa will range between about 2 to 240 minutes depending on the base/salt combination selected and the length of application time.

The term "onset of anesthesia" is intended to mean the time to peak effect on the individual nerves. Onset of anesthesia principally depends upon the lipid solubility, molecular size, and quantity of available, un-ionized form of the local anesthetic. Thus, anesthetics with a high lipid solubility or a low pK_a, or both, have a more rapid onset of anesthesia.

The term "duration of anesthesia" as used herein means the period of time during which the local anesthetic measurably blocks nerve conduction. The foregoing depends upon all of the factors listed for onset of anesthesia, as well as on the extent of protein binding of the anesthetic agent.

The anesthetic agent free base can penetrate intact skin to a limited degree, and will more rapidly penetrate the skin if the keratin layers are abraded. In the case of the oral mucosa, the anesthetic base will penetrate much more readily due to the different keratin composition and the resulting difference in the hydrophilicity as compared to the stratum corneum of intact skin.

As a general rule, the salt forms of the aforementioned anesthetics do not appreciably penetrate intact skin, but the un-ionized base form do penetrate to a limited degree. Both forms, salt and base, will penetrate abraded keratin layers. The salt as well as the base will penetrate, to a differing degree, the buccal mucosa due to the buccal mucosa's hydrophilicity, as compared to the stratum corneum of intact skin. Generally, the higher the lipid content of the mucosal membrane, the more rapidly the base form of the anesthetic agent will be absorbed. Therefore, when the composition is used for application to oral or buccal mucosa, the different lipid contents of the gum (gingiva) and the alveolar mucosa must be kept in mind in order to obtain the optimal penetration rate.

Although applicants do not intend to be bound by any theory or proposed mechanism of operation, it is believed that the base which is lipid soluble has a rapid onset of anesthesia since it enters the lipo-protein nerve membrane preventing the depolarization and ion exchange involved in stimulus conduction. On the other hand, the salt which is not lipid soluble, penetrates to the lipo-protein nerve membrane only after the buffering capacity of the skin or mucosal tissue converts the salt to the base, the final result being a delayed onset of anesthesia.

The salts of this invention in the combination composition are selected on the basis of onset of anesthesia and duration of anesthesia. Adjusting the ratio of base to salt affects the relative onset as well as the duration of anesthetic action. The greater the amount of anesthetic agent having a rapid onset of action, the shorter the onset of anesthesia. Similarly, the greater the amount of the anesthetic agent having a prolonged duration of

anesthesia, the more prolonged the duration of anesthesia. More than two anesthetic agents may be used to have a broader spectrum of activity. Moreover, the composition can include other drugs used concomitantly.

Generally, the concentration of solubilized anesthetic agent can range, on a weight basis, between about 1 and about 50% or more, preferably between 2.5 and 40% and more preferably between 5 and 30% of the total weight of the composition. In a preferred embodiment of the combination of this invention, the concentration of dissolved base is 20% by weight of the total composition. The base used in the preferred embodiment for a single ingredient preparation is lidocaine.

Generally, for the hydrochloride salts the ratio by weight of base to salt is about 90:10 to about 60:40, preferably about 75:25 to about 60:40, and more preferably about 70:30 to about 60:40. For other salts, the ratios are comparable based on relative molar amounts. In a preferred embodiment of the invention, the ratio is about 2:1 base to salt, respectively. The base used in the preferred embodiment is lidocaine and the preferred salt is a salt of prilocaine, bupivacaine, dyclonine, mepivacaine, or tetracaine, preferably the hydrochloride salt.

Table 1 below summarizes the peak and duration of action of selected local anesthetics based primarily on application to skin or mucous membranes:

TABLE 1

Local Anesthetic	Minimum Adult Dose	Maximum Adult Dose (mg)	Peak Effect (minutes)	Duration of Effect (minutes)
Dibucaine		25	< 15	120-240
Lidocaine		750	2-5	30-60
Benzocaine		5000	1	30-60
Cocaine		50	2-5	30-120
Tetracaine		50	3-8	30-60
Dyclonine		100	< 10	< 60
Pramoxine		200	3-5	NA

NA: Not Available.

Source: Drug Facts and Comparisons, 1990 edition, J.B. Lippincott Company, St. Louis, MO. Page 601.

In general, the relative speed of onset of anesthesia and duration of anesthesia for any given form of anesthetic agent is available in the literature or can be calculated by standard tests.

Onset time, as well as duration of anesthesia, will vary from individual to individual as well as on the basis of the site of application. When applying the composition to highly keratinized dermal tissues, the onset of anesthesia may take as long as 2 to 4 hours.

The composition of this invention can be manufactured by numerous methods known in the art which permit the achievement of a microdispersed anesthetic agent, including extruding, molding, solvent casting, coating, and all other methods which employ a solvent to disperse the drug in a carrier prior to shaping of the carrier.

Contrary to the typical method for manufacturing a drug in a solvent containing adhesive, the preparation is either not dried so as to force removal of the solvent from the adhesive or a solvent

is used which is not substantially evaporated during the conditions of manufacture. The composition in question can then be applied to a flexible backing or a combination of backings which will serve to define the size and shape of a single dosage of the composition. Such backing may be a three dimensional material such as paper, a non-woven fabric or natural or synthetic polymer substance. Methods of coating backings are well-known in the art and include techniques involving Mayer rod, gravure, and knife-over roll. Further processing of backings may involve the use of converting equipment for die cutting.

The finished dosage form will be substantially occlusive to water permeation in in-vivo.

For example, the anesthetic agents are dissolved in a solvent, preferably a polyhydric alcohol, and then the resulting mixture is added to an adhesive prior to being placed onto the flexible form or backing. The final form in which the composition of the invention will be applied depends upon the anatomical site of application.

The phrase "flexible, finite" with reference to the pharmaceutically acceptable carrier, is intended to mean a solid capable of conforming to a surface with which it comes into contact and capable of maintaining the contact so as to facilitate topical application without any adverse physiological response, and which can be used to establish the compositions herein in their preferred solid form without being appreciably decomposed by aqueous contact during administration to a patient.

An important characteristic of the present invention relates to the substantially water-free and water-insoluble nature of the composition. By the term "substantially water-free" is meant that the

preparation contains less than about 10% by weight water, and preferably less than 5%, and most preferably less than 3%. In general, it is desirable to avoid the addition of water entirely and to eliminate, as far as possible, the presence of water in the other ingredients of the composition. By the term "substantially water insoluble" is meant that the composition remains "finite" and does not generally detach from the skin or other dermal membrane at the site of application and under the conditions of regular, intended use for a period of at least 3 hours. The advantages to be derived from the substantially water-free and water-insoluble nature of the compositions of the present invention include achievement of higher concentrations of drug. Another advantage of these compositions is minimization of precipitation of drug into crystals, which precipitation affects processing of the composition, affects rate of delivery of the drugs and in certain cases can affect sensitivity of the subject to be treated to the drug.

Suitable adhesive carriers include any of the non-toxic polymers, particularly those of the type used to carry drugs for transdermal delivery including natural or synthetic elastomers, such as polyisobutylene, styrene, butadiene, styrene isoprene block copolymers, acrylics, urethanes, silicones, styrene butadiene copolymers, methyl acrylate copolymers, acrylic acid, polyacrylates, and polysacchrides such as, karaya gum, tragacanth gum, pectin, guar gum, cellulose, and cellulose derivatives such as methyl cellulose, propyl cellulose, cellulose acetate and the like, along with other substances known for use in transdermal preparations capable of forming a solid colloid that can adhere to skin and mucosa, used alone or in

combination with other suitable carriers. A particularly preferred carrier is a bioadhesive and more preferably a polysaccharide bioadhesive for application to the dermis, preferably the mucosa. The adhesive can be modified so as to adhere to the skin or mucosal tissue, depending on the intended application site.

The term "adhesive" as used herein means a substance, inorganic or organic, natural or synthetic, that is capable of surface attachment to the intended application site.

The term "bioadhesive" as used herein means an adhesive which attaches and preferably strongly attaches to a live or freshly killed biological surface such as skin or mucosal tissue upon hydration. Indeed, to qualify as a bioadhesive, a substance must be capable of maintaining adhesion in moist or wet in *in-vivo* or *in-vitro* environments. The final composition of the present invention is "self-adhesive" in that it attaches to the site of interest without the need to reinforce its attachment by way of another adhesive which is applied to the composition.

The strength of adherence can be measured by standard tests for measuring the force, e.g. in dynes per square centimeter, as disclosed in U.S. 4,615,697. Suitable bioadhesives include those prepared from optionally partially esterified or etherified polyacrylic acid polymers, including but not limited to, polyacrylic acid polymers lightly cross-linked with a polyalkenyl polyether or other cross-linking agent such as those commercially available from B.F. Goodrich, Cincinnati, Ohio, under the trademarks Carbopol 934, 934P, 940 and 941.

Other suitable bioadhesives include natural or synthetic polysaccharides. The term "polysaccharide" as used herein means a carbohydrate

decomposable by hydrolysis into two or more molecules of natural or synthetic monosaccharides or their analogs or derivatives. Suitable polysaccharides include cellulose derivatives such as methylcellulose, cellulose acetate, carboxymethylcellulose, hydroxyethylcellulose and the like. Other suitable bioadhesives are pectin, a mixture of sulfated sucrose and aluminum hydroxide, hydrophilic polysaccharide gums such as natural plant exudates, including karaya gum, ghatti gum, tragacanth gum, xanthan gum, jaraya gum and the like, as well as seed gums such as guar gum, locust bean gum, psillium seed gum and the like.

In addition to the above ingredients, there may also be incorporated other additives selected from among the various pharmaceutically acceptable additives available to those skilled in the art. These additives include binders, stabilizers, preservatives, penetration enhancers, flavorings and pigments. In the preferred embodiment, the compositions of the present invention also contain a binder or emulsifier such as lecithin which promotes dispersion of the other ingredients having differing solubilities, thereby enhancing the uniform consistency of the final composition.

The composition is administered in appropriate sizes, typically having a surface area of from about 0.1 to about 200 cm^2 or conveniently 0.2 to 100 cm^2. The anesthetic agent is loaded into the composition in as high a concentration as necessary to effect therapy, e.g., in a range from about 0.1 mg/cm^2 to about 50 or more mg/cm^2.

In general, the composition can have the following types and amounts of ingredients:

Ingredient	Typical Range (% by weight)	Preferred Range (% by weight)	Optimum Range (% by weight)
Adhesive	15 to 60	20 to 50	20 to 35
Solvent	2 to 75	5 to 70	20 to 40
(plasticizer included in solvent)	1 to 50	5 to 50	10 to 30
Anesthetic agent (single ingredient)	1 to 50	5 to 40	10 to 30
Anesthetic agent (multiple ingredient)			
(a) Anesthetic base	.7 to 50	5 to 40	7 to 20
(b) Anesthetic salt	.3 to 25	2 to 30	3 to 20

In one embodiment, the flexible, finite, bioadhesive composition for topical application comprises:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active

agent is present in non-crystallized form in the composition.

In another embodiment, the flexible, finite composition of the invention comprises;

a composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a pharmaceutically acceptable, adhesive-containing carrier containing a solvent for the first and second local anesthetic agents.

wherein the composition is preferably substantially free of water, and substantially water insoluble and is self-adhesive; and wherein the anesthetic agents are in non-crystallized form in the composition.

Preferably, the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive carrier is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition. More preferably, the composition is comprised of 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and is further comprised of a binder in or emulsifier an amount sufficient to bind the other ingredients.

Another embodiment of the invention relates to a method of administering one or more local anesthetics to a subject in need of such local anesthetic. The term "administering" is intended to mean any mode of application which results in the physical contact of the composition with an anatomical

site in need of anesthesia. The term "subject" is intended to include all warm-blooded mammals, including humans.

The following examples will further describe the instant invention, and are used for the purposes of illustration only, and should not be considered as limiting in any way the invention being disclosed herein. Percent (%) as used in these examples refer to percentage of the liquid formulation on a weight to weight basis and temperatures are given in degrees celsius (°C).

Example 1

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (prilocaine hydrochloride)	14

The final product is manufactured by first blending the lidocaine base, prilocaine hydrochloride, propylene glycol, lecithin and glycerin at about 70 to 90°C until all of the drug is dissolved. The solution is then cooled to 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven, polyester film (for example, the film sold under the trademark Sontara 8100, manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed to about 100°C to accelerate the formation of the gel into its final, finite form.

Example 2

Ingredient	% (w/w)
Adhesive (karaya gum)	30
Solvent/plasticizer (glycerin)	30
Solvent (propylene glycol)	39
Anesthetic agent base (lidocaine base)	0.7
Anesthetic agent salt (prilocaine hydrochloride)	0.3

The procedure set forth in Example 1 is used with appropriate substitutions of quantities to prepare this formulation.

Example 3

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	4
Solvent (propylene glycol)	3
Solvent (isocetyl alcohol)	7
Solvent/plasticizer (glycerin)	26
Anesthetic agent base (lidocaine base)	26
Anesthetic agent salt (tetracaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 4

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Solvent (propylene glycol)	29
Solvent/plasticizer (glycerin)	4
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (dyclonine hydrochloride)	12

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 5

Ingredient	% (w/w)
Adhesive (karaya gum)	26
Binder (lecithin)	10
Solvent (propylene glycol)	7
Solvent (butylene glycol)	17
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (lidocaine base)	20
Anesthetic agent salt (dyclonine hydrochloride)	10

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 6

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	27
Anesthetic agent salt (bupivacaine hydrochloride)	13

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 7

Ingredient	% (w/w)
Adhesive (karaya gum)	27
Binder (lecithin)	12
Solvent (propylene glycol)	8
Solvent/plasticizer (glycerin)	13
Anesthetic agent base (lidocaine base)	13
Anesthetic agent salt (bupivacaine hydrochloride)	27

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 8

Ingredient	% (w/w)
Adhesive (karaya gum)	21
Binder (lecithin)	11
Solvent (propylene glycol)	7
Solvent/plasticizer (glycerin)	19
Anesthetic agent base (lidocaine base)	28
Anesthetic agent salt (mepivacaine hydrochloride)	14

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 9

Ingredient	% (w/w)
Adhesive (Carbopol 934P, a polycarboxylic acid sold by B.F. Goodrich Chemical Company)	20
Solvent (propylene glycol)	15
Solvent/plasticizer (glycerin)	20
Anesthetic agent base (lidocaine base)	30
Anesthetic agent salt (bupivacaine hydrochloride)	15

The procedure of Example 1 is used with appropriate substitution of ingredients to prepare this formulation.

Example 10

Ingredient	% (w/w)
Adhesive (karaya gum)	24
Solvent (propylene glycol)	3
Solvent/plasticizer (glycerin)	14
Solvent (isocetyl alcohol)	7
Binder (lecithin)	4
Anesthetic agent base (lidocaine base)	32
Anesthetic agent salt (tetracaine hydrochloride)	16

The above formulation is prepared by a procedure which is analogous to that set forth in Example 1.

The addition of up to 2% by weight water in this formulation did not result in precipitation of the anesthetic agent(s) prior to addition of the karaya gum. The addition of 3% to 10% water results in increased precipitation, which at 10% water results in a crystalline mass.

Example 11

Ingredient	% (w/w)
Adhesive (tragacanth gum)	24
Adhesive (pectin)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	12
Anesthetic agent base (mepivacaine base)	35
Anesthetic agent salt (lidocaine hydrochloride)	12

The above formulation is prepared by a procedure analogous to that of Example 1.

Example 12

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The final product is manufactured by first blending the lidocaine base, lecithin, propylene glycol, dipropylene glycol and glycerine at about 70 to 90°C until all of the drug is dissolved. The solution is then chilled to about 20 to 40°C prior to adding the karaya gum. Once the karaya gum is added, the final composition is applied to a suitable backing material such as a non-woven polyester film (for example the film sold under the trademark Sontata 8100 manufactured by DuPont de Nemours, E.I. and Co., Wilmington, DE) and warmed at about 70 to 130°C to accelerate the formation of the gel into its final

solid form. This gel can be directly applied to the oral mucosa or overlaid with a skin contact adhesive for skin adhesion.

Example 13

Ingredient	% (w/w)
Bioadhesive (karaya gum)	33
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	33
Anesthetic agent base (lidocaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 14

Ingredient	% (w/w)
Bioadhesive (karaya gum)	35
Binder (lecithin)	5
Solvent (propylene glycol)	7
Solvent (dipropylene glycol)	12
Solvent/plasticizer (glycerin)	36
Anesthetic agent base (lidocaine base)	5

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 15

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 16

Ingredient	% (w/w)
Bioadhesive (karaya gum)	20
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	10
Solvent (benzyl alcohol)	5
Anesthetic agent base (lidocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 17

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	8
Solvent (isocetyl alcohol)	5
Solvent (propylene glycol)	12
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (prilocaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 18

Ingredient	% (w/w)
Bioadhesive (karaya gum)	25
Binder (lecithin)	4
Solvent (propylene glycol)	6
Solvent (benzyl alcohol)	10
Solvent (dipropylene glycol)	10
Solvent/plasticizer (glycerin)	5
Anesthetic agent base (tetracaine base)	40

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 19

Ingredient	% (w/w)
Bioadhesive (karaya gum)	30
Binder (lecithin)	8
Solvent (propylene glycol)	12
Solvent (dipropylene glycol)	25
Solvent (benzyl alcohol)	5
Solvent/plasticizer (glycerin)	10
Anesthetic agent base (dibucaine base)	10

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation.

Example 20

Ingredient	% (w/w)
Bioadhesive (karaya gum)	28
Bioadhesive (Carbopol 934 Trademark of B.F. Goodrich)	2
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	15
Binder (lecithin)	9
Anesthetic agent base (lidocaine base)	25

The procedure of Example 12 is used with appropriate substitution of ingredients to prepare this formulation. The only difference is that the carbopol 934 is added to the original blend prior to heating it.

Example 21

Ingredient	% (w/w)
Bioadhesive (tragacanth gum)	27
Bioadhesive (pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is used with the solvents and anesthetic agent base added in the initial step followed later by the adhesives addition.

Example 22

Ingredient	% (w/w)
Bioadhesive (cellulose acetate)	27
Solvent (dipropylene glycol)	33
Anesthetic agent base (prilocaine base)	20
Solvent/plasticizer (glycerin)	10

This formulation is prepared according to the procedure which is analogous to the procedure set forth in Example 1.

Example 23

Ingredient	% (w/w)
Bioadhesive (Xanthan gum)	27
Bioadhesive (Pectin)	6
Binder (lecithin)	9
Solvent (propylene glycol)	6
Solvent (dipropylene glycol)	15
Solvent/plasticizer (glycerin)	17
Anesthetic agent base (lidocaine base)	20

The procedure of Example 12 is followed with the appropriate substitution of ingredients.

Example 24

Ingredient	% (w/w)
Drug (miconazole nitrate)	2
Solvent (propylene glycol)	67
Thickener (hydroxymethylcellulose)	1
Adhesive (karaya gum)	30

This formulation is prepared by dispersing the hydroxymethylcellulose into the propylene glycol. Once the hydroxymethylcellulose is dispersed, the drug is added at a temperature between 50 and 80°C and mixed until dissolved. The sample is then cooled to approximately 20 to 35°C prior to adding the karaya gum. Once the karaya gum is added, the formulation is applied to a sheet of backing material, then the individual dosage forms are cut to the desirable shape to contain the desired amount of drug.

Example 25

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	32.5
Plasticizer (glycerin)	32.5
Adhesive (karaya gum)	30.0

Example #25 is prepared just as Example #24.

Example 26

Ingredient	% (w/w)
Drug (miconazole base)	5.0
Solvent (dipropylene glycol)	17.5
Plasticizer (glycerin)	30.0
Solvent (propylene glycol)	7.0
Binder (lecithin)	10.5
Adhesive (karaya gum)	30.0

Example #26 is prepared just as Example #24.

Example 27

Ingredient	% (w/w)
Drug (miconazole base)	10
Solvent (propylene glycol)	35
Plasticizer (glycerin)	25
Adhesive (karaya gum)	30

Example #27 is prepared just as Example #24.

Example 28

Ingredient	% (w/w)
Drug (clotrimazole)	1.0
Solvent (propylene glycol)	41.3
Plasticizer (glycerin)	24.7
Adhesive (karaya gum)	33.0

Example #28 is prepared just as Example #24.

Example 29

Buccal formulations containing, respectively, 5%, 10%, 20%, and 25% lidocaine were prepared according to the procedure of foregoing

examples. A patch containing no drug (placebo patch) was also used.

The patches were tested on nine human subjects. The patch was applied to the buccal cavity of the mouth and removed after 15 minutes. The patch was placed on the gingival surface, since the gingival surface was found to be the best site to examine for a dose response relationship.

The extent of anesthesia at 5, 10, 15, 30, 45, and 60 minutes after application was determined by measurement of the extent of anesthesia. The exent of anesthesia was determined by a base line discomfort tolerance limit determined by application of a tip of a periodontal probe, to the treated surface. The patient was asked to determine the depth penetration they could tolerate at the various timed intervals.

Five minutes after initiation of treatment there was no statistical differences in pain toleration between the treatment groups, including the placebo and no-patch.

At ten minutes post application the 25% lidocaine patch produced the greatest mean change in response threshold followed by the 10 and 20% lidocaine patches. There was little difference between the 5% lidocaine and placebo patch. Lidocaine concentrations greater than 5% were necessary to produce a significant increase in pain threshold responses, and there was a distinct trend in dose proportionality in the range of 10% - 25% lidocaine.

The median change in response thresholds for the gingival surface group displayed the same relationship. The 25% lidocaine patch provided the greatest anesthetic effect followed by the 10% and 20% lidocaine patches.

When all the sites were combined into one group and the median change from baseline was plotted,

the graph revealed a dose response profile where the doses appear in order of concentration from 10 to 30 minutes post application. The 25% lidocaine patch provided the greatest increase in response threshold. The 10% and 20% lidocaine patch responses were similar with the 20% lidocaine patch being slightly better.

There were no signs of inflammation, tissue damage, or other adverse effects associated with application of the patches.

Similar studies were conducted in which the patch was applied to the gingival sulcus and the interproximal sulcus.

Certain of the lidocaine preparations were distinguised in that they resulted in the numbness of the teeth, an effect not generally observed with topical anesthetics applied in fluid vehicles.

The foregoing examples are illustrative embodiments of the invention and are merely exemplary. A person skilled in the art may make variations and modification without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as described in this specification and the appended claims.

Indeed, the present invention is intended to encompass and be suitable for any pharmaceutically active agent, especially any of the following drugs as the pharmaceutically active agent in the composition:

1. Analgesic anti-inflammatory agents such as, acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, l-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, alclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen, protizidic acid, fentiazac, tolmetin,

tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and the like;

2. Drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like;

3. Antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like;

4. Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like;

5. Steroids such as, androgenic steriods, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17β-estradiol, 17β-estradiol esters such as 17ß- estradiol

valerate, equilin, mestranol, estrone, estriol, 17β-estradiol derivatives such as 17ß-ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17α-hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like;

6. Respiratory agents such as, theophylline and β_2-adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, and the like;

7. Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like;

8. Antimicrobial agents including antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides, nitrofrantoin, anti fungals, such as, clotrimazole, miconazole, chloramphenicol, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like;

9. Antihypertensive agents such as, clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like;

10. Antihypertensive diuretics such as, chlorothiazide, hydrochlorothrazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like;

11. Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like;

12. Coronary vasodilators such as, organic nitrates such as, nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like;

13. Vasoconstrictors such as, dihydroergotamine, dihydroergotoxine, and the like;

14. β-blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like;

15. Calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like;

16. Anti-convulsantants such as, nitrazepam, meprobamate, phenytoin, and the like;

17. Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like;

18. Tranquilizers such as, reserprine, chlorpromazine, and antianxiety benzodiazepines such as, alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like;

19. Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, triflupromazine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranqulizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like;

20. Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine;

21. Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like;

22. Respiratory agents such as, codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like;

23. Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like;

24. Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like for dermatologically use;

25. Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like;

26. Enzymes such as, lysozyme, urokinaze, and the like;

27. Herb medicines or crude extracts such as, glycyrrhiza, aloe, Sikon (Lithospermi radix), and the like;

28. Miotics such as pilocarpine, and the like;

29. Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like;

30. Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like;

31. Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, hydroxyamphetamine, and the like;

32. Psychic energizers such as, 3-(2-aminopropy)indole, 3-(2-aminobutyl)indole, and the like;

33. Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE_1, $PGE_{2\alpha}$, and $PGF_{2\alpha}$, and the PGE_1 analog misoprostol.

34. Antispasmodics such as, atropine, methantheline, papaverine, cinnamedrine, methscopolamine, and the like;

35. Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like;

36. Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like;

37. Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like;

38. Anti-allergenics such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like;

39. Decongestants such as, phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like;

40. Antipyretics such as, aspirin, salicylamide, and the like;

41. Antimigrane agents such as, dihydroergotamine, pizotyline, and the like;

42. Anti-malarials such as, the 4-aminoquinolines, alphaaminoquinolines, chloroquine, pyrimethamine, and the like;

43. Anti-ulcer agents such as, misoprostol, omeprazole, enprostil, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsuflate, and the like;

44. Peptides such as, growth releasing factor, and the like;

45. Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like.

The drugs mentioned above can be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. If the drugs have a carboxyl group, their esters can be employed.

All the drugs used are in solid form at ambient, namely room, temperatures and pressures. However liquid drugs can also be employed to the extent that such drugs, in the forms and amounts used do not undesirably affect the adhesive properties of the carrier.

The acid mentioned above may be an organic acid, for example, methanesulfonic acid, lactic acid, tartaric acid, fumaric acid, maleic acid, acetic acid,

or ann inorganic acid, for example, hydrochloric acid, hydrobromic acid, phosphoric acid or sulfuric acid. The base may be an organic base, for example, ammonia, triethylamine, or an inorganic base, for example, sodium hydroxide or potassium hydroxide. The esters mentioned above may be alkyl esters, aryl esters, aralkyl esters, and the like.

When a drug different than an anesthetic agent is used the solvent selected is one in which the drug is soluble. In generally the polyhydric alcohol can be used as a solvent for a wide variety of drugs. Other useful solvents are those known to solubilize the drugs in question.

CLAIMS

1. A flexible, finite, bioadhesive composition for topical application comprising:

a therapeutically effective amount of at least one pharmaceutically active agent which is in solid form at ambient temperatures and pressures;

a pharmaceutically acceptable solvent for the pharmaceutically active agent, in an amount from about 5 to about 70 weight percent based on the weight of the whole composition, said solvent including about 5 to about 50 weight percent of a plasticizer for the bioadhesive;

in admixture with the pharmaceutically active agent in the solvent, a pharmaceutically acceptable polysaccharide bioadhesive in an amount from about 20 to about 50 weight percent based on the weight of the whole composition;

wherein the composition is substantially free of water, substantially water insoluble and self-adhesive; and wherein the pharmaceutically active agent is present in non-crystallized form in the composition.

2. The composition of claim 1, wherein the pharmaceutically acceptable solvent is in an amount from about 20 to about 53 weight percent based on the weight of the whole composition, of which the plasticizer represents about 10 to about 30 weight percent based on the weight of the whole composition, and the bioadhesive is in an amount from about 20 to about 34 weight percent based on the weight of the whole composition.

3. The composition of claim 1, wherein the pharmaceutically active agent is at least one local anesthetic in an amount of about 10 to about 40 weight percent based on the weight of the total composition.

4. The composition of claim 1, wherein the pharmaceutically active agent is from a class of drugs selected from the group consisting of analgesic anti-inflammatory drugs, central nervous system drugs, antihistaminic or antiallergic drugs, acitonide anti-inflammatory drugs, androgenic and estrogenic steroids, respiratory drugs, sympathomimetic drugs, antimicrobial drugs, antihypertensive drugs, cardiotonic drugs, coronary vasodilators, vasoconstrictors, beta blocking and antiarrhythemic drugs, calcium antagonistic and other circulatory anticonvulsants, anti-vertigo-tranquilizing drugs, antipsychotic drugs, muscle-reactants drugs, anti-Parkinson drugs, non-steroidal hormones, anti-hormones, vitamins, anti-tumor, enzymes, herb medicines or crude extracts, miotics, cholinergic agonists, antimuscarinic or muscarinic cholinergic blocking drugs, mydriatics, psychic energizers, humoral agents, antispasmodic drugs, antidepressants, antidiabetics, anorexic drugs, anti-allergic drugs, decongestants, antipyretics, anti-migraine drugs, antimalarial, antiulcer drugs, peptides, and anti-estrogens.

5. The composition of claim 4, wherein the antimicrobial drugs is an antifungal agent selected from the group consisting of chlotrimazole, miconazale and chloramphenicol

6. The composition of claim 4, in which the pharmaceutically active agent is one or more steroids selected from the group consisting of androgenic steroids, including testosterone; methyltestosterone; fluoxymesterone; estrogenic steroids, including conjugated estrogens, esterified estrogens, estropipate, 17ß-estradiol, 17ß-estradiol esters such as 17ß-estradiol valerate, equilin, mestranol, estrone, estriol; 17ß- estradiol derivatives such as

17β-ethinyl estradiol; diethylstilbestrol, progestational agents, including progesterone and progesterone analogs such as 19-norprogesterone, hydroxyprogesterone caproate, 17α-hydroxyprogesterone, dydrogesterone, medroxyprogesterone acetate; and norethindrone, norethindrone acetate, melengestrol, chlormadinone; ethynodiol diacetate, norethynodrel, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and anti-estrogen or anti-androgenic steroids.

7. The composition of claim 3, wherein the anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, chloroprocaine, tetracaine, bupivacaine, and etidocaine and is in the form of the base or an acid-addition salt or both forms.

8. The composition of claim 7, wherein the acid-addition salt is hydrochloride.

9. The composition of claim 1, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

10. The composition of claim 9, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum, guar gum, cellulose, and cellulose derivatives.

11. The composition of claim 1, wherein the solvent for the anesthetic agent is at least one polyhydric alcohol.

12. The composition of claim 11, wherein the polyhydric alcohol is a polyalkylene glycol.

13. The composition of claim 12, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol,

polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

14. The composition of claim 1, further comprising a backing material conforming to the size and shape of a single dosage of the composition.

15. The composition of claim 1 comprising about 20 to 34 weight percent of karaya gum, about 20 to 53 weight percent of at least one glycol, and about 10 to 25 weight percent of lidocaine base and further comprising a binder in an amount sufficient to bind the other ingredients.

16. The composition of claim 15 comprising about 30 weight percent of karaya gum, about 6 weight percent propylene glycol, about 15 weight percent of dipropylene glycol, about 15 weight percent of glycerine, about 25 weight percent of lidocaine base and about 9 weight percent of lecithin.

17. The composition of claim 15, comprising about 33 weight percent of karaya gum, about 7 weight percent of propylene glycol, about 12 weight percent of dipropylene glycol, 33 weight percent of glycerin, about 10 weight percent lidocaine base and about 5 weight percent lecithin.

18. The composition of claim 1 wherein the pharmaceutical agent comprises a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, local anesthetic agent in acid-addition salt form.

19. The composition of claim 18, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine

salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

20. The composition of claim 21, wherein the acid-addition salt is the hydrochloride.

21. The composition of claim 20, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

22. The composition of claim 21, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

23. The composition of claim 22, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

24. The composition of claim 23, wherein the polyhydric alcohol is a polyalkylene glycol.

25. The composition of claim 24, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, butylene glycol, hexylene glycol, polypropylene glycol, and sorbitol.

26. A method of administering one or more pharmaceutically active agent to a subject comprising the steps of:

providing the composition set forth in claim 1; and

contacting an area of skin or mucous membrane with the composition to administer the pharmaceutically active agent.

27. The method of claim 26, wherein the pharmaceutically active agent is an anesthetic agent selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine, chloroprocaine, tetracaine, bupivacaine, etidocaine, and dibucaine.

28. The method of claim 27, wherein the anesthetic agent is administered in the form of a free base.

29. The method of claim 28, wherein the anesthetic agent is administered in the form of an acid-addition salt.

30. The method of claim 29, wherein the solvent is at least one polyhydric alcohol.

31. The method of claim 30, wherein the polyhydric alcohol is a glycol or cycloalkanepolyol.

32. The method of claim 31, wherein the glycol is selected from the group consisting of dipropylene glycol, propylene glycol, polyethylene glycol, glycerin, butylene glycol, hexylene glycol, polypropylene glycol, sorbitol, and ethylene glycol.

33. The method of administering a pharmaceutically active agent of claim 26, wherein the pharmaceutically active agent is a combination of a therapeutically effective amount of a first local anesthetic agent in base form; and a therapeutically effective amount of a different, second local anesthetic agent in an acid-addition salt form.

34. The method of claim 33, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in acid-addition salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

35. The method of claim 34, wherein the acid-addition salt is hydrochloride.

36. The method of claim 35, wherein the bioadhesive is selected from the group consisting of polyacrylates, polyacrylic acids, gums and celluloses.

37. The method of claim 36, wherein the gum is selected from the group consisting of karaya gum, tragacanth gum, pectin gum, xanthan gum and guar gum.

38. The method of claim 37, wherein the solvent for the anesthetic agents is at least one polyhydric alcohol.

39. The method of claim 38, wherein the polyhydric alcohol is a polyalkylene glycol or cycloalkanepolyol.

40. The method of claim 39, wherein the glycol or polyol is selected from the group consisting of dipropylene glycol, propylene glycol, ethylene glycol, polyethylene glycol, and sorbitol.

41. The composition of claim 1, wherein the pharmaceutically active agent is an anti-microbial agent.

42. The composition of claim 41, in which the anti-microbial agent in an antifungal agent.

43. The composition of claim 42 in which the anti-microbial agent is clotrimazole.

44. The composition of claim 43 in which the anti-microbial agent is miconazole.

45. A composition for topical application comprising a therapeutically effective amount of a first local anesthetic agent in base form and a therapeutically effective amount of a different, second local anesthetic agent in salt form in a flexible, finite, pharmaceutically acceptable adhesive-containing solvent for the first and second local anesthetic agents.

46. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, lidocaine,

prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine, and chloroprocaine.

47. The composition of claim 45, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

48. The composition of claim 45, wherein the first local anesthetic agent in base form is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent in salt form is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

49. The composition of claim 48, wherein the salt is the hydrochloride.

50. The composition of claim 45, wherein the adhesive is a bioadhesive.

51. The composition of claim 50, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

52. The composition of claim 50, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

53. The composition of claim 50, wherein the bioadhesive is karaya gum.

54. A method of delivering local anesthetic agents which comprises the topical administration to a mammal of a composition comprising:

a therapeutically effective amount of a first local anesthetic agent in base form and

a therapeutically effective amount of a different, second local anesthetic agent in salt form

in admixture with a flexible, finite, pharmaceutically acceptable, adhesive; and

a solvent in the adhesive for the first and second local anesthetic agents.

55. The method of claim 54, wherein the first local anesthetic agent is selected from the group consisting of procaine, dyclonine, lidocaine, prilocaine, mepivacaine, benzocaine, propoxycaine and chloroprocaine and the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt, and a dibucaine salt.

56. The method of claim 55, wherein the salt is a hydrochloride.

57. The method of claim 54, wherein the adhesive is a bioadhesive.

58. The method of claim 57, wherein the first local anesthetic agent is selected from the group consisting of procaine, lidocaine, prilocaine, mepivacaine, dyclonine, dibucaine, benzocaine, propoxycaine and chloroprocaine.

59. The method of claim 57, wherein the second local anesthetic agent is selected from the group consisting of a dyclonine salt, a prilocaine salt, a tetracaine salt, a bupivacaine salt, a mepivacaine salt, a lidocaine salt, a procaine salt, an etidocaine salt and a dibucaine salt.

60. The method of claim 57, wherein the bioadhesive is karaya gum.

61. The method of claim 59, wherein the salt is a hydrochloride.

INTERNATIONAL SEARCH REPORT

International Application No PCT/US 92/01730

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 A 61 K 9/70 A 61 L 15/44

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	A 61 K A 61 L

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	DD,A, 217989 (ERNST MORITZ ARNDT UNIVERSITÄT GREIFSWALD) 30 January 1985, see the whole document	9
A	EP,A,0250187 (JOHNSON & JOHNSON PRODUCTS INC.) 23 December 1987, see page 3, line 1 - page 4, line 41; pages 7-9, examples 2-4; pages 11,12, examples 6,7	1-61
A	EP,A,0363224 (BLOCK DRUG CO. INC.) 11 April 1990, see pages 7,8, examples 1,2	1-61
A	WO,A,8910740 (INNOVATA BIOMED LTD) 16 November 1989 -/-	1-61

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
16-07-1992	11. 08. 92
International Searching Authority: EUROPEAN PATENT OFFICE	Signature of Authorized Officer: Mme Dagmar FRANK

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	LU,A, 52460 (ASTRA PHARMACEUTICAL PRODUCTS) 25 June 1968, see the whole document, in particular page 5, lines 17-23; page 18, example 7	1-61

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/01730

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: please see remark
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-40 and 54-61 are directed to a method of treatment of the human/animal the search has been carried out and based on the alleged effects of the composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. US 9201730 SA 58216

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 04/08/92
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DD-A- 217989		None	
EP-A- 0250187	23-12-87	US-A- 4713243	15-12-87
		AU-A- 7415587	17-12-87
		JP-A- 63019152	26-01-88
		US-E- RE33093	17-10-89
EP-A- 0363224	11-04-90	AU-A- 4265689	12-04-90
		CA-A- 2000277	07-04-90
		JP-A- 2196717	03-08-90
WO-A- 8910740	16-11-89	None	
LU-A- 52460	25-06-68	BE-A- 690383	29-05-67
		DE-A- 1617282	06-02-75
		FR-M- 6733	24-02-69
		GB-A- 1108837	
		NL-A- 6616878	31-05-67

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

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(54) Title: WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE AND DEVICES PROVIDED THEREWITH FOR EMPLACEMENT IN A MUCOSA-LINED BODY CAVITY

(57) Abstract

Water-soluble pressure-sensitive adhesives include a water-soluble polymer that is made tacky at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable polymers are solid at room temperature; and have a hydrophilicity as measured by water uptake greater than about 25 %; they are liquid at room temperature and have a boiling point higher than about 80 °C. The adhesives according to the invention may conveniently be provided in dry film form. Preferred water-soluble pressure-sensitive adhesives of the invention adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity that has a mucosal lining. Also, a laminated device for the controlled release of a substance within a mucosa-lined body cavity includes the substance dissolved or dispersed in either or both of a water-soluble pressure-sensitive adhesive layer and optionally one or more water-soluble polymer layers. Also, devices for administering a substance over an extended time for relief of sore throat or cough, or for administering a breath freshening agent, particularly a mint odorant, include a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

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WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE AND DEVICES PROVIDED THEREWITH FOR EMPLACEMENT IN A MUCOSA-LINED BODY CAVITY

Background

Technical Field

This invention relates to mucoadhesives and to mucoadhering devices. Additionally and particularly this invention relates to compositions that adhere both to mucosal surfaces and to a variety of materials that may constitute a part of a device or prosthesis to be held in a body cavity, such as the oral cavity or the vagina or the rectum, that has a mucosal lining. Additionally this invention relates to mucoadhering devices useful for controlled release of substances within a body cavity that has a mucosal lining, such as for example the oral cavity, and particularly to such devices that are provided with adhesives suitable for fixation of the device within the oral cavity. Additionally and particularly this invention relates to administering breath-freshening agents, and particularly mint odorants, into the oral cavity of a person over extended time periods, for freshening the person's breath. And additionally this invention relates to administering agents into a person's oral cavity over extended times for relief of sore throat pain and cough.

Background Art

For a number of practical purposes, it can be useful to affix a device within a mucosa-lined body cavity, such as the oral cavity, the vaginal

cavity, or the rectal cavity. Devices that may usefully be positioned within a mucous-lined body cavity include, for example, denture prostheses and devices for controlled release of medicaments.

In one approach for such purposes, the device can be affixed to a mucosal surface of the body cavity by means of an adhesive. Various bioadhesives have been proposed for use in establishing adhesive contact with mucosal surfaces.

For example, U.S. Patent No. 4,713,243 describes an extruded film for use in controlled release of medicaments, including a water-soluble or swellable polymer matrix capable of adhering to a wet mucous surface, made up of 40 - 95 % hydroxy propyl cellulose, 5 - 60 % poly(ethylene oxide), optionally up to 10 % of a water-insoluble polymer (ethyl cellulose, propyl cellulose, polyethylene or polypropylene) and 2 - 10 % of a plasticizer introduced to facilitate processing, and containing the medicament. There is no disclosure in the '243 patent that this composition can adhere to materials that may be used in oral prosthesis or other devices, or that it is pressure-sensitive.

Adhesives for affixing dental prostheses in the mouth are conventionally in the form of pastes or creams. These are messy and inconvenient to use, and generally adhere poorly or not at all after extended periods.

U.S. Patent No. 4,529,748 describes a dental prosthesis adhesive in powder form, in which the particles are made from carboxy methyl cellulose, poly(ethylene oxide), poly(acrylic acid), and karaya gum. Some portion of the particles are coated with a cellulose or acrylate polymer film that dissolves slowly in saliva.

U.S. Patent No. 4,948,580 describes a bioadhesive composition for delivery of anti-bacterials, including a copolymer of ("PVME/MA"), and gelatin, dispersed in an ointment base.

International Patent Publication No. WO 91 16041 (Oct. 31, 1991) describes a pharmaceutical composition, to be held under the tongue, in the

form of a thin starch wafer capable of molding to the contours of the sub-lingual cavity, thereby allowing for absorption of medicaments contained within the wafer through the sub-lingual mucosa.

Conventionally, medications for treatment for relief of sore throat and cough are provided in a form such as a lozenge to be held in the mouth of the person being treated, or in the form of a mouthwash or spray. These forms of delivery work generally by shedding the medication into the saliva, which bathes the tissues of the oral cavity and throat as it passes posteriorly toward the esophagus. Such forms remain in the oral cavity only for short periods of time, generally in the range up to about 10 or 20 minutes, and they cannot provide for delivery of the medication to the oral cavity over extended times. In these forms the treatment must be readministered at short time intervals to be effective. The rate at which the medication is delivered from a lozenge can depend upon how actively the user agitates it, that is, how vigorously the user sucks on the lozenge, and whether the user breaks it with the teeth.

Moreover, the presence of a lozenge in the user's mouth can be annoying or distracting, and may interfere with speech or with ingestion of fluids. Holding the lozenge in the mouth—that is, avoiding either swallowing it or spitting it out—requires conscious effort, and inadvertent loss can be embarrassing.

U.S. Patent No. 4,927,634 (May 22, 1990) describes a incorporation of Dyclonine HCl and phenol into base vehicles such as lozenges, drops or troches. U.S. Patent No. 4,503,070 (March 5, 1985) describes administering zinc gluconate to the oral mucosa in the form of a troche or lozenge to reduce the duration of common cold symptoms.

U.S. 4,139,627 (Feb. 13, 1979) describes including a pharmaceutically acceptable acid in a process for making a lozenge containing Dyclonine HCl; the acid acts as a stabilizing agent during processing to prevent degradation of the Dyclonine HCl.

Nearly everyone at least occasionally has malodorous breath. Bad breath may be caused by consumption of strongly flavored food or drink or by use of tobacco, for example, or it may be caused by poor oral hygiene. It may be a symptom of, or may result from, a disease or metabolic condition. The condition may be temporary or chronic, and may be mild, so as to be merely somewhat unpleasant, or may be so severe as to interfere with ordinary social interaction.

Because bad breath (often termed "halitosis", particularly when the condition is severe) is so common a source of embarrassment, considerable attention has been directed to trying to prevent or mask it. In some instances, the condition may not be prevented except by correction of an underlying disease or metabolic disorder, or by improvement in oral hygiene. Some instances of halitosis are so extreme that they cannot be masked. Many cases of ordinary bad breath can be masked by use of an odorant in the mouth and throat that contributes a pleasant smell to the exhalant breath of the person. In many cultures, various mint odorants are commonly accepted on the breath.

Odorants, such as mint odorants, are conventionally administered to the mouth in the form of a spray or mouthwash. Sprays and mouthwashes provide only very temporary mask, as they are quickly washed away by ordinary salivary secretions.

Also conventionally, odorants are administered in a lozenge, or in chewing gum. Lozenges can provide for somewhat more extended administration than sprays or mouthwashes, as the odorant is continuously shed as the lozenge dissolves in the saliva. Chewing gums can also provide for somewhat more extended administration, although the odorant may after some fairly short time be delivered at such a slow rate as not to be effective. As note above, the presence of a lozenge or chewing gum in the person's mouth can be annoying or distracting, and may interfere with speech or with ingestion of fluids. Other persons can be distracted or annoyed by a

person's chewing gum, and in some social circumstances chewing gum is not accepted.

Summary of the Invention

We have discovered water-soluble pressure-sensitive mucoadhesives that can be used for affixing devices within a mucosa-lined body cavity. The water-soluble pressure-sensitive adhesives of the invention can be used in construction of devices for emplacement within a body cavity that has a mucosal lining, as for example on a mucosal surface within the body cavity. Some of the water-soluble pressure-sensitive mucoadhesives according to the invention additionally adhere to a variety of materials, such as polymers, that are conventionally employed in the construction of devices, such as dental prostheses, which are held in the mouth.

Thus the mucoadhesive compositions according to the invention can be used to affix any device within the body cavity, such as, for example, a dental plate. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

The pressure-sensitive adhesives of the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the adhesive eventually dissolves completely within the body cavity in which it is placed, and the dissolved or dispersed matter is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal. Pressure-sensitive adhesives according to the invention require no moistening prior to contact with the mucosal or the polymer surface.

The adhesives are additionally particularly useful in construction of laminated devices for controlled delivery of substances within a mucosa-lined body cavity. The invention therefore provides devices having an adhesive surface suitable for affixing to a mucous surface of a mucosa-lined

body cavity such as the mouth or throat, the vagina, or the rectum, or that is suitable for affixing to the dental surface or to the surface of various forms of prosthesis that may be used in the body cavity, such as for example dentures. Devices according to the invention are provided in various configurations, each configuration providing for controlled delivery of one or more substances from a single device according to one of a variety of schedules. Selected devices according to the invention can provide, for example, delayed onset delivery, pulsed delivery, and sequential delivery of two or more substances.

In some configurations, the adhesive itself serves as a reservoir for the substance to be delivered, and releases the substance into the body cavity as the adhesive dissolves. In some configurations a laminate construction includes at least one polymer layer in addition to the adhesive layer. Each such configuration releases one or more substances according to a desired timed delivery regime. In various configurations, for example, onset of release may be delayed following placement of the device within the body cavity; or, for example, a substance may be released at different rates over time, or in pulses with intervening periods in which substantially no release occurs; or, for example, two or more substances may be sequentially released, with or without an intervening period in which substantially no substance is released. The pattern of release is established according to the invention by the sequential arrangement of laminae containing the substance(s) and, in some configurations, laminae not containing the substance(s) or containing fewer than all the substances. The release rate for a substance from a particular layer is determined principally by the rate at which the layer dissolves or disperses in the fluid milieu of the body cavity, together with the concentration of the substance in the layer. Release from a particular more basally situated layer is delayed by overlying layer(s), and the duration of the delay in delivery from such a particular layer is determined principally by the time required for the overlying layer(s) to disperse.

To a limited extent, whether or not a particular layer dissolves or disperses in the fluid milieu of the body cavity, a substance may in time move diffusionally out from the layer, so that the concentration of the substance within the layer falls. Such diffusional movement may result in release of the substance into the body cavity or, where the layer is the mucoadhesive layer, release of the substance transmucosally through the contacting mucosal surface. Or, where the particular layer is covered by an overlying layer, the substance may diffuse into and through the overlying layer. Where such diffusional release is undesirable, it may be limited by rendering the overlying layer substantially impermeable to the substance, so that release from the overlain layer is occluded until such time as the overlying layer has dissolved or dispersed. Suitably occluding layers can be constructed of a water-soluble polymer composition containing as an additive a nonorganic filler such as silica gel, or a fatty acid filler such as magnesium stearate, or a wax such as a paraffin, for example. For extended delayed onset, for example, a slow-dissolving substantially substance-impermeable top layer can be constructed of a hydrophobic material such as hydroxypropyl cellulose, thereby achieving a temporary occlusive (partially occlusive, at least) effect. Such a modification may be made by a change in the polymer constituents of the top layer, or by introduction of additives into the layer itself.

The adhesive can be mucoadhesive, or it can adhere to the surface of the teeth or to a variety of materials, such as polymers, that can be used in the construction of devices that are emplaced within the mucosa-lined body cavity (such as, for example, poly(methyl methacrylate), commonly used in dental prosthesis in the oral cavity). Some adhesives according to the invention are mucoadhesive and adehere to polymer surfaces such as PMMA. The adhesive can be a moistenable adhesive or, alternatively and in some instances preferably, it can be a pressure-sensitive adhesive.

In some embodiments of laminated devices of the invention all the layers are water-soluble (or, for example, are digestible), and they therefore

dissolve or disperse entirely in the fluids secreted within the body cavity. In such embodiments the adhesive layer and the additional polymer layer(s) dissolve and are carried away at or following the time when the substance(s) have diffused away from the device. Preferred materials for the polymer layers as well as for the adhesive layers are for some applications therefore GRAS-certified or NF-certified, so that they are fully acceptable for oral use and for ingestion by humans.

We have further discovered that active substances, useful for relief of sore throat or of cough, can be delivered into the oral cavity over extended times by including the active substance within a water soluble pressure sensitive mucoadhesive device, and applying the mucoadhesive device to a mucosal surface within the oral cavity.

Such a device for temporary relief of sore throat or cough may be a layered composite, including a polymer layer that contains the active substance, and a mucoadhesive layer that serves to affix the active-containing layer to a mucosal surface such as the palate, the gum, or the cheek. Because the materials of the layers are water soluble, and therefore fully soluble in secretions present in mucous-lined body cavities, the device eventually dissolves completely within the oral cavity, and passes on to the alimentary canal. As the material of the active-containing layer dissolves in the fluid secretions, within the oral cavity, the active disperses in the fluid secretions and is distributed throughout the oral cavity and on to the throat.

In many applications delivery of an active substance into a mucosa-lined body cavity desirably is provided over an extended time. We have developed polymer compositions that dissolve slowly within the fluid secretions of the oral cavity, and that can include an active substance and can be deployed in a suitably thin layer within the oral cavity to deliver the active substance over extended times in excess of 1 hour. A desired rate of dissolution for a particular device configuration can be selected by choice of materials and proportions of materials in the active-containing polymer

composition. Generally, the dissolution rate, together with the thickness of the active-containing polymer layer, determines the extent of the delivery time for the active substance.

The rate of delivery of the active substance over the delivery time can be selected by choosing an appropriate amount of the active substance in the active-containing layer as well as by choosing an appropriate polymer composition. Polymer compositions according to the invention are capable of delivery of active substances over extended times.

Preferred water soluble adhesives may be permeable to particular active substances; that is, while the active substance is released into the oral cavity as the active-containing polymer layer dissolves, it may additionally pass by diffusion into and through the adhesive layer, and then into and through the mucosal surface onto which the adhesive layer is affixed. Where delivery of the active substance to the mucosa underlying the device is not desired, an additional water-soluble layer, poorly permeable to the active substance, may be interposed between the active-containing layer and the adhesive layer, to substantially prevent movement of the active substance into the adhesive layer.

Any of a variety of active substances may be delivered using delivery devices constructed according to the invention. For relief of sore throat pain, for example, substances such as benzocaine, lidocaine, dyclonine, and the like, which are available over the counter in syrup or tablet form, may be used. For relief of cough, for example, substances such as dextromethorphan HBr, noscpine, codeine phosphate, menthol, and the like, may be used. Further, both a sore throat medication and a cough suppressant can be combined within and delivered from a single device according to the invention.

The invention provides for continuous delivery of the medication over an extended time, providing for relief of sore throat pain for longer times, in the range up to about 1 to 4 hours, than can be provided by conventional means. Location of the disc on the upper palate helps localize the

medication nearer to the site of soreness upon swallowing during normal salivary flow.

We have further discovered that odorants suitable for masking bad breath, and particularly mint odorants, can be administered into the oral cavity over extended times by including the odorant within a suitable water soluble pressure sensitive mucoadhesive device, and applying the mucoadhesive device to a mucosal surface within the oral cavity.

The breath freshening device may be a layered composite, including a water soluble polymer layer that contains the mint odorant, and a water soluble mucoadhesive layer that serves to affix the odorant-containing layer to a mucosal surface such as the palate, the gum, or the cheek. Because the materials of the layers are water soluble, and therefore fully soluble in secretions present in mucous-lined body cavities, the device eventually dissolves completely within the oral cavity, and the dissolved material passes on to the alimentary canal. As the material of the odorant-containing layer dissolves in the fluid secretions, within the oral cavity, the odorant disperses in the fluid secretions and is distributed throughout the oral cavity.

We have developed polymer compositions that dissolve slowly within the fluid secretions of the oral cavity, and that can include an odorant and can be deployed in a suitably thin layer within the oral cavity to deliver the odorant over extended times in excess of 1 hour. A desired rate of dissolution for a particular device configuration can be selected by choice of materials and proportions of materials in the odorant-containing polymer composition. Generally, the dissolution rate, together with the thickness of the odorant-containing polymer layer, determines the extent of the delivery time for the odorant.

The rate of delivery of the odorant over the delivery time can be selected by choosing an appropriate amount of the odorant in the odorant-containing layer. Polymer compositions according to the invention are capable of delivering odorants over extended times at high enough

concentrations to contribute a continuous pleasant smell to the exhalant breath sufficient to mask bad breath odor.

Preferred water soluble adhesives may be permeable to certain mint odorant components; that is, certain of the mint odorant components may by diffusion pass into and through the adhesive layer, to the mucosal surface onto which the adhesive layer is affixed. Because some mint odorant components may be irritating to the mucosa or may cause an unpleasant local numbing effect on the mucosa when present in higher amounts, it may be desirable to avoid delivery of the odorant to the underlying mucosa. This can be accomplished according to the invention by interposing an additional water-soluble layer, poorly permeable to the odorant components, between the odorant-containing layer and the adhesive layer, to substantially prevent movement of the odorant components into the adhesive layer.

Any of a variety of odorants may be delivered according to the invention, and any of various mint odorants, as described below, may be particularly desirable.

Because the device according to the invention remains affixed to a surface of the oral cavity during use, no conscious effort by the user is required to hold the device in place, and the likelihood that it may be swallowed or spit out of the mouth during use is diminished. As the device has a thin profile, and conforms smoothly to the surface of the oral cavity, it is not mechanically annoying and does not interfere with speech or with ingestion of foods or fluids.

Disclosure of the Invention

Water-Soluble Pressure-Sensitive Adhesives

In one general aspect, the invention features a water-soluble pressure-sensitive adhesive including a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable

polymers are characterized as being solid at room temperature (that is, as having a glass transition temperature T(g), or melting point T(m), higher than about 25 °C, and more preferably higher than about 30 °C, and lower than about 120 °C, and more preferably lower than about 100 °C); and having a hydrophilicity as measured by water uptake greater than about 25 %. Suitable plasticizers are characterized as being liquid at room temperature and having a boiling point higher than about 80 °C.

Suitable polymers include polysaccharides such as for example cellulose-type materials and natural gums, polypeptides, and water-soluble synthetic polymers. Particular examples of such suitable polymers which are GRAS certified include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934 (B.F. Goodrich), starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In some embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, as well as to human skin.

In other embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50

weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k.

In another general aspect, the invention features a water-soluble pressure-sensitive adhesive film made up of a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In preferred embodiments the thickness of the film is in the range of about 5 - 20 mils, and is shaped to fit and to conform generally to a mucosal surface-contacting portion of a dental prosthesis such as a dental plate. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Such a film can be used as a denture adhesive, that can adhere to oral mucosal surfaces and to dental prosthesis for an extended period, typically of more than about 5 hours. The film can be used as part of a system for delivery of substances through the oral mucosa (as a buccal transmucosal patch), or for delivery of substances into the oral cavity itself.

Device Having a Water-Soluble Pressure-Sensitive Adhesive for Emplacement in a Mucosa-Lined Body Cavity

In another general aspect, the invention features a laminated device for controlled release of one or more substances within a mucosa-lined body cavity, having an adhesive layer by means of which the device can be affixed within the body cavity.

In some embodiments the mucoadhesive layer is water-soluble, constructed in some embodiments of a water-soluble moistenable mucoadhesive, and in some embodiments of a water-soluble pressure-sensitive mucoadhesive; in some embodiments the adhesive adheres to a

variety of materials, such as polymers, that can be used in construction of devices for emplacement on a
mucosal surface or within a body cavity that has a mucosal lining; or it is mucoadhesive and additionally adheres to such materials. Preferably the water-soluble pressure-sensitive adhesive requires no moistening prior to contact with the mucosal or the polymer surface. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments for oral mucosal contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 65 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere well to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments for oral mucosal contact a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 100 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 5 - 35 weight %). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more

preferably between about 100 k and about 300 k. The water-soluble pressure-sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In preferred embodiments the device includes at least one water-soluble polymer layer in addition to the water-soluble pressure-sensitive adhesive layer. This water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof. In a particular embodiment, sorbitan monostearate (SPAN 60) with hydroxypropyl cellulose (HPC LF) is useful.

The pressure-sensitive adhesive layer and, in some embodiments, one or more of the polymer layers in the device according to the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the pressure-sensitive adhesive layer and the water-soluble polymer layers eventually dissolve completely within the body cavity in which the device is placed, and the material of the dissolved layers is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal.

According to the invention, the adhesive serves to keep the device in place within the body cavity, and release of the substance or substances is controlled by the particular arrangement of layers.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

In a further general aspect, the invention features a device for emplacement within a mucosa-lined body cavity of a subject, the device

including a portion made of a water-soluble pressure sensitive adhesive composition. A surface of the water-soluble pressure sensitive adhesive portion forms a basal surface of the device which, when the device is in use, is affixed to a surface of the body cavity.

The adhesive compositions providing an adhesive surface of the device of the invention are pressure-sensitive; that is, the adhesive surface of the device requires no wetting prior to contacting it with the body cavity surface to which it is to be affixed.

The adhesive compositions are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the adhesive eventually dissolves completely within the body cavity in which the device is placed, and is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the device is emplaced within the body cavity by contacting the adhesive surface with a mucosal surface within the body cavity or with a surface of a prosthesis that is employed within the body cavity, and for such embodiments the water-soluble pressure sensitive adhesive composition preferably includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to

about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to mucosal surfaces as well as to surfaces of prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k. In some embodiments the device is a device for delivery of one or more substances into the body cavity or across the mucosa. Typically the device has a laminated structure, and the water-soluble pressure sensitive portion is a basal layer of the device. Conveniently, the water-soluble pressure sensitive adhesive portion of such a device is constructed as a film made up of an adhesive composition as described above. In preferred embodiments the film has a thickness in the range about 5 - 20 mils, and is shaped to fit and to conform generally to the surface to which the device is intended to be attached for use. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In some embodiments the device when in place within the body cavity provides a protective barrier for the area of the mucosal surface to which it is affixed which is covered by the device. The barrier may protect the underlying mucosal surface from mechanical abrasion or erosion, for example, or, for example, it may serve to protectively isolate the underlying mucosal surface from some substance in the fluid of the milieu of the body cavity.

Where the device is a laminated device for delivery of an active agent, and includes an upper active-containing layer laminated to an adhesive layer, or where the device provides a protective barrier, and includes an upper barrier layer laminated to an adhesive layer, the upper layer is preferably constructed of a hydrophobic polymer material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

The rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component: a given polymer type dissolves or disperses more slowly at higher molecular weights than at lower molecular weights. In some embodiments the active-containing layer includes a polymer such as hydroxypropyl cellulose, and may additionally include a plasticizer such as glycerin. In a particular embodiment, hydroxypropyl cellulose (HPC Klucel LF), having a molecular weight of 80,000, with glycerin as a plasticizer, is useful.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

In yet another general aspect, the invention features a layered composite mucoadhesive device for delivery of an active substance into the oral cavity, having an active-containing layer that includes the active substance dispersed or dissolved in a water soluble polymer, and a water soluble adhesive layer.

In some embodiments the active-containing water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The

material may further be hot water dispersible and may have non-tacky surface properties upon moistening. As noted above examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

Also as noted above, the rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component; a desired release rate can be specified by choice of the polymer or polymer combination.

In some embodiments the adhesive for use in the adhesive layer of the invention is a water-soluble pressure-sensitive adhesive according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

Additional ingredients, such as, for example, deodorants or reodorants or flavorants, may be delivered along with the active substance as the active-containing layer disperses within the oral cavity. Such additional ingredients include, for example, sweeteners such as aspartame, and breath fresheners such as menthol.

In another general aspect the invention features a method for administering a substance over an extended time period for relief of sore throat or cough. The method involves dissolving or dispersing the substance in a laminated water soluble device that has a water soluble pressure sensitive adhesive layer. The device is affixed to the mucosal surface of the oral cavity.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

In still another general aspect, the invention features a laminated composite device for administering an odorant into the oral cavity over an extended time. The device has at least two layers, including a basal layer constructed of a water soluble pressure sensitive mucoadhesive polymer composition; and an odorant-containing water soluble polymer layer.

In some embodiments the basal adhesive layer is mucoadhesive and additionally adheres to a variety of materials, such as polymers, that can be used in construction of devices for emplacement on an oral mucosal surface or within the oral cavity. The basal adhesive layer preferably is constructed of a water soluble pressure sensitive adhesive that requires no moistening prior to contact with the mucosal or the polymer surface. The adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the odorant containing layer includes a polymer such as a hydroxypropyl cellulose, and in a particular embodiment may additionally include a plasticizer such as glycerin. The rate of release of the odorant within the oral cavity can be specified by selection of particular polymer or polymer combinations, as noted generally above under the heading "Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity". In a particular embodiment, a hydroxypropyl cellulose (HPC Klucel GF), having a molecular weight of 300,000, is useful.

The water soluble odorant containing layer may take the form of a film which preferably is about 20 - 30 mils thick. Suitable slow-dissolving polymers such as HPC are typically not sufficiently flexible to conform with the irregularly curved surfaces of the oral cavity or of oral or dental prostheses, and addition of a plasticizer to the polymer or polymer mixture of films would be required for these applications. Suitable plasticizers can include glycerin, for example.

In some embodiments the odorant is an essential oil of a plant material, or a refined fraction of an essential oil, or a combination of the chief aromatic constituents of an essential oil. Preferably the odorant is a mint odorant. We have discovered that, surprisingly, the essential oils that are commonly used as flavorings, particularly oil of wintergreen, oil of peppermint, and oil of spearmint, are themselves effective as plasticizers. For breath freshener devices for delivering a mint odorant, therefore, the odorant containing layer therefore can consist of the polymer and the mint odorant (and, optionally, a sweetener and a preservative), without any requirement for a plasticizer other than the mint odorant.

Accordingly, in another aspect the invention features a laminated composite device for administering a mint odorant into the oral cavity over an extended time, comprising a basal layer constructed of a water soluble pressure sensitive mucoadhesive composition and an upper layer containing a water soluble polymer, such as a HPC, and a mint oil.

Extended delivery of odorant can be obtained according to the invention from devices whose composite thickness is 35 mils or less. The devices according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Breath freshening devices according to the invention can deliver a mint odorant such as a peppermint continuously over a period of up to two hours or longer from a single device, and can provide breath freshening for even greater periods of time.

Description of Preferred Embodiments

Preferred embodiments of the invention will now be described, beginning with a brief description of the drawings.

Brief Description of the Drawings

Fig. 1 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances at two different rates.

Fig. 2 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances.

Fig. 3 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances in a sequence of pulses.

Fig. 4 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances while minimizing diffusion of the substance(s) at the edges of the device.

Figs. 5 through 7 are rough hypothetical plots showing quantity of an active substance released by devices of the invention configured on the plans shown in Figs. 1 through 3, respectively.

Fig. 8 is a sketch in transverse sectional view showing a bilaminate device according to the invention.

Fig. 9 is a sketch in transverse sectional view showing a trilaminate device according to the invention.

Fig. 10 is a plot of data showing the cumulative release of Dyclonine HCl into water from a mucoadhesive disc according to the invention, and from a Sucrets® lozenge.

Fig. 11 is a plot of data comparing release of benzocaine into distilled water from mucoadhesive discs according to the invention, having different molecular weight polymers in the active-containing layer.

Fig. 12 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 13 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 14 is a graph comparing tack characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with tack characteristics of conventional films.

Fig. 15 is a graph comparing adhesion characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with adhesion characteristics of conventional films.

Fig. 16 is a graph comparing elastic moduli of HPC films, illustrating the plasticizing effect of mint odorants.

Fig. 17 is a graph comparing menthol release over time from a breath freshening device according to the invention and from a conventional commercially marketed "breath mint" (Certs®).

As will be appreciated, the drawings are not made to scale, and, in particular, no attempt has been made to represent relative thicknesses of the layers proportionately, and the thicknesses of the various layers are exaggerated for clarity of presentation.

Modes of Carrying out the invention

Water-Soluble Pressure-Sensitive Adhesives

1. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software

package (Stable Micro Systems, Ltd.), as follows. A sample of the film on a release liner is mounted upon a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by submersion of a sample of the film in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes. 2. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

3. Preparation of dental prosthesis adhesive film.

A water-soluble pressure-sensitive adhesive film made as described above can be die-cut in a shape that conforms to that portion of the dental prosthesis that closely fits the mucosal surface of the mouth, such as the part of the dental plate that fits against the palate. The shaped film pieces can be packaged dry. For use, the dry film is pressed onto the appropriate surface

of the dental prosthesis so that it adheres. Then the dental prosthesis with the adhesive affixed is inserted into the correct position in the mouth and pressed against the mucosal surface until adhesion is achieved.

The following Example is intended to illustrate but not to limit the invention.

Example I

Breath Freshening Device

A dissolvable mucoadhesive device capable of releasing a flavor into the oral cavity was constructed as follows: A solution was made up by co-dissolving 15.4 grams of polyvinyl pyrrolidone PVP (K90) and 6.0 grams of glycerin in 80 grams of isopropanol (IPA). The resulting solution was coated at a thickness of 30 mils onto a polyester release liner and allowed to dry for 15 hours at room temperature. The resulting dry film was tacky at room temperature and had a final thickness of about 5 mils. A second solution containing 43 grams of IPA, 42 grams of water, 15 grams of HPC EF, 2.5 grams of peppermint oil and 3.0 grams of Nutrasweet™ brand sweetener containing aspartame was prepared by mixing all the components until fully dissolved. The solution was then coated at a thickness of 50 mils onto a polyester release liner. The film was allowed to dry at room temperature for 15 hours to a final thickness of about 5 mils.

The two dry films were laminated together. Discs having a diameter of about 1.2 cm were cut from the laminate. The discs were tested *in vivo* by adhering a single disc to the upper palate of three volunteers. The discs adhered well to the mucosal surface and upon hydration with saliva immediately began releasing peppermint oil and aspartame as noticed by taste. The total time of dissolution in the mouth was about 10 minutes, during which time a pleasant, refreshing mint flavor was perceived.

<u>Device Having a Water-Soluble Pressure-Sensitive Adhesive for Emplacement in a Mucosa-Lined Body Cavity</u>

1. Water-soluble pressure-sensitive adhesive layer.

The preferred water-soluble pressure-sensitive adhesive layer of the device according to the invention provides the foundation upon which the device operates. There follows first a description, by way of examples, of protocols for making exemplary water-soluble pressure-sensitive adhesives and films suitable for use in the adhesive layer.

a. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software package (Stable Micro Systems, Ltd.), as follows. A sample of the film is first mounted onto a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by immersing a sample in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes.

b. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

2. Device configurations.

a. Device having two substance-containing layers:

Referring to Fig. 1, there is shown by way of example a device **10** having a basal adhesive layer **12** which in use adheres to mucosal surface **M** and an upper polymer layer **14**, in which a substance or substances to be delivered are contained in both layers. As the upper layer is bathed by the fluids in the body cavity (for example by saliva and ingested fluids in the mouth), dissolution of the upper layer begins first and is substantially complete when dissolution of the basal layer begins. Where a different substance is contained in each layer, the substances are released sequentially. The two layers can be made to have different dissolution rates or swelling rates, resulting in one release rate for the substance or substances in the basal adhesive layer, and another release rate for the substance or substances in the upper polymer layer. If, for instance, the dissolution rate of the upper layer is slower than that of the lower layer, the resulting release regime is of a slow release of the substance in the upper layer, followed by a relatively rapid release of the substance in the basal layer. Or, alternatively, the two layers can have approximately the same dissolution

rates, but be loaded with the substance at different concentrations, resulting in a higher rate of delivery from that layer having the substance present in higher concentration.

Fig. 5 shows a rough diagrammatic plot of the release of active over time from a device made on the plan in Fig. 1. As will be appreciated, the different rates need not be linear, nor need the break between the rates be abrupt as shown.

Such a configuration can be useful in a breath freshener for oral use, by way of example, in which the basal layer can have a relatively slow dissolution rate and can be loaded with an antimicrobial, while the upper layer can have a relatively fast dissolution rate and can be loaded with a flavor or a reodorant. Such can result in a rapid release of flavorant or reodorant after emplacement in the mouth, followed by a slower release of the antimicrobial. Or, both layers can be loaded with a microbial, resulting release in an early burst followed by a more sustained delivery.

In one embodiment of this configuration, the basal layer is made of a polymer that becomes sticky on moistening, such as, *e.g.*, HPC or PAA.

In a modification of this configuration, the two layers described above can constitute middle and upper layers, respectively, of a three-layer device that is provided with a basal layer that is a water-soluble pressure-sensitive adhesive, so that the device need not be moistened prior to placement within the body cavity. As is described above, suitable compositions for such an adhesive layer include PVP as a polymer (95 - 65 weight %) and glycerine as plasticizer (5 - 35 weight %).

b. Device providing delayed-onset delivery:

Referring now to Fig. 2, there is shown a device **20** having a basal adhesive layer **22** which in use adheres to the mucosal surface **M**, a middle substance-containing water-soluble layer **26**, and an upper layer **28**, not containing the substance, that dissolves relatively slowly in the fluid environment of the body cavity. As in the device shown in Fig. 1, the adhesive layer is a water-soluble adhesive, which may be a mucoadhesive

that becomes tacky when moistened. More preferably, the basal adhesive layer is a water-soluble pressure-sensitive adhesive as described above; and in some embodiments the middle layer is eliminated and the substance to be delivered in loaded into the adhesive layer. However, where loading is so high (upwards of 25 % by weight, for example) that it would compromise the adhesive capacity of the adhesive layer, a system having the substance to be delivered loaded in a middle layer can be preferred.

Fig. 6 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 2. Here, as in Fig. 5, the rate need not be linear, nor need the onset be abrupt as shown.

Such a delayed-onset release configuration can be useful, by way of example, in a breath freshener that can be emplaced in the mouth before retiring for sleep, and which provides for release several hours later, so that the breath is fresh upon waking.

c. Device providing pulsed delivery:

A more complex release pattern can be achieved using several layers, in which altering layers contain the active, as shown by way of example in Fig. 3. The basal adhesive layer **34** of device **32** can be made, as in the devices of Figs. 1 and 2, either as a moistenable adhesive, or as a water-soluble pressure-sensitive adhesive. A moistenable adhesive may be preferred for reasons of greater stability. Basal layer **34** adheres to mucosal surface **M** when the device is in use and contains a substance to be delivered. Layers **36, 38** contain a substance to be delivered, while alternating layers **35, 37** are slowly dissolving layers not containing the substance.

Fig. 7 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 3. Here, as in Figs. 5 and 6, the rates for each delivery phase need not be linear, nor need the onset be abrupt as shown.

Such a configuration can be useful, for example, in an oral after-meals breath freshener, which provides for release of a flavor or reodorant

or deodorant at intervals corresponding with post-mealtimes, with no release during mealtimes or at other times.

Such a configuration can be useful, to cite another example, for pulsed delivery of actives that can be toxic if administered continuously. Such actives include, by way of example, anti-bacterials such as Cetyl Pyridinium Chloride ("CPC"); pulsed release can give adequate antibacterial protection without raising toxicity concerns.

d. Device having suppressed marginal release.

In any of the devices described above, dissolution at the edges or margins of the device, as well as from the upper surface, can be expected to result in release of the substance or substances within the layers whose edges are exposed. Loss of the desired release pattern can result, particularly where, as in Fig. 2, delayed onset is desired, or where, as in Fig. 3, pulsed release is desired. To minimize loss from the margins, a peripheral adhesive can be provided, as shown in Fig. 4, by way of example of a delayed onset release device having a marginal adhesive. The device **40** includes a moistenable mucoadhesive layer **44** containing the substance or substances to be delivered, which in use adheres to the mucosal surface **M**, and which is overlain by a water-soluble pressure-sensitive adhesive layer **46** whose edges extend beyond the edges of the mucoadhesive layer **44** on all sides and there adhere to the mucosal surface, forming a seal to prevent escape of the substance from the edges of the mucoadhesive layer **44** until the water-soluble pressure-sensitive adhesive layer has dissolved. The water-soluble pressure-sensitive adhesive layer is in turn covered by a slowly dissolving layer **48** not containing the substance. The slowly dissolving layer **48** provides a delay before the water-soluble pressure-sensitive adhesive begins to dissolve, which in turn prevents release of the substance until the upper surface of the substance-containing mucoadhesive layer is exposed.

Examples of substances that can be delivered within the oral cavity include: reodorants such as peppermint oil and other flavors, deodorants

such as for example the odor-preventive antimicrobial CPC, anti-bacterials such as chlorhexidine, sore-throat medicants such as Hexylresorcinol/Phenol derivatives/Menthol, cough suppressants such as Dextrathomorphan Hydochloride, agents to prevent mouth dryness, benzocaine for treatment of rhinitis, *etc.*

3. Particular devices.

Example II

Two-layer device having a water-soluble pressure-sensitive adhesive layer

A two-layer device according to the invention was made according to the following protocol. First the necessary components (polymers, additives, *etc.*) for each layer were dissolved or dispersed in an appropriate solvent. For an upper layer, the casting solution in one prototype consisted of 41 parts isopropyl alcohol ("IPA"), 40 parts water, 14 parts hydroxypropyl cellulose ("HPC") EF (MW ~ 80,000), 2.4 parts peppermint oil and 2.8 parts Aspartame. The casting solution for the basal layer consisted of 79 parts IPA, 15 parts poly(vinyl pyrrolidone) ("PVP") (Kollidon 90), and 6 parts glycerin. Each of these two casting solutions was coated onto a polyester release liner, to provide a substratum for forming the layer, at the desired thicknesses of 50 mils for the upper layer and 25 mils for the basal layer. The layers were then allowed to dry on the respective release liners overnight (at least 15 hours) at room temperature inside a hood). The dry films were then carefully hand-laminated together to provide a two-layer system consisting of a non-tacky upper layer containing the substances to be released, and an adjacent tacky pressure-sensitive-adhesive soluble basal layer.

Alternatively, manufacture of the pressure sensitive adhesive device can be carried out by extruding a blend of the components for each layer through a slit die to form a thin film. The upper and basal films can then be laminated together through rollers, with the tacky layer protected by a release liner from contact with the rollers.

Alternately, the substances to be delivered (*e.g.*, peppermint oil or other printable material or materials) can be printed onto an extruded pure HPC EF or other similar extruded film, as described in Miranda *et al.* U.S. Patent No. 4,915,950, which is hereby incorporated by reference.

Example III

Two-layer device having a moistenable mucoadhesive layer, and capable of delivering at two different constant rates

An alternative two-layer device according to the invention was made as follows. The upper layer was made by first co-dissolving HPC HF and CPC in IPA in the following proportions: 10 parts HPC EF, 0.135 parts CPC, and 90 parts IPA. The solution was then coated at a thickness of 15 mils onto a polyester release liner, and allowed to dry at room temperature overnight (at least 15 hours). This film formed an upper layer having a dry thickness of 1.5 mils. The basal layer was made by first co-dissolving HPC EF, CPC and IPA in the following proportions: 2 parts HPC HF, 0.0054 parts CPC, and 98 parts IPA. The solution was then coated at a thickness of 50 mils onto a polyester release liner, and dried in an oven at 70 °C for 6 hours. The dry film was then collected and ground to a coarse powder using a mortar and pestle. This powder was then pressed in a heated Carver laboratory press to form a film having a thickness about 2 mils. Then the upper (EF) and basal (HF) films were laminated together and then bonded by compressing in a heated (275 °F) Carver press.

Example IV

Multilayer device providing pulsed release

A multilayer device was made by first co-dissolving poly(vinyl propylene) ("PVP") (K 90), glycerine, methylene blue and IPA in the following proportions: 7.2 parts PVP (90), 2.8 parts glycerine, 90 parts IPA and 0.030 parts methylene blue. The solution was coated onto a polyester release liner at a thickness about 25 mils wet, and then dried at room temperature for 15 hours. The resulting dry film constituted the active

layer material. A second film was prepared by pressing HPC EF powder to a thickness of about 4 mils, using the heated Carver press.

The PVP/glycerin/methylene blue film and the HPC EF film were then arranged in alternating fashion to produce a laminate of six layers, three containing and three not containing the substance to be delivered. The PVP/glycerin/methylene blue layers served as an adhesive to bond the laminate composite, and served as a reservoir for the substance (methylene blue, in this illustrative example) to be released from each layer as it dissolved. The HPC EF layers provided for periods of time between releases, providing the pulsed release profile.

Example V

Delayed-Onset device

A delayed-onset device was made by first blending hydroxypropyl cellulose (HPC LF) and sorbitan monostearate (SPAN 60) as dry powders in a 1:1 ratio by weight. This blend was pressed using a heated Carver press at

200 °F to a thickness of 15 mils. The resulting polymer film was flexible having a waxy, hydrophobic surface.

An adhesive film was made by blending the following components:

HPC MF	1.0 gram
Kollidon PVP (K90)	2.0 grams
Glycerin	2.0 grams

After blending at room temperature, the resulting mixture was pressed in a heated Carver press at 200 °F to a thickness of 10 mils. This adhesive layer was used to adhere the HPC LF:SPAN 60 film to the top layer of the 25 min. breath disc described above in Example II.

The multilayer disc was tested over-night by adhering the disc to the upper palate just prior to going to sleep for the night. There was no noticeable mint flavor initially and during the several minutes thereafter before actually falling asleep. Approximately 5.5 hours later, however, the

disc released a burst of peppermint oil into the mouth strong enough to stimulate and awaken the wearer.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

Any of a variety of devices, in any configuration and for any intended use when emplaced within a body cavity of a subject, are within the scope of the claims. The invention is illustrated below by way of example only; the examples are not intended as limiting the scope of applicants' contribution to the art, and other types and arrangements of devices are within the scope of the invention.

Example VI

Laminated Composite Device for Delivery of Antimicrobial

By way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide delivery of an active substance into the body cavity, Fig. 12 shows generally at **70** a device having a basal water-soluble pressure-sensitive adhesive layer **72**, and an overlying polymer layer **74** containing the active substance **78**. The device is shown removably affixed by the adhesive surface to a release liner **76**.

The adhesive layer can be constructed as follows. An HPC polymer is thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture is formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described below, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams.

The active containing layer can be constructed as follows. Using 85 grams of ethyl alcohol as the solvent, 13.5 grams of hydrohypropyl cellulose (HPC EF) was dissolved with stirring with 1.5 g CPC. The mixture was blended until uniform, at which time the thickened solution was cast as a film onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a heated Carver press to form an active containing layer of 25 mils thickness.

The tack and work of adhesion of the adhesive surface of the device as described in this example, as an indication of its adhesive properties, was measured for three samples as follows.

Sample 1 peak: -0.561 kg; area:-0.0177 kg

Sample 2 peak: -0.420 kg; area:-0.0097 kg

Sample 3 peak: -1.306 kg; area:-0.0352 kg

Example VII

Protective Barrier Device

Additionally by way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide a protective barrier for the underlying mucosal surface, Fig. 13 shows generally at **80** a device having a basal water-soluble pressure-

sensitive adhesive layer **82**, and an overlying protective layer **84** constructed of a relatively abrasion-resistant water soluble polymer. The device is shown removably affixed by the adhesive surface to a release liner **86**.

In this example, the adhesive layer can have the composition, and can be constructed, as described generally above and particularly, for example, as described for the adhesive layer of Example VI.

The overlying protective layer can be constructed, for example, of a water soluble polymer as would be suitable for an active containing layer for delivery into the body cavity; and the protective layer can be constructed as described generally and particularly above. Particularly suitable polymers include for example HPC HF, polyvinyl alcohol ("PVA"), and hydroxymethyl cellulose.

A device made according to this example can be used, for example, as a temporary covering for an area of injury to the mucosal surface, such as an area of cheek of lip that has been abraded or cut. Or, the device can provide an abrasion preventive for areas of mouth tissue that are subject to abrasion by, for example, orthodontural devices.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

1. Construction of the device

Preparation of a mucoadhesive disc for containing a sore throat medication.

A medication-containing mucoadhesive laminated disc according to the invention can be made by forming and then laminating an adhesive film and an active substance-containing polymer film generally as follows.

a. The adhesive layer. A water-soluble adhesive layer can be formed from an adhesive polymer film, according to the following general protocol. First, the polymer (or polymers) and the plasticizer are thoroughly mixed, using where necessary a suitable solvent such as ethyl alcohol. Where a solvent is used, the resulting mixture is then coated on a release liner, and the solvent is allowed to evaporate to produce a dry film.

Dry film samples are then collected and pressed to the desired final film thickness. Where no solvent is used, the mixture can be pressed to a film of the desired thickness.

b. The active substance-containing layer. First, the polymers and one or more desired active agents and one or more desired flavorants are dissolved, for example by stirring, in an appropriate solvent. Then the resulting thickened solution is formed into a thin (wet) film, for example by casting onto a release liner, and then the solvent is permitted to evaporate to a dry film. Then the dry film is pressed to a desired thickness and is affixed, for example by pressing, onto an adhesive layer prepared as described above.

Hydroxypropyl cellulose (HPC) can be a particularly suitable polymer for construction of the active-containing layer. HPC dissolves completely in aqueous fluids such as the fluids of the oral cavity, and within a selected range of molecular weights, HPC dissolves (or disperses) in the oral cavity sufficiently slowly to provide substantially continuous delivery of the active substance over an extended period. HPC is flexible, so that it conforms well to irregular curved surfaces of the oral cavity; HPC is not tacky when moistened, and has a pleasant texture in the mouth. It is thus comfortable and unobtrusive for the user. HPC blends well with a variety of active substances.

Glycerol, which may be added as a plasticizer in the active-containing layer, may additionally (or alternatively) act to inhibit crystallization of some active substances that might otherwise occur at the loading concentrations employed (for example, menthol).

c. Laminated devices are then cut from the laminated film by, for example, die-cutting, to the desired size and shape. Typically, circular or oval shapes may be preferred. The devices can be stored on a release liner affixed to the adhesive surface, and removed from the liner as needed by the user.

A laminated device according to the invention may be bilaminate, having an adhesive layer and an active-containing layer, as shown for example in transverse sectional view in Fig. 8. Or, the device may be trilaminate, having a third water soluble layer, poorly permeable to the active substance, interposed between the adhesive layer and the active-containing layer, as shown for example in transverse sectional view in Fig 9. This layer may be made of a material such as for example polvinyl acetate ("PVAc") or ethyl cellulose, or such, for example, one of the Eudragit family of polymethacrylic copolymers commercially available from Rohm (*e.g.*, Eudragit S100, L100, E100, L100-55). The Eudragit polymethacrylic copolymers are characterized by being variously soluble at various pH; Eudragit S100 has a suitably low solubility at the typical pH of the normal human saliva. The interposed third layer may where desired be made more flexible by addition of a plasticiser such as, for example, glycerine, in amount up to, for example, about 20 %.

Referring now to Fig. 8, a bilaminate device **50** includes a polymer layer **52** containing the active substance **54**, laminated onto an adhesive layer **56**. The device is shown removably affixed to a release liner **58**.

Referring to Fig. 9, a trilaminate device **60** includes a third polymer layer **72**, poorly permeable to the active substance, laminated between polymer layer **62** containing the active substance **64**, laminated onto an adhesive layer **66**. The device is shown removably affixed to a release liner **68**.

2. Use of the device

As the need for relief of sore throat or cough arises, the user simply peels a laminated device away from the release liner, and affixes it to a surface within the oral cavity. It can be preferred to affix the device to the mucosal surface at the roof of the mouth, as that provides for direct flow of the active substance toward the rear of the mouth and the throat.

The following examples, are intended for illustration only, and are not intended to limit the scope of the invention.

Example VIII

Disc for Delivery of Cineole

The active containing layer was constructed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	1.0 grams
Cineole	1.0 grams
Aspartame	0.3 grams
Menthol	1.7 grams
HPC Klucel LF	16 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to form an active containing layer of 25 mils thickness.

The adhesive layer was constructed as follows. An HPC polymer was thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture was formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described above, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 8.5 milligrams of menthol and 5 milligrams of cineole.

Example IX

Disc for Delivery of Dyclonine HCl

The active containing layer was formed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	2.0 grams
Dyclonine HCl	0.6 grams
Menthol	1.0 grams
Aspartame	0.3 grams
HPC Klucel LF	16.1 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in the hood overnight to allow the solvent to evaporate, forming a dried film.

The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to 25 mils thickness. This pressed film was then laminated to an adhesive film, 5 mils thick, made as described in Example 1, to form a bilaminate composite. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 5 mg of menthol and 3 mg of Dyclonine HCl.

Example X

Comparison of release of Dyclonine HCl from a mucoadhesive disc and from a Sucrets® lozenge: disc affixed to glass.

The release profile of Dyclonine HCl into water from a prototype mucoadhesive disc according to the invention and from Sucrets® lozenge were compared as follows.

A Sucrets® lozenge containing 3.0 mg Dyclonine HCl was placed in a Pyrex® flask. A laminated disc made as described in Example 2 above, and containing 3.0 mg Dyclonine HCl, was removed from the release liner and affixed to the inner surface of a second Pyrex® flask by pressing the adhesive surface onto the flask wall. 100 ml deionized water at 25 °C were added to the flasks and the contents of the flasks were stirred priodically.

Thereafter sample aliquots of the aqueous phase were removed from each flask at intervals, and analyzed using UV spectroscopy to determine the amount of Dyclonine HCl released.

The resulting release profiles for both the prototype mucoadhesive disc and the Sucrets lozenge are shown in Fig. 10. Fig. 10 shows the cumulative release of Dyclonine HCl into the water. Although both dosage forms initially contained equivalent amounts of Dyclonine HCl (3.0 mg), the disc gives an appreciably extended and more uniform delivery of the Dyclonine HCl.

Example XI

Release of Dyclonine HCl from a mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as follows.

A laminated disc was made generally as described in Example IX above, except that it was die cut to 3/8 inch diameter so that it contained 1.11 mg Dyclonine HCl. The disc was removed from the release liner and affixed to a piece of palate tissue (porcine palate) by pressing the adhesive

surface of the disc onto a surface of the palate tissue. Then the palate tissue with the disc affixed was immersed in deionized water at 25 °C in a flask the contents of the flask were stirred prior to removing the sample.

After 2 hours, the disc was removed from the palate tissue and the disc was returned to the flask and allowed to dissolve completely (with stirring). Then the amount of Dyclonine HCl in the water was measured. The Dyclonine HCl not accounted for was taken to be an amount that had been delivered to the palate tissue. That is, the difference between the amount of Dyclonine HCl initially present in the disc and the amount that was released into the water is the amount released into the mucous tissue. The results are shown in Table I.

Table I

Dyclonine HCl initially in the disc	1.11 mg
Dyclonine HCl released to water	1.04 mg
Dyclonine HCl not accounted for	.07 mg

As Table I shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.07 mg of Dyclonine HCl (5.8 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue.

Example XII

Inhibition of release of Dyclonine HCl from a trilaminate mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was constructed with a third layer interposed between the adhesive layer and the active substance-containing layer, for limiting the rate of movement of the active substance into and through the adhesive layer. The trilaminate disc was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as described in Example XI.

A laminated disc was made generally as described in Example IX above, except that a thin film (5 mil thickness) of a polymethacrylic copolymer (Eudragit S100) was laminated between the adhesive later and the active substance-containing layer, and the disc was die cut to 3/8 inch diameter so that it contained 1.02 mg Dyclonine HCl. The trilaminate disc was removed from the release liner and affixed to porcine palate tissue, and the release to the palate tissue was determined as described in Example XI. The results are shown in Table II.

Table II

Dyclonine HCl initially in the disc	1.02 mg
Dyclonine HCl released to water	0.98 mg
Dyclonine HCl not accounted for	.04 mg

As Table II shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.04 mg of Dyclonine HCl (3.9 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue. The interposition of the limiting layer between the Dyclonine HCl-containing layer and the adhesive layer reduced the amount of Dyclonine HCl diffused into the palate tissue from 5.8% to 3.9%.

Example XIII

Comparison of release of Dyclonine HCl through a semipermeable membrane from a trilaminate mucoadhesive disc and from a bilaminate mucoadhesive disc to which the disc is affixed.

In this Example, bilaminate and trilaminate mucoadhesive discs containing Dyclonine HCl according to the invention were constructed generally as described in examples XI and XII. The discs were affixed to a semipermeable membrane, and the quantity of Dyclonine HCl released through the membrane over an extended time was determined as described in Example 4. Briefly, the disc (1/2 inch diameter) was placed in a horizontal Franz cell (7.5 ml capacity) separated by a mesh barrier (70 μm Teflon), by

affixing an adhesive surface of the disc onto the mesh barrier. Both sides of the cell were filled with nano-filtered water; water in the "donor" side of the cell bathed the surface of the active layer, and water in the "receiver" side of the cell bathed the mesh barrier. The results are shown in Table III.

Table III

	Sample	Dyclonine Release
Bilaminate disc	1	9.65 %
Bilaminate disc	2	10.91 %
Bilaminate disc	3	8.82 %
	Mean	9.79 ± 1.05 %
Trilaminate disc	1	1.45 %
Trilaminate disc	2	1.43 %
Trilaminate disc	3	0.30 %
	Mean, Samples 1 & 2	1.44 ± 0.014 %

As Table III shows, the total quantity of Dyclonine passing from the active-containing layer into and through the adhesive layer and then through the semipermeable membrane was greatly reduced by interposition of the occlusive layer between the adhesive layer and the active-containing layer. Particularly, in three experiments for each disc type (bilaminate and trilaminate) shows an average decrease in the release of Dyclonine HCl into the receiver side, from 9.79 ± 1.05 % to 1.44 ± 0.014 %, after a period of two hours.

Example XIV

Release of benzocaine into distilled water from a mucoadhesive disc according to the invention: effect of different molecular weight of polymer in the benzocaine-containing layer.

In this Example, bilaminate mucoadhesive discs containing benzocaine were constructed generally as described in Example IX, substituting benzocaine for Dyclonine. Discs were made using HPC both at the same molecular weight as described in Example 2 (80 k), and at a higher molecular weight (300 k), and the release into distilled water was tested as described in Example X. The results are shown in Fig. 11. These results show a decrease in release rate of benzocaine with increasing molecular weight of HPC in the active-containing layer.

Example XV

Transport of Dyclonine HCl and of benzocaine through pig mucosa.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to porcine buccal mucosa and mounted on Franz diffusion cells as described in Example XIII. Average amounts of active substance was measured using HPLC, and percents were expressed as a percent of the total initially in the disc.

Particularly, the donor side of the cell was filled with pH 6 buffer and the receiver side was filled with phosphate buffered saline ("PBS"). Samples were taken from the receiver side every thirty minutes for three hours, and the samples were analyzed by HPLC. The average amount and the average percent of active substance appearing in the receiver side after three hours are shown in Table IV.

Table IV

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	284.63	3.29
15 % Dyclonine HCl	282.77	3.94

The average amount delivered reflects the cumulative amount of drug transported through the mucosa over the three hour period. The average percent delivered represents the cumulative amount of drug transported, in terms of percent of drug contained in the device at the outset. The data show that very low values of benzocaine or Dyclonine HCl were transported through the tissue, and demonstrate that such devices, placed within a mucosa-lined body cavity, such as the oral cavity, can be expected to deliver relatively little of such active substances through the mucosa during the period that the active substance is administered into the body cavity itself.

Example XVI

Transport of Dyclonine HCl and of benzocaine through human stratum corneum.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to human stratum corneum and mounted on Franz diffusion cells. The donor side of the cell was filled with pH 6 buffer and the receiver side was filled with PBS. Samples were taken from the receiver side and analyzed using HPLC, and the average amount and percentage of active substance appearing in the receiver cell were determined. The average amount and the average percent of active substance appearing in the receiver side are shown in Table V.

For both benzocaine and Dyclonine HCl the amount of active substance delivered through the human stratum corneum (Example XVI) is lower than the amount of active substance delivered through the pig buccal mucosa (Example XV). For administration of Dyclonine HCl or benzocaine

into the oral cavity of a human subject, so that the active substance is carried by the saliva to the irritated tissues of the mouth and throat, it is desirable to limit the amount of active substance delivered through the oral mucosal surface to which the device is affixed. Preferably a device for delivery of active substances for relief of cough and sore throat is affixed to the palate. The transfer coefficient for human palate tissue is lower than that for pig buccal mucosa and higher than that for human stratum corneum, and Examples XV and XVI thus provide an approximate range within which the extent to which delivery of active substances across the underlying human palate mucosa can be expected to fall. For a device according to the invention, affixed to the palate, the great majority of benzocaine or Dyclonine HCl can be expected to be delivered into the oral cavity.

Table V

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	255.56	2.42
15 % Dyclonine HCl	14.60	0.18

Interposition of a third layer, relatively impermeable to the active agent, between the active agent-containing layer and the adhesive layer, as described for example in Example XII, can reduce further the quantity of active agent passing through the mucosa. As the results in Examples XV and XVI show, however, a bilaminate system can be suitable for delivery.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

Generally, the breath freshening device according to the invention is constructed as a laminated composite including a basal adhesive layer constructed of a water soluble pressure sensitive mucoadhesive composition; and an odorant containing layer constructed of a water soluble polymer

mixed with the odorant. Optionally the device may include a third layer, interposed between the adhesive layer and the odorant containing layer, constructed of a water soluble polymer that is substantially impermeable or is poorly permeable to the constituents of the odorant.

The device may be made by forming the respective layers as films and then laminating the films, and finally cutting (as, for example, by die cutting) the device from the laminate.

The films may be made from polymer mixtures by any of a variety of techniques known in the polymer film-forming art, including casting, calendaring, coating, and extrusion. Batch processing techniques may be employed, but for large scale production, continuous processing can be preferred. Die extrusion through a slit is a particularly suitable continuous processing technique for making the films for use in the devices according to the invention.

Lamination may be carried out by contacting the films and applying pressure. Laminated films may be made in small quantities by use of a press, but for continuous processing the films can be pressed together using one or more rollers. Heat may be applied to the films as they are brought together, for example by heating the press or by heating the roller or rollers.

Referring again now to Fig. 8, a bilaminate device configuration according to the invention suitable for a breath freshening device is shown generally at **50**. The device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**.

A trilaminate device configuration suitable for a breath freshening device is shown generally at **60** in Fig. 9. The trilaminate device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**, generally

as in the bilaminate device shown in Fig. 8. The trilaminate device additionally includes a third layer **62**, interposed between layer **52** and layer **56**, constructed of a water soluble polymer that is substantially impermeable or poorly permeable to the constituents of the odorant.

The devices as shown in the Figs. are provided with a release liner **58**, which is peeled away from the device just prior to use.

The content of the layers is described in greater detail below.

1. The adhesive layer.

Suitable GRAS certified polymers for use in the water soluble pressure sensitive mucoadhesives include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In particular embodiments the water soluble pressure sensitive mucoadhesive includes as a polymer PVP (about 30 - 60 weight %), HPC (about 10 - 30 weight %); and glycerin as a plasticizer (about 10 - 60 weight %). In these formulations, the molecular weight of the PVP is in the range about 30,000 - 1,000,000; and the molecular weight of the HPC is in the range about 60,000 - 1,000,000. Such compositions adhere quickly on contact and without moistening to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, and continue to adhere well to such surfaces for extended times in the milieu of the oral cavity.

The water soluble pressure sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick.

Preferably the adhesive layer additionally includes a preservative, such as for example BHA or BHT, in a suitable small quantity. The adhesive additionally may include a certified colorant.

2. The odorant-containing layer.

Suitable GRAS certified polymers for use in the odorant containing layer include, particularly, hydroxypropyl cellulose ("HPC").

The term "odorant", as used herein, refers to a substance or combination of substances which, when present in the fluids of a subject's oral cavity, impart a pleasing smell to the person's exhalant breath. A breath freshening substance may work in part by addition of a desirable odor to the breath, and in part as a "reodorant", that is, by masking an unpleasant odor in the subject's breath, and the term "odorant" herein includes such reodorant effects.

As is well recognized in the flavorist's art, the appreciation of flavor is a complex response, principally, to the senses of aroma and taste. *See generally, e.g.,* G. Reiniccius, ed. (1994), *Source Book of Flavors*, 2d Ed., Chapman & Hall (herein, the "*Source Book of Flavors*"). The various tastes (sweet, salt, sour, bitter) are due to nonvolatile components of the flavor, while the aroma or odor is due to volatile components. The chemical makeup of a flavor, and particularly of the volatile components of a flavor, may be exceedingly complex, with a number of volatile components contributing significantly to the distinctive aroma. On the other hand, certain chemical compounds are by themselves when smelled reminiscent of a particular flavor, even where the flavor that is recalled is in fact complex. Such character impact compounds include, for example, Menthol (having the character impact of peppermint); L-Carvone (spearmint); Methyl salicylate (wintergreen); and Citral (lemon).

A straightforward way to provide desired odorant in the odorant-containing layer of a breath freshening device according to the invention is to add to the polymer of the layer an essential oil (*i.e.,* a volatile oil) of a plant material. The *Source Book of Flavors* describes essential oils that are

in common use in the flavoring industry, including descriptions of methods for their industrial production and an account of their chemistry.

Any of a variety of breath freshening odorants may be delivered to the oral cavity by adding into the polymer of the odorant-containing layer a flavoring that includes the odorant. In at least some cultures, mint-like odorants are acceptable and even desireable on the breath, and accordingly the odorant containing layer of a suitable breath freshening device can include a mint flavoring, as described more fully below.

Preferably the odorant containing layer additionally includes a preservative, such as for example BHA or BHT in a suitable small quantity. Optionally the odorant containing layer additionally includes a sweetener, most preferably a non-sugar sweetener, such as aspartame in a suitable small quantity.

3. Mint odorants.

Mint odorants can be provided by essential oils derived by extraction and distillation from leaves and/or flowering parts of any of various plants. The composition of such distillates depends, among other things, upon the species and variety of plant, as well as its geographical origin, and upon the method of extraction and degree of distillation. A variety of mint flavorings are described, for example in the *Source Book of Flavors*. They include, particularly for example, oil of peppermint, the chief aromatic constituents of which are menthol, menthone, and menthyl acetate; oil of spearmint, the chief aromatic constituent of which is L-Carvone; and oil of wintergreen, the chief aromatic constituent of which is Methyl salicylate.

4. Device fabrication.

As pointed out generally above, the layers can be produced using techniques known in the art of polymer film fabrication, by conventional batch process or by continuous process, as for example by conventional die extrusion through a slit. Typically, for example, batch processing can be carried out as follows. The components making up each layer (*e.g.*, the

adhesive layer, or the odorant containing layer, or an intermediate layer) are blended together either with a suitable solvent to aid in mixing or, as may be more preferable, without a solvent. The blending may be carried out at an elevated temperature (particularly where no solvent is employed), to aid in homogeneous mixing of the components. The blended components of each layer are thereafter pressed to a film having the desired final layer thickness using a heated Carver press. The resulting films are then laminated, for example by contacting them and applying pressure.

Generally, for example, a conventional continuous die extrusion process entails feeding the components of the layer to an extruder, such as a twin screw extruder. The extruder melt blends the components of the layer and then forces the blended mixture continuously through a slit whose thickness is selected to provide the desired thickness in the resulting film. The individual films may be rolled for temporary storage before lamination, or the lamination may be carried out immediately following extrusion. The films are containuously laminated by bringing the films into contact and pressing them together over a roller or between rollers, which may as appropriate be heated to facilitate the lamination process.

Individual devices are then cut from the completed laminate, for example by punching or die cutting, and stored for use.

The examples that follow are presented by way of illustration only, and are not meant as limiting the invention.

Example XVII

Construction of Device for Delivery of Peppermint

This example illustrates the construction of a device for delivery of a refined (reduced) oil of peppermint. The oil of peppermint used in this example is a "Reduced Oil of Peppermint FCC/NF "Rose Mitcham" ", which is commercially available from the A.M. Todd Company of Kalamazoo, MI. It contains the following mint flavor components:

menthofuran (GLC)	02.6 %
menthol	57.0
menthone	24.8
menthyl acetate	07.4

As provided from the commercial source, this reduced oil of peppermint has a specific gravity .903, an optical rotation -28.2, and a refractive index 1.4600. It is soluble in three volumes of 70 % ethanol.

1. Construction of the odorant containing layer.

In this example, the odorant containing layer is constructed by thoroughly mixing the peppermint oil (as described above), a non-sugar sweetener (Aspartame), and a preservative (BHA) with a hydroxypropyl cellulose ("HPC") polymer, and then extruding the odorant containing polymer mixture through a slit to form a film. Preferably a twin screw extruder is employed, and the components are continuously fed into the extruder, in which the blending is effected. In this particular example, the odorant containing layer has these ingredients in the following proportions.

Klucel HPC GF	83.5 %
Peppermint oil	15.0
Aspartame	1.50
BHA	0.0083

2. Construction of the adhesive layer.

In this example, the adhesive layer is constructed by thoroughly mixing an HPC polymer with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and then extruding the adhesive polymer mixture through a slit to form a film. In this particular example, the adhesive layer has these ingredients in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

The formed adhesive film and odorant containing film are then laminated by passing the films together between rollers under pressure, and the individual devices are die cut from the resulting laminated composite.

Example XVIII

Tack and Adhesion Properties of the Adhesive Layer

The properties of tack and adhesion of the water soluble pressure sensitive mucoadhesive employed in the breath freshening device of the invention were tested as follows.

An adhesive film was made generally as described in Example XVII.

Tack and work of adhesion were measured using a Texture Technologies TXA.XT2 Texture Analyzer in which a PMMA probe was used in place of the usual SS probe. A 5 mil thick adhesive film made as described in Example XVII was tested under the following conditions.

Probe speed (penetration):	1.0 mm/sec
Penetration depth:	0.10 mm
Dwell time:	10 sec
Probe speed (withdrawal)	5.0 mm/sec
Probe diameter:	0.80 cm

All measurements were made at room tepmerature (20 - 25 °C).

The resulting trace of the force during withdrawal versus time allowed for a determination for each sample of both the tack (the peak maximum, in Kg) as well as the work of adhesion (area under the peak curve, in Kg-sec). Films were tested dry as well as after moistening by

spraying the dry film surface with a fine mist of distilled water, followed by a resting time of 60 seconds to allow for hydration of the sample.

In this example, the above test protocol was applied to films according to the invention (indicated as "BFD" in the Figs.), and to constructed with the following compositions.

"279-190":	60 % PEO 301; 30 % HPC MF; 5 % PE; 3 % PG; 2 % PEG 400 (described in Schiraldi U.S. 4,731,243).
"279-191":	55.3 % NaPAA; 37.5 % HPC HF; 6.3 % Glycerin (described in Chang U.S. 4,373,036).
"310-30B#2":	40 % HPC HF; 35.5 % PVP 90 F; 20 % HPC LF; 2 % Mentha Oil; 2 % Menthol; 0.5 % Fennel Oil (described in Hisahige JP 63-209797).
"310-44"	44.5 % PVP 90 F; 30 % HPC LF; 10 % HPC HF; 10 % PEG 400; 2.5 % Menthol; 2.0 % Mentha Oil; 1.0 % Fennel Oil (described in Hisahige JP 63-209797).

The results are shown in Figs. 14 and 15. In these tests the adhesive film according to the invention is significantly more adhesive toward the PMMA probe in the dry state (*i.e.*, before moistening) than did four other formulations tested. Following moistening the adhesive film according to the invention was comparably adhesive or was more adhesive toward the PMMA probe than were the other tested formulations.

Example XIX

Flexibility of Odorant Containing Layer

As noted above, water soluble polymers such a hydroxypropyl cellulose that dissolve suitably slowly in the milieu of the oral cavity may not themselves be sufficiently flexible for use in an odorant containing layer in a device according to the invention. Conventionally, the layer would be rendered more flexible by addition of a suitable plasticizer such as glycerol. We have discovered that the essential oils of Spearmint, or Peppermint, and

of Wintergreen can provide substantial and sufficient plasticizing effect when mixed with HPC in quantities suitable for extended delivery of mint odorant to the oral cavity at breath freshening rates.

In this example, the elastic moduli (as a measure of flexibility) are compared for film preparations of HPC containing no additional components, and of film preparations containing 15 weight % of oil of peppermint, oil of spearmint, oil of wintergreen, and oil of lemon. This conventional measurement entails measuring the tensile force per unit cross sectional area (stress) of a sample of the film during elongation of the sample at a fixed rate (strain). The elastic modulus is derived from the stress/strain curve. In this example, the test was carried out on bone-shaped film samples 5 mils thick and 0.25 inch wide, gage length 1.0 inch, at an elongation rate of 0.2 inch/min. All samples were tested at room temperature (20 - 25 °C).

The results are shown in Fig. 16. As the Fig. shows, addition of any of the mint odorants to the HPC composition results in a substantially and sufficiently flexible film, while addition of lemon oil does not sufficiently lower the elastic modulus of the film. Thus, where a mint odorant is used, no additional plasticizer is required in the odorant containing layer.

Example XX

Delivery of Peppermint over Extended Times

In this example, the capacity for delivering a breath-freshening substance into an aqueous medium was compared in devices according to the invention and in a "breath mint" that is commercially marketed under the name "Certs®". A flavor containing film was constructed, generally as described in Example XVII. Portions of the film 1/2 inch in diameter and 25 mils thick, each containing 8.6 mg menthol were immersed in distilled water, and breath mint tablets each containing 4.3 mg menthol were immersed in distilled water in separate flasks, and the flasks were continuously shaken. Samples were withdrawn from the flasks after elapsed

times of 15 min., 30 min., 45 min., 60 min., and 120 min., and the quantity of menthol was analyzed by gas chromatography.

The results are shown in Fig. 17. On average, the breath freshening device of the invention had by the first (fifteen minute) sample interval released about 0.7 mg menthol, and thereafter the device delivered menthol at a continuous steady rate throughout the sampling period; at the two hour sampling interval, approximately 2.0 mg of the original 8.6 mg of menthol had been released from the device, and rate of delivery was continuing at slightly less than 0.25 mg per hour. By contrast, each breath mint had on average by the first sampling interval released nearly half its total quantity of menthol, and had nearly exhausted their delivery capacity at the second (thirty minute) sampling interval.

In a person's mouth, the saliva is swallowed more or less continuously, and once a conventional breath mint has been completely dissolved, the breath freshening effect wanes quickly as the residual odorant is flushed away. As the example shows, the invention can provide for a sustained and steady supply of the breath freshening odorant to the saliva flow, resulting in an extended breath freshening effect.

Example XXI

Evaluation of Breath-Freshening Effect

In this example, the breath freshening effectiveness of devices according to the invention, constructed generally as described in Example XVII above, were informally evaluated by volunteers. The volunteers reported that the device was convenient to use, was non-obtrusive, did not materially interfere with speech, and left a pleasant taste and odor in the mouth.

Other Embodiments

Other embodiments are within the following claims.

For example, the water-soluble pressure-sensitive adhesives according to the invention can be used to affix transdermal devices to human skin.

Because the materials in the adhesive are GRAS certified, they can result in an adhesive product having very low skin irritation and reaction.

The water-soluble pressure-sensitive adhesives of the invention can act as a reservoir for diffusional delivery of a substance into the mucosa-lined body cavity (such as the oral cavity or gastrointestinal tract, or the vaginal cavity), or for delivery of a substance transmucosally through the area of adhesive contact. Preferably for such applications, the adhesive is provided in film form, and is loaded with a suitable quantity of the substance to be delivered. For use in transmucosal delivery, one surface of the adhesive film makes adhesive contact with the mucosal surface; preferably the other surface of the adhesive film is covered with a substance-occlusive backing layer made of a material that is poorly soluble in water or in the fluid secretions of the body cavity in which the film is used. Examples of substance-occlusive poorly soluble materials that are safe for oral use include poly(dimethyl siloxane), poly(tetrafluoro ethylene), cellulose acetate, and copolymers of neutral methacrylic acid esters with one or both of methacrylic acid and diethylaminoethyl methacrylate.

In a dental prosthesis adhesive film application, for example, the adhesive can be loaded with a flavoring or a mouth deodorant to act as a breath freshener, or with an antibacterial. Suitable flavorings, mouth deodorants, and antibacterials are known in the oral hygiene art. As the adhesive slowly dissolves, the agent is gradually released into the oral cavity.

Or, in a dental prosthesis adhesive film application, the adhesive can be loaded with a substance to be delivered transmucosally; in this configuration, the dental prosthesis works as an occlusive backing.

The water-soluble pressure-sensitive adhesives of the invention can be employed as an adhesive layer in a laminated device for diffusional delivery of an agent within a mucosa-lined body cavity. Such laminated devices can take any of a variety of forms, and may have just one layer in addition to

the adhesive (such as the substance-occlusive poorly soluble layer described above, for example), or many additional layers.

Water-soluble pressure-sensitive adhesive films according to the invention can be made by other processes than described above. Where a press is used to form the film, for example, different temperatures may be used, according to the particular polymer composition.

Alternatively, the molten polymer may be extruded through a slit die to form a film of the desired thickness; or it can be extruded or cast as a single film between release surfaces. In the latter case, the product can be cut to a shape appropriate to the particular application, and the release liners can be peeled away just prior to use.

Other embodiments are within the following claims, and variations on the embodiments shown by way of example above have been made and can be altered as may be desired. For example, with reference to Examples 1 and 2, aspartame can be left out and a flavor imparting a different taste or odor can be added instead. Also, the loading of actives dyclonine HCl, menthol, and cineole can be controlled by either varying the concentration or changing the thickness of the disc. Other active substances useful for relief of sore throat pain or cough can be delivered according to the invention.

Claims

1. A water-soluble pressure-sensitive adhesive comprising a water-soluble polymer and a water-soluble plasticizer, said polymer having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

2. The water-soluble pressure sensitive adhesive of claim 1 wherein said polymer has a T(g) or a T(m) greater than about 30 °C.

3. The water-soluble pressure-sensitive adhesive of claim 1, said polymer comprising poly(vinyl pyrrolidone) and said plasticizer comprising glycerol.

4. The water-soluble pressure-sensitive adhesive of claim 3, said polymer further comprising hydroxy propyl cellulose.

5. The water-soluble pressure-sensitive adhesive of claim 3, comprising 95 - 40 weight % poly(vinyl pyrrolidone), 0 - 50 weight % hydroxy propyl cellulose, and 11 - 60 weight % glycerol.

6. The water-soluble pressure-sensitive adhesive of claim 5, said glycerol being present in the range 30 - 50 weight %.

7. The water-soluble pressure-sensitive adhesive of claim 1, in film form.

8. A dental prosthesis adhesive, comprising the water-soluble pressure-sensitive adhesive film of claim 7, shaped to conform to a portion of the mucosal surface-contacting surface of the dental prosthesis.

9. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer; and

a water-soluble polymer layer;

wherein the substance is dissolved or dispersed in either or both of said adhesive or polymer layers.

10. The device of claim 9 wherein delivery of the substance is characterized by a delayed onset.

11. The device of claim 10 wherein the polymer layer is substantially impermeable to the substance and does not contain the substance.

12. The laminated device of claim 11, said polymer layer being insoluble in water that is below 40 °C.

13. The laminated device of claim 12, said polymer layer comprising hydroxypropyl cellulose and sorbitan monostearate.

14. The device of claim 13 wherein the substance is a breath reodorant.

15. The device of claim 9 wherein the adhesive layer comprises and an adhesive selected from the group consisting of a pressure-sensitive adhesive and a moistenable adhesive.

16. The device of claim 15 wherein the adhesive comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

17. The device of claim 9 comprising one or more polymer layers and two or more substances to be delivered.

18. The device of claim 17 wherein the substances are delivered sequentially.

19. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer;

a first water-soluble polymer layer; and

a second water-soluble polymer layer;

wherein the substance is dissolved or dispersed in any or all of said adhesive or polymer layers.

20. The device of claim 19 wherein the adhesive layer and the second polymer layer contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer, and wherein the device provides for pulsatile delivery of the substance.

21. The device of claim 20 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

22. The device of claim 19 further comprising a third polymer layer wherein the first and the third polymer layers contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer and the second polymer layer is disposed between the first polymer layer and the third polymer layer and wherein the device provides for pulsatile delivery of the substance.

23. The device of claim 22 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

24. A laminated device for the controlled release of a substance within a mucosa-lined body cavity comprising the substance dissolved or dispersed in a water-soluble pressure-sensitive adhesive layer.

25. The device of claim 24 wherein the water-soluble adhesive layer comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

26. A laminated composite device for delivering a substance into the oral cavity for relief of sore throat or cough, comprising a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

27. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of sore throat pain.

28. The laminated composite of claim 27 wherein the active ingredient is selected from the group consisting of benzocaine, lidocaine and dyclonine.

29. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of cough.

30. The laminated composite of claim 29 wherein the active ingredient is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate, menthol.

31. The laminated composite of claim 27 additionally comprising a medicament for the relief of cough.

32. The laminated composite of claim 26 wherein the active-containing water soluble layer comprises a hydrophobic material that will not dissolve in water below 40°C and is hot water dispersible.

33. The laminated composite of claim 32 wherein the active-containingwater soluble layer is selected from the group of materials consisting of monoglycerides, triglycerides, waxes, fatty acids, fatty alcohols and mixtures thereof.

34. The laminated composite of claim 26 wherein the pressure sensitive adhesive is comprised of a water soluble polymer with a glass transition temperature above about 25°C and a hydrophilicity greater than about 25%, and a plasticizer that is liquid at room temperature and has a boiling point higher than about 80°C.

35. The laminated composite of claim 34 wherein the polymer is selected from the group consisting of poly(vinyl pyrrolidone), poly(vinyl alcohol), hydroxy propyl cellulose, poly(ethylene oxide), poly(acrylic acid), polyacrylates, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose, xanthan gum, karaya gum, and gelatin or mixtures thereof.

36. The laminated composite of claim 34 wherein the plasticizer is selected from the group consisting of glycerin, sorbitol, glycol, polysorbate 80, triethyl citrate, acetyl triethyl citrate and tributyl citrate.

37. The laminated composite of claim 26 further including a third polymer layer interposed between the adhesive layer and the active-containing layer.

38. A method for administering a substance over an extended time period for relief of sore throat or cough, comprising dissolving or dispersing the substance in a laminated water soluble device having a water soluble pressure sensitive adhesive layer, and affixing the device onto a mucosal surface of the oral cavity.

39. The method of claim 38 wherein the substance is a medicament for the relief of sore throat pain.

40. The method of claim 39 wherein the medicament is selected from the group consisting of benzocaine, lidocaine and dyclonine.

41. The method of claim 38 wherein the substance is a medicament for the relief of cough.

42. The method of claim 41 wherein the medicament is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate.

43. The method of claim 42 additionally comprising a medicament for the relief of cough.

44. A device for emplacement within a mucosa-lined body cavity of a subject, said device including a portion made of a water-soluble pressure sensitive mucoadhesive composition, said water-soluble pressure sensitive adhesive portion having a surface that forms a basal pressure-sensitive adhesive surface of said device.

45. The device of claim 44, being a device for delivery of a substance to the subject.

46. The delivery device of claim 45, said device being constructed to deliver a substance into the body cavity in which the device is emplaced.

47. The delivery device of claim 45, said device being constructed to deliver a substance across a mucosal surface to which the basal pressure-sensitive adhesive surface of the device is affixed.

48. The device of claim 44, being a laminated device structure, wherein the water-soluble pressure sensitive portion comprises a basal layer of the device.

49. A laminated device for administering a mint aroma into the oral cavity over an extended time, said device including a basal layer comprising a water soluble pressure sensitive mucoadhesive polymer composition, and an upper layer comprising a water soluble polymer composition and a mint flavoring.

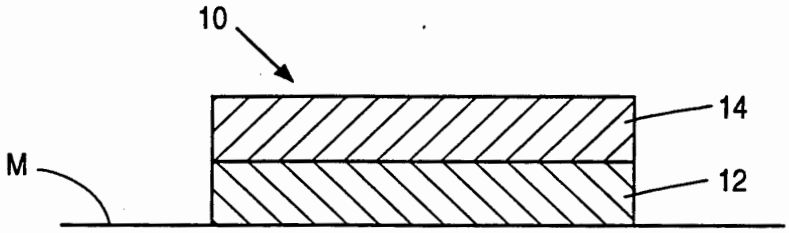

FIG. 1

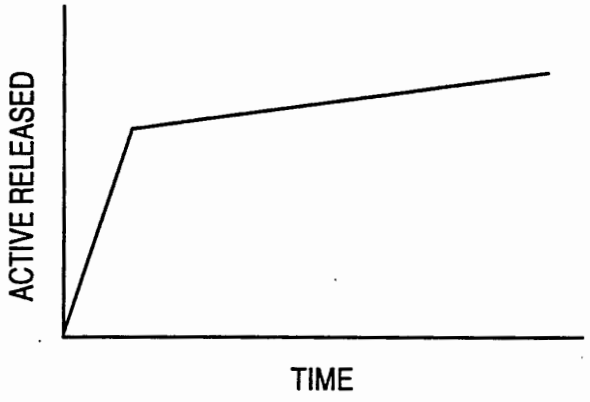

FIG. 5

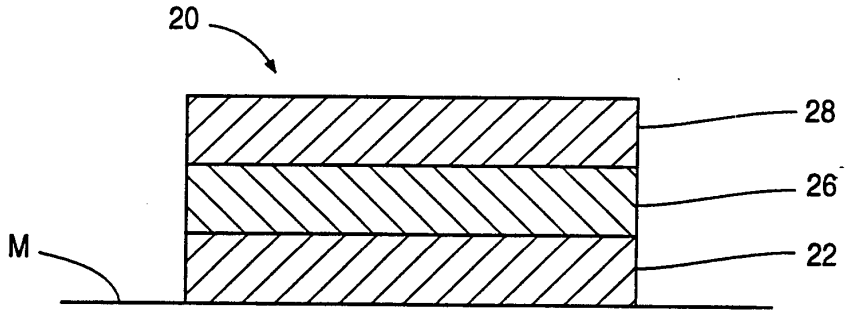

FIG. 2

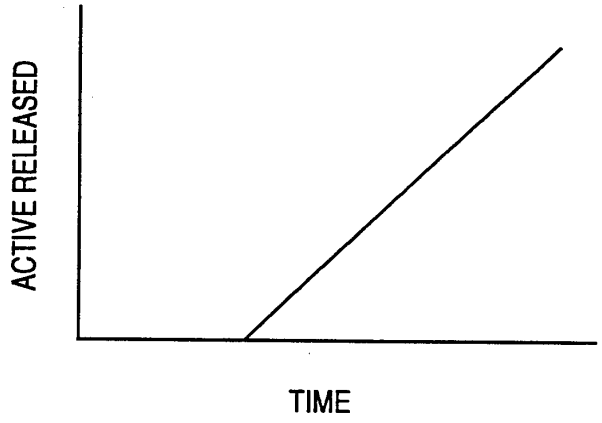

FIG. 6

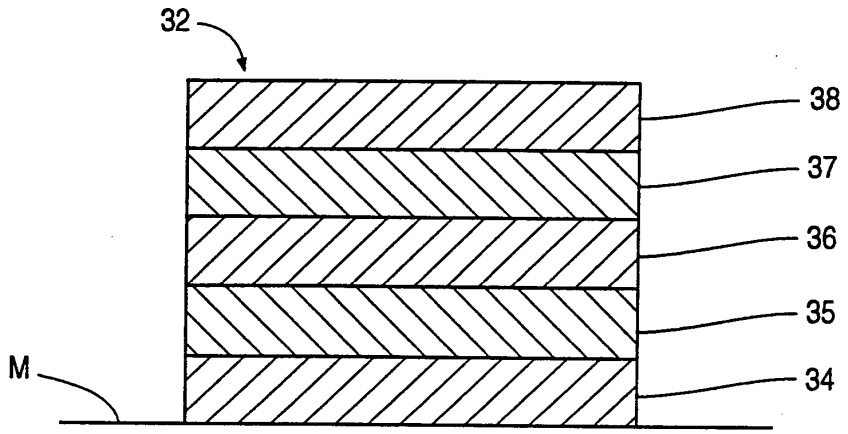

FIG. 3

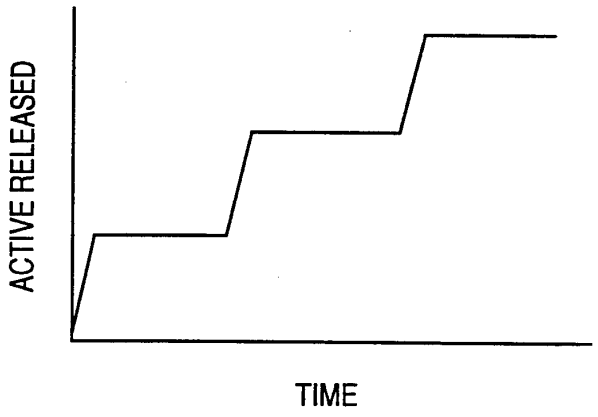

FIG. 7

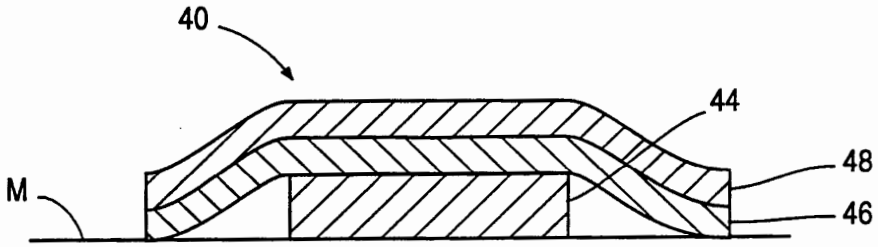

FIG. 4

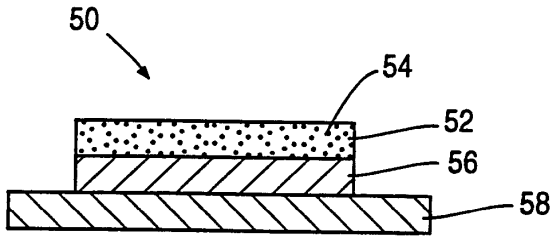

FIG. 8

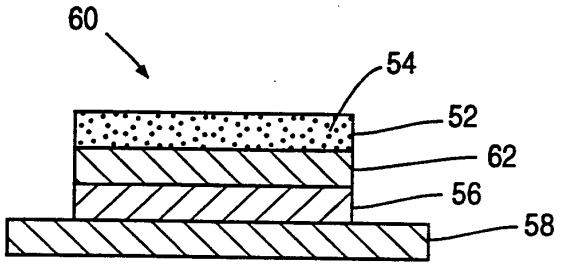

FIG. 9

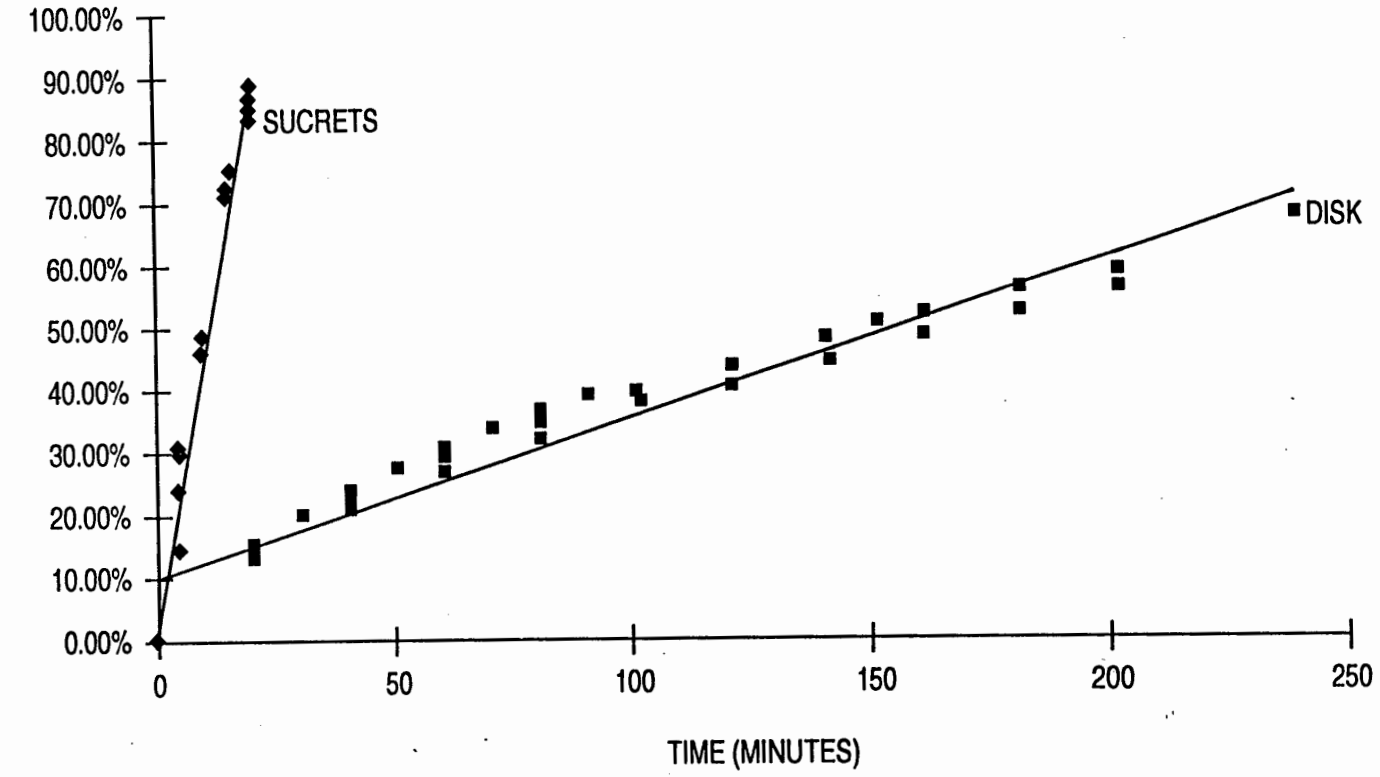

FIG. 10

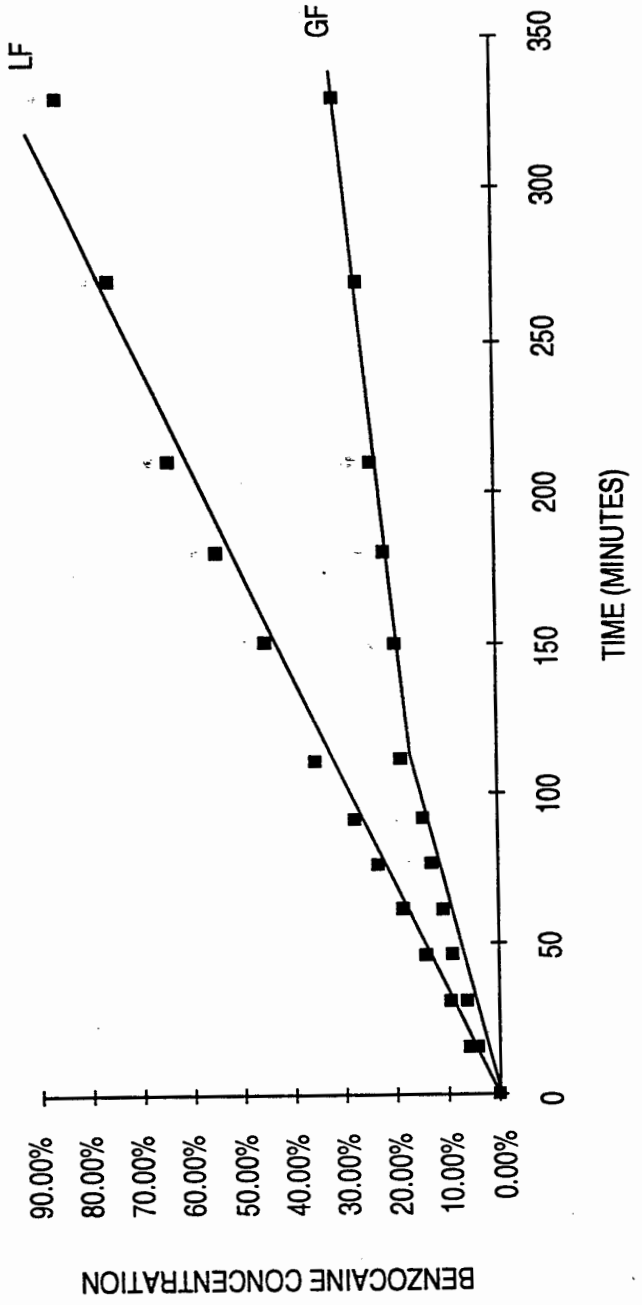

FIG. 11

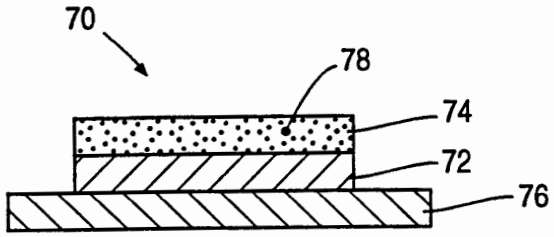

FIG. 12

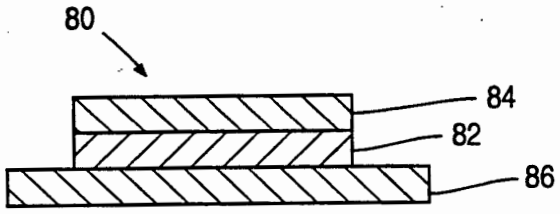

FIG. 13

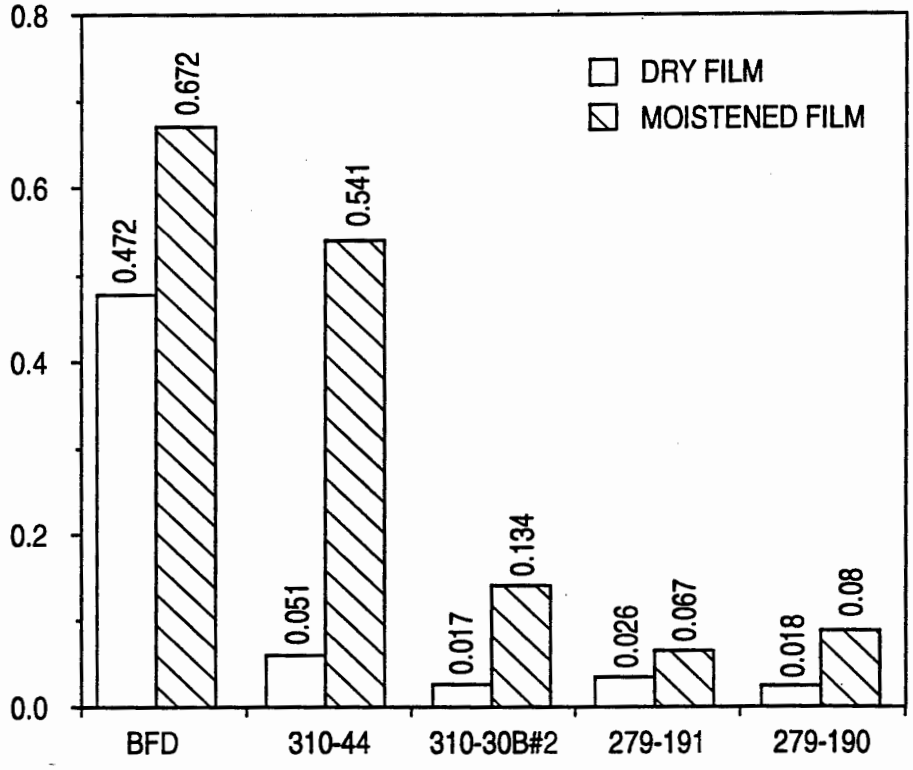

FIG. 14

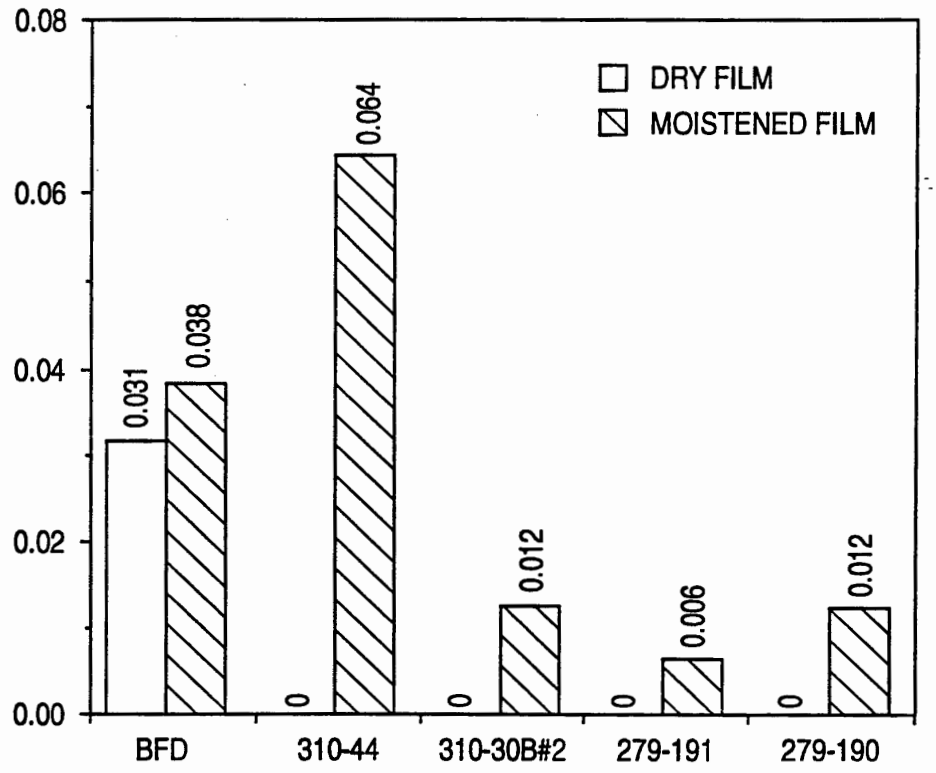

FIG. 15

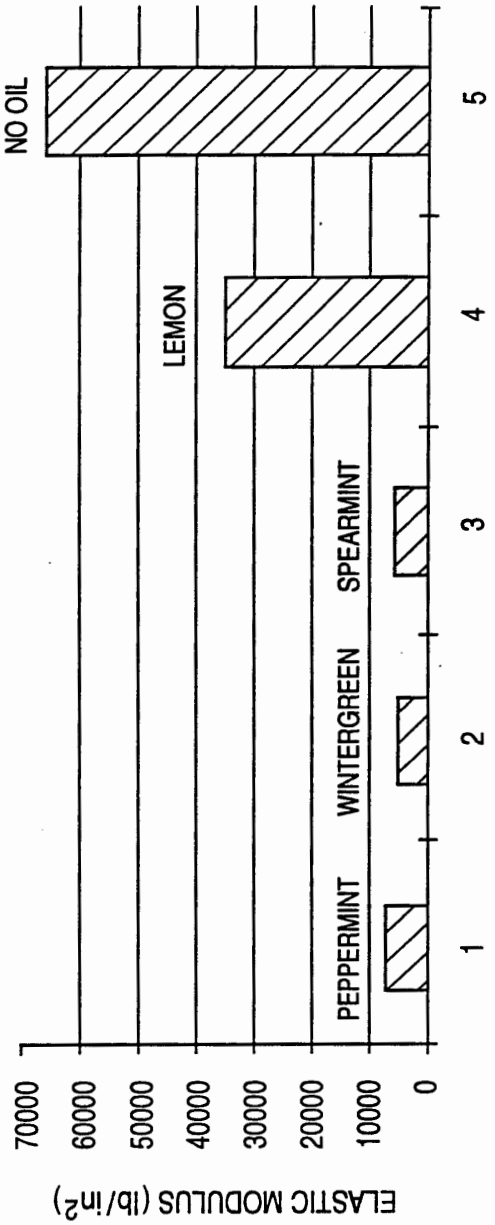

FIG. 16

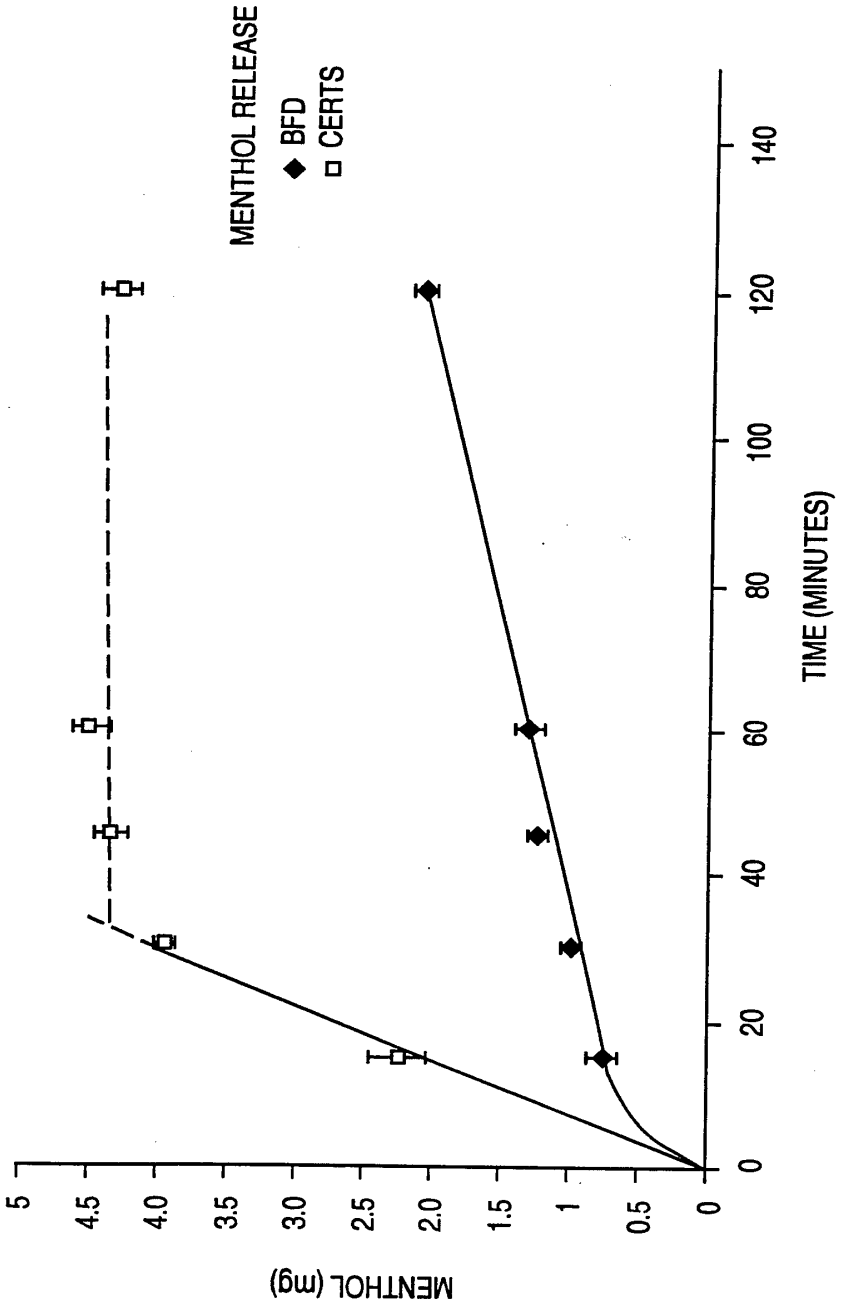

FIG. 17

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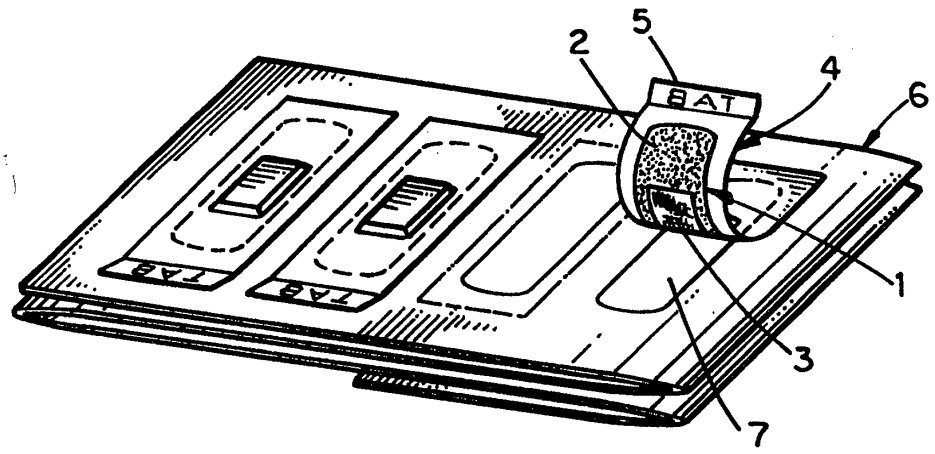
(54) Title: PAKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES



(57) Abstract

The present invention provides an encased article combination that includes a support member (100, 6, 53, 71), a cover member (104, 4, 50, 72), and an encased article (101, 1, 52, 70). The encased article is in the form of adhesive bandages (1), chemical applicator pads (52), and doses of medicine (70). In particular, the invention in part allows access to and use of such items with a single hand.

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PACKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES

This invention relates to a dispensing device for sterile articles such as adhesive bandage strips, chemical applicator pads, and medication. More particularly, this invention permits one-handed access, removal, and application or use of adhesive bandages, chemical substances, or medication.

While adhesive-backed articles such as adhesive bandage strips are known in the art, they are commonly sealed in sterile, individual wrappings and packaged within paper or metal boxes. Examples include the well-known "Band-Aid®" brand bandage strips. While popular, these products suffer certain disadvantages such as the fact that the bandages themselves can be difficult to remove from the wrappings and difficult to apply to the desired location. The user generally must remove the bandage from the wrapping, remove the nonstick layers from the

adhesive portion of the bandage and then attempt to apply the bandage to the desired location in its sanitary and sterile condition without the bandage curling or adhering to itself.

Previous attempts to improve upon this concept include U.S. Patent No. 4,993,586 to Taulbee, et al., which discloses a bandage dispenser device in which a continuous strip is grasped with one hand and a bandage is removed with the other hand. This is accomplished by the use of a continuous strip with a first and second layer. Bandages are placed on sterile mounting pads affixed to the first layer. The bandages and the first layer are then enclosed by a second layer and stacked or rolled within a container. In use, the sheet is pulled through a splicer attached to the container that cuts the first and second layers. The second layer is then lifted and removed. The first layer is then grasped with one hand and a bandage is removed with the other.

U.S. Patent No. 5,133,477 to Etheredge, et al. also discloses a bandage dispensing device employing the use of a continuous strip. The strip has a nonstick coating upon which one end of a bandage is affixed. The other end of the bandage and the cotton gauze area of the bandage are covered with a release sheet. In use, the continuous sheet is grasped with one hand the bandage is grasped and removed with the other hand. The bandage is then applied to the desired location by affixing the exposed half to the skin. Once applied, this end of the bandage is held in place while the release sheet is removed from the bandage and the other end of the bandage is applied to the skin.

Despite these and other prior art devices, there remains a need for a packaging and dispensing device for adhesive-coated articles, such as adhesive bandage strips, by which the article may be grasped with one hand from the front of dispenser and then applied, also one-handedly, to the desired location without the article curling or adhering to itself. Both Taulbee and Etheredge require the use of two hands to remove and apply a bandage strip, and neither addresses the

problem of the bandage strip curling or adhering to itself. Further, the device disclosed by Taulbee would entail considerable manufacturing costs due to the splicer structure. Similarly, there is still a need for a packaging and dispensing device that allows convenient, and in some cases, one-handed access to sanitary applicators and doses of medication.

While the prior art has improved upon access to sanitary articles, there is a need for both improved access to the article and improved applicability of the article. As an example, a lab technician who is drawing blood from a patient could use the improved access to such articles to apply an adhesive bandage strip with one hand while maintaining pressure on the puncture with the other.

Similarly, there remains a need for a device used for the application of chemical substances such as alcohol, makeup, sunscreen and other lotions, antiseptics and medicaments to the skin of the human body in a sterile and sanitary fashion with the use of a single hand. Additionally, there is also a need for convenient, and in some cases, one-handed access to doses of medicine.

The encased article combination of this invention includes a support member, a cover member and an encased article. The encased articles may be packaged either individually, as an assemblage of articles, or as an assemblage of articles in a dispensing device. In one embodiment of this invention the encased article is an adhesive coated article such as a conventional adhesive bandage or other form of wound dressing. In other embodiments of this invention the article is an applicator for chemicals, such as medicines, cosmetics, ointments, salves and the like. In yet another embodiment of this invention pills, capsules, or capelets, or other forms of medicinal dosage units are enclosed for dispensing.

The support member of this invention may take the form of a continuous sheet, coated or uncoated, or a series of molded housings for the articles to be

dispensed. In the most preferred embodiments the support member is flexible so that it can be loaded into a dispensing device in folded or rolled form.

The cover member of this invention is typically adhered to the support member to form the encasement for the article. In certain preferred embodiments the cover member has either one or two adhesive coatings for releasable adherence to the support member and to the encased article. In another preferred embodiment the cover member includes means for gripping the cover member for removal to enable one-handed application or use of the encased device.

In the practice of this invention it is important that the assembly of the support member, the cover member and the encased article form bonds of appropriate adhesive strengths to ensure correct release characteristics. A first adhesive bond is typically formed between the support member and the adhesive surface of the encased article. Such a first bond is typically found in the adhesive bandage encasement embodiment of this invention. A second adhesive bond is formed between the support member and the cover member. A third adhesive bond is formed between the cover member and the encased article. It is important that the third adhesive bond (between the cover member and the encased article) be adhesively stronger than either the first or second adhesive bond. This relationship of the first, second, and third adhesive bonds is important to the practice of this invention. Likewise, it is important that the third adhesive bond be weaker than the bond between the adhesive surface of the encased article and the surface to which it is ultimately applied (recipient surface).

Generally, the present invention comprises an apparatus for packaging and dispensing a sterile article such as an adhesive bandage, a swab-type or sponge-like applicator that may be pretreated with the substance to be applied, or a dose of medicine.

In the present invention, adhesive-coated items are encased within self-contained, sanitary packaging. The adhesive-coated item, such as an adhesive bandage usually has two substantially flat sides. The bottom (or adhesive) side or surface, which is the side applied to the skin in the case of standard adhesive bandages, is coated at least in part with a first adhesive and typically has a sanitary pad affixed thereto.

The adhesive-coated article such as an adhesive bandage is packaged by sandwiching the item between a dispensing support structure, layer, or sheet and a cover layer or strip. The adhesive-coated article is removably adhered to the support sheet by the first adhesive, which forms a first bond with the support sheet. The length and width dimensions of the support sheet exceed those of the adhesive-coated article. Alternatively, sterile, nonstick mounting pads may be affixed to the support sheet and an adhesive-coated article such as an adhesive bandage may instead be removably adhered to each of the mounting pads. If the support sheet is made of suitable material, then nonstick mounting pads are not necessary.

The packaging or encasement is further accomplished by forming or removably adhering a cover structure or layer, which also exceeds the dimensions of the adhesive-coated article, both to the top surface of the adhesive-coated article and to an additional peripheral area of the support sheet surrounding the article. A second adhesive may be used to removably adhere the cover layer to the top surface of the adhesive-coated article by forming a second bond therebetween. The second adhesive forms an additional bond between the peripheral area of the cover strip extending beyond the edges of the adhesive-coated article and the corresponding peripheral area of the support sheet. The second bond, that formed between the adhesive-coated article and the cover strip, is of greater strength than the first bond, that between the adhesive-coated article and the support sheet, so that when the cover strip is removed, usually by grasping a tab portion of the cover strip or any other suitable gripping means attached to the cover strip, the

adhesive-coated article is detached from the support sheet, while the top surface of the adhesive-coated article remains removably attached to the cover strip.

The adhesive-coated article can then be transported to and applied to the receiving surface, such as the human skin, with single handed use of the cover strip. Once the bottom surface of the adhesive-coated article, containing the first adhesive, is applied to the receiving surface, the first adhesive forms a strong bond between the receiving surface and the bottom surface of the article such that the strength of this bond with the receiving surface exceeds that of the bond between the cover layer and the top surface of the article so that subsequent pulling force exerted upon the cover layer will cause the cover layer to become detached from the top surface of the article, thereby leaving the article suitably applied to the receiving surface.

In another form, the present invention comprises an apparatus for packaging and dispensing a swab-type or sponge-like applicator, which is packaged by sandwiching it between a support structure, layer, or sheet and a cover structure, layer, or strip. In this application, the swab-type or sponge-like applicator, such as a piece of gauze, cotton, cloth, sponge, or other material is attached to a cover strip having length and width dimensions that exceed those of the applicator. The cover strip is attached to the applicator with an adhesive or some other suitable means of attachment. A peripheral area of the cover strip surrounding the applicator is coated with an adhesive which forms a temporary bond between the peripheral area of the cover strip extending beyond the edges of the applicator and the corresponding peripheral area of the support sheet. When the cover strip is pulled, the applicator is removed with the cover sheet, thereby exposing the applicator so that it may be moved to the receiving surface. The applicator can be pretreated with antiseptics, lotions, sunscreens, makeup or any medicament or other chemical to be applied, but does not necessarily have to be pretreated.

In yet another form, the present invention comprises an apparatus for packaging and dispensing doses of medicine such as capsules, capelets, pills, or other units of medicine. In this embodiment, capsules, for example, are packaged in trays which function as the support member and which contain troughs for holding the capsules. The capsules are further packaged with the use of a cover sheet which is removably adhered to at least the peripheral area of the trays. The package may or may not include an additional, protective, thin burstable film between the cover sheet and the capsules. The inner dimensions of the troughs may or may not be slightly smaller than the outer dimensions of the capsules in at least one dimension. If the troughs are slightly smaller than the capsules, then the user must exert force on the troughs to eject the capsules once the troughs have been removed from the cover layer with the use of a tab or other suitable gripping means attached to or formed as part of the tray. If the troughs are of the same or equal size as the capsules, then a portion of the underside of the cover layer may be coated with a temporary adhesive that removably adheres the capsules to the cover layer and removes the capsules from the troughs when the cover layer is removed.

Embodiments of this invention include the individual packaging and dispensing of individual or multiple adhesive bandages of virtually any shape, or applicators as well as the packaging and dispensing of multiple bandages, applicators, or doses of medicine positioned on individual or continuous sheets or rolls or in trays packed within a dispenser.

The dispenser itself may be a desktop or wall-mounted refillable container constructed of metal, plastic or paper. The dispenser has an opening or a window to provide access to sterile, individually wrapped adhesive bandages or applicators affixed to single or continuous sheets or rolls, or doses of medicine in trays formed from single or continuous sheets or rolls. A continuous support sheet of bandages or applicators may be layered or rolled in the bottom of the dispenser and fed across the dispenser window so that the leading end of the sheet either

exits through one end of the dispenser or is attached to a spool. As the bandage strips or applicators are removed via the access window and used, the support sheet may be pulled through the aperture or the spool may be turned, thus exposing additional bandages or applicators in the dispenser window. If medicine is dispensed then single sheets or multiple layers of single sheets of trays of medicine may be loaded into the dispenser and the trays may be accessed through the access window for use.

An aperture may be in addition to or instead of the access window. The aperture allows single or multiple packaged bandages, applicators or packets of medicine to be dispensed from one side of the dispenser for immediate or subsequent use. In a dispenser containing both an access window and an aperture, the aperture also allows the packaging material remaining from bandages, applicators, or pills accessed through the access window to be removed and discarded.

Thus, it is an object of the present invention to provide an improved package and dispenser for sterile articles such as adhesive bandages, chemical applicators, and doses of medicine.

It is also an object of present invention to provide a device that allows the user to apply a common sterile adhesive bandage or chemical substance using only one hand in the process of removing the bandage or substance applicator from the dispenser and applying it to the desired location.

It is a further object of this invention to provide an apparatus for application of a bandage strip to its desired location with the use of a single hand without the bandage strip curling or adhering to itself.

Yet another object of this invention is to provide an apparatus for the application of a chemical substance to a surface with the use of a single hand.

It is still a further object of the invention to provide a convenient dispenser which displays several adhesive bandages or substance applicators for immediate use, eliminates the handling of individually wrapped bandages or substance applicators, and reduces the amount of immediately discarded wrapping material.

Other objectives, features and advantages of the present invention will become apparent upon reading the following specification, when taken in conjunction with the drawings and the claims.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 3 is a side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 5 is a side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 6 is a perspective view showing an adhesive bandage strip removably adhered to a cover strip containing a pull tab.

FIG. 7 is a perspective view showing the positioning of adhesive bandage strips and non-continuous cover strips on a continuous support layer.

FIG. 8 is a perspective view showing the positioning of adhesive bandage strips and continuous cover strips on a continuous support layer.

FIG. 9 is an exploded perspective view of a single adhesive bandage strip encased according to the present invention.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip with a cover strip to a recipient's skin.

FIG. 11 is an exploded perspective view of one embodiment of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 12 is a side cut away view showing the dispenser of FIG. 11 packed with a fan folded continuous member of adhesive bandage strips.

FIG. 13 is a perspective view of the dispenser of FIG. 11.

FIG. 14 is a perspective cut away view of one embodiment of a dispenser for adhesive bandages packaged on continuous support member.

FIG. 15 is a perspective view of a portion of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 16 is a cut away perspective view of a wall mounted dispenser containing a spool for dispensing adhesive-coated bandages packaged on a roll according to the present invention.

FIG. 17 is a cut away perspective view of a wall mounted dispenser containing a roll of adhesive coated bandages on a roll packaged according to the present invention.

FIG. 18 is an exploded perspective view showing an applicator packaged according to the present invention.

FIG. 19 is an exploded perspective view showing a plurality of applicators packaged on a single support member according to the present invention.

FIG. 20 is a perspective view showing one embodiment of a dispenser for a plurality of applicators packaged on a single support member according to the present invention.

FIG. 21 is a perspective view of one embodiment of a dispenser for dispensing the applicators shown in FIG. 19.

FIG. 22 is an exploded perspective view of one embodiment of capsules packaged according to the present invention.

FIG. 23 is an exploded perspective view of another embodiment of capsules packaged according to the present invention.

FIG. 24 is a bottom perspective view of the packaged capsules shown in FIG. 23.

FIG. 25 is a perspective view of a user ejecting capsules packaged according to the present invention.

FIG. 26 is a cut away perspective view of one embodiment of a dispenser for dispensing
medicine packaged according to the present invention.

FIG. 27 is an exploded cut away perspective view of another embodiment of a dispenser for dispensing medicine packaged according to the present invention.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention. FIG. 1 shows adhesive-coated article 101 having first adhesive surface 102 encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by the second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of another embodiment of an adhesive-coated article encased according to the present invention. Adhesive-coated article 101 having first adhesive surface 102 is encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween. Cover member 104 is also removably adhered to the adhesive-coated article 101 by third adhesive coating 106 which forms a third adhesive bond therebetween which is stronger than the second adhesive bond.

FIG. 3 further shows the encased adhesive-coated article of FIG. 2 with the addition of contact between the appropriate layers and adhesives, and also shows the addition of means for gripping 107 to facilitate removal of cover member 104.

FIG. 6 shows an application of the present invention to the packaging of an adhesive bandage strip. The adhesive bandage strip 1 is the adhesive-coated

article. The cover member in this embodiment is cover strip 4, as these terms may be used interchangeably in this configuration. The support member in this embodiment is support sheet 4. FIG. 6 shows a perspective view of an adhesive bandage strip 1 joined to a cover strip 4 with a pull tab 5. The adhesive bandage strip 1 is generally constructed of plastic, paper, or cloth material with an adhesive substance applied to the adhesive side 2 of the strip and a cotton gauze area 3 in the middle of this adhesive side 2 of the strip 1. A conventional adhesive bandage strip, such as the "Band-Aid®" brand bandage strip, may be used.

The adhesive bandage strip 1 is joined to a cover strip 4 by a temporary adhesive. Examples of the temporary adhesive substance include "DryLine™" temporary adhesive made by the Gillette Company. The cover strip 4 may be constructed of any suitable material, including paper or plastic. The temporary adhesive used to join the cover strip 4 to the adhesive bandage strip 1 forms a stronger bond between the cover strip and the bandage than the bond formed by the adhesive substance between the adhesive side 2 of the adhesive bandage strip 1 and the support sheet 6 of FIG. 7. The cover strip 4 also contains a suitable means for gripping, such as pull tab 5, for ease of removal, as explained below.

FIG. 7 is a perspective view showing the positioning of the adhesive bandage strips 1 and non-continuous cover strips 4 on a continuous support sheet 6. The continuous support sheet 6 may be constructed out of any suitable material, including paper or plastic. The support sheet 6 can be of any suitable length and can be fan folded as shown in FIG. 7, or rolled as shown in FIGS. 16 and 17.

FIG. 8 shows a perspective view of an embodiment of the invention in which adhesive bandage strips are dispensed on a fan folded continuous support sheet 6 and covered and dispensed with the use of continuous cover strips 18 formed by the perforation or cutting of a continuous cover layer 19.

In the embodiments utilizing either continuous or non-continuous cover strips, a variable number of sterile, nonstick mounting pads 7, as shown in FIG. 7, may be permanently affixed to or incorporated into the continuous support sheet 6. The sterile, nonstick mounting pads 7 are generally constructed out of paper, such as the release liner-type paper manufactured by Rhinelander Paper Company. The adhesive bandage strips 1 are positioned on the sterile, nonstick mounting pads 7 such that the adhesive side 2 of a bandage strip 1 is in contact with the sterile, nonstick mounting pads 7. Alternatively, the continuous support sheet 6 itself can be treated with a nonstick substance such that the adhesive bandage strips 1 may be placed directly on the support sheet 6.

If non-continuous cover strips 4 are used as shown in FIG. 7, then a cover strip 4 is joined to each of the adhesive bandage strips 1 as discussed above. The cover strip 4, covers the adhesive bandage strip 1 and adheres to that area of the support sheet 6 immediately surrounding the adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed within the cover strip 4 and the support sheet 1. This enclosure ensures that the adhesive bandage strips 1 remain sterile until use. The support sheet 6 may be scored or perforated between a predetermined number of packaged bandages so that individual or groups of packaged bandages may be torn off for immediate or subsequent use as shown in FIGS. 14 and 15. This also allows the user to remove and discard portions of the support sheet 6 remaining after any number of bandages has been used.

If continuous cover strips 18 are used, as shown in FIG. 8, then a continuous cover sheet 19 covers any number of adhesive bandage strips 1 and adheres to the area of the continuous support sheet 6 immediately surrounding each adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed between a portion of the continuous cover sheet 19 and the continuous support sheet 6, maintaining sterility. The continuous cover sheet 19 is cut or perforated into individual cover strips 18 so that bandages 1 can be removed and applied individually.

In this embodiment, the continuous support sheet 6 and continuous cover sheet 19 may both be scored or perforated between any number of adhesive bandages 1 as shown in FIGS. 8 and 13, thereby allowing any number of packaged bandages to be removed individually or in groups and also allowing removal of portions of the continuous support sheet 6 after any number of bandages 1 has been used.

FIG. 9 shows an exploded perspective view of an individual, packaged adhesive bandage that has been removed from a continuous support sheet of adhesive bandages having perforations between bandages and that also has cover strips cut or perforated from a continuous cover sheet.

Referring to FIG. 7, in operation, the cover strip 4 is grasped via the pull tab 5. When the pull tab 5 is pulled, the adhesive bandage strip 1 and the cover strip 4 are peeled together from the continuous support sheet 6, or from alternative, nonstick mounting pad 7 and the continuous support sheet 6. The temporary adhesive joining the bandage strip 1 and the cover strip 4 is of sufficient strength to overcome the bond between the adhesive side 2 of bandage strip 1 and sterile, nonstick mounting pad 7 or the support sheet. The adhesive bandage strip 1, still backed by cover strip 4, is then applied to the desired location on the recipient's skin.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip 1 with a cover strip 4 to a recipient's skin. Once the adhesive bandage strip 1 is applied, because the temporary adhesive joining the adhesive bandage strip 1 and the cover strip 4 forms a bond that is weaker than the bond formed between the adhesive side 2 of bandage strip 1 and the recipient's skin, the cover strip 4 is peeled away from both the adhesive bandage strip 1 and the recipient's skin, thereby leaving the adhesive bandage strip 1 applied to the recipient's skin. The cover strip 4 may then be discarded.

FIG. 11 is an exploded perspective view showing the elements of a dispenser 10 for the packaged bandages described. The dispenser 10 consists of a top half 11 defining an access window 12, a bottom half 13, a support ledge 14, a spool 15, and a knob 16. As shown, the support ledge 14 is positioned within top half 11 directly underneath access window 12 and is supported by bottom half 13. The bottom half 13 is generally hollow so as to provide space for the packing of the continuous sheet 6. The spool 15 is generally located on one end of the lower half 13 and communicates with knob 16 on the exterior of the dispenser 10. Optionally, the dispenser 10 may also contain an aperture through which prepackaged bandages, or portions of support sheet remaining from bandages accessed through the access window 12, may pass for use or discarding.

The dispenser 10 can be manufactured out of any suitable material including metal, plastic or paper. The dispenser 10 may be refillable and may be used on a desktop or mounted to a wall.

FIG. 12 is a side cut away view showing a dispenser 10 packed with a fan folded continuous support sheet 6 of adhesive bandage strips 1. The continuous support sheet 6 is fed through and across support ledge 14 such that the adhesive bandage strips 1 are exposed through access window 12. The leading end 8 of continuous support sheet 6 is attached to spool 15 such that the continuous support sheet 6 can be advanced by rotating knob 16 as the adhesive bandage strips 1 are removed. Alternatively, the leading end 8 of continuous support sheet 6 may be fed through optional aperture 15a so that either packaged bandages can be removed for subsequent use, or portions of continuous support sheet 6 that remain after bandages have been removed via access window 12 may be removed and discarded.

FIG. 13 is a perspective view of the dispenser of FIGS. 11 and 12, showing the optional dispensing aperture.

FIG. 14 shows an alternate embodiment of a dispenser for packaged bandages or other adhesive-coated articles, in which the dispenser contains an access window 12 and a dispensing aperture 15a, but does not contain a spool and knob. The continuous support sheet 6 may be pulled through the aperture 17 so as to advance the continuous support sheet 6 after adhesive bandage strips 1 are removed through the access window 12. Alternatively, the dispenser 10 may allow bandages packaged on the continuous support sheet 6, and which were not removed while exposed in the access window 12, to pass through the aperture 17 and be removed at perforations in the continuous support sheet 6 either individually or in groups for later use.

FIG. 15 shows a perspective view of a portion of yet another embodiment of a dispenser for packaged bandages or other adhesive-coated articles. In this embodiment, multiple adhesive-coated articles are visible on access shelf 20.

FIG. 16 shows a perspective cut away view of a wall-mounted dispenser for bandages or other adhesive-coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled.

FIG. 17 shows a perspective cut away view of yet another embodiment of a dispenser for adhesive coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled. In this configuration, the dispenser contains no spool for coiling the remaining portions of the support sheet after removal of adhesive-coated articles.

While the invention has been disclosed with respect to an adhesive bandage strips, it will be appreciated that the invention is equally well suited for other shapes of adhesive bandages as well as other types of adhesive-backed articles such as bumper stickers, adhesive-backed name tags, and the like.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention. A sterile article 133 is effectively encased for dispensing or distribution by its attachment to cover member 132. The sterile article 133 is further encased by removably adhering cover member 132 to support member 130 with first adhesive coating 131 to form an adhesive bond therebetween.

FIG. 5 is a conceptual side view of another embodiment of the present invention, showing a sterile article adhered to cover member 132 by second adhesive 134, forming a second bond therebetween. As in the embodiment of FIG. 4, the sterile article 133 is encased by removably adhering cover member 132 to support member 130 with the use of first adhesive coating 131 to form a first bond therebetween and functionally encase the sterile article 133.

FIG. 18 shows an exploded perspective view of an embodiment of the invention in which the sterile article is a chemical substance applicator 52 such as a cotton swab, a portion of gauze, sponge, cloth, or other material and is affixed to a cover 50 which serves as the cover member. The applicator 52 is further packaged by placement of the applicator 52 on a support sheet 53 which serves as the support member. The portion of the cover 50 extending beyond the periphery of the applicator 52 is coated with a temporary first adhesive which removably adheres that portion of the cover 50 to a corresponding region of the continuous support sheet 53, thereby sealing the applicator 52 in a sanitary package. The adhesive surrounding the applicator 52 used to removably adhere the periphery of the applicator 52 to the support sheet 53 may also be used to adhere the cover 50 to the applicator 52.

Multiple covers may be formed from a continuous sheet that is cut, scored, or perforated between adjacent applicators or they may formed from separate pieces of material. The covers 50 may contain a corner-type tab 54 as shown in 18, an edge-type tab 55 as shown in FIG. 19, or any other means for gripping that

facilitates the removal of the cover 50 and applicator 52 from the support sheet 53. The cover 50 may contain an additional handle or gripping device on its surface to further assist the user in removing or holding the cover 50.

The applicator 52 may be pre-treated with any chemical substance to be applied such as antiseptics, makeup, lotions, medicaments or any other suitable substance for application. Alternatively, the applicator 52 may not be pre-treated. If the applicator 52 is pre-treated, then the user will pull the tab 55, thereby removing the applicator 52 from the support sheet 53, and exposing the applicator 52 for application to the recipient surface such as human skin. If the applicator 52 is not pre-treated, then after removal from the support sheet, the applicator 52 may be used as a sanitary wipe, or the user may apply any suitable substance such as bottled alcohol, makeup, or lotion, or any other suitable substance to the applicator and then apply the applicator to a recipient surface. In this embodiment, it is contemplated that both pretreated and non-pretreated swabs will have application beyond the medical field and will provide a convenient swab or applicator for the application of any number of chemical substances in any number of commercial or household applications.

Applicators of this embodiment may be dispensed from single or continuous sheets or rolls. FIG. 19 shows an embodiment in which multiple applicators 52 are packaged on a single support sheet 53. The encased, or packaged, applicators of FIGS. 18 and 19 may be dispensed with the use of the dispensers of FIGS. 20 and 21 respectively. Alternatively, the encased articles may be dispensed with dispensers not shown in the figures, but which may be similar or identical to the dispensers of FIGS. 14 and 15 in which any such articles may be dispensed via the aperture at the end of an access shelf of the dispenser. In yet another configuration not shown, such encased sterile articles may be dispensed on rolled sheets with dispensers similar or identical to the dispensers of FIGS. 16 or 17.

FIG. 22 shows another embodiment in which the invention is used to dispense doses of medication such as capsules, capelets, pills, or other units of medicine. In this embodiment, a dosage of medicine, such as capsule 70, is packaged in dispensing tray 71 which functions as the support member and which contains holding troughs 73. In one embodiment, the size of the capsule 70 exceeds the interior size of the holding trough 73 in at least one dimension so that some pressure may be required for the removal of capsules 70 from the trough 73. The capsules 70 are further packaged with the use of a cover sheet 72 which functions as the cover member and which is coated in part on one side with an adhesive that removably adheres peripheral and central portions of the cover sheet 72 to corresponding portions of the dispensing tray 71 so as to retain the capsules 70 in a completely enclosed sanitary package. The tray 71 may contain a suitable means for gripping, such as pull tab 75 in one or more corners or along one or more edges for ease in removing the tray 71 from the cover sheet 72.

In this embodiment, filled packages may be dispensed through a dispenser such as that shown containing a spool and aperture in FIG. 27 or an aperture only as in FIG. 26. Trays 71 may be pulled with tab 75 through access window 81. Alternatively, complete, unused packages may be dispensed through an aperture 82 for immediate or subsequent use and are perforated or scored between single or multiple packages. If complete, unused packages are dispensed through an aperture, then, the user removes capsule 70 by peeling back the tray 71 with the use of tab 73 or a suitable handle or grasping device affixed to the exterior of the tray 71. The user then squeezes the trough 73 to eject the capsule 70 therefrom, as shown in FIG. 25.

In another embodiment, as shown in FIGS. 23 and 24, a thin, burstable film 74, made of paper, plastic, metal foil, or any other suitable material, is adhered to the top surface of dispensing tray 71 so as to form an intermediate layer between cover sheet 72 and dispensing tray 71. In this embodiment, the cover sheet 72 is removably adhered to the film 74. Once the cover sheet 72 is

removed, the user must then squeeze the trough 73 to force the capsule 70 to penetrate or break through the film 74 and eject the capsule 70 from the package for use.

For any of the embodiments used in dispensing medication, the dispensing trays may be formed individually or from single or continuous sheets of material. The cover sheets may be spaced or may be formed by cutting, perforating, or scoring of a continuous sheet of material. If multiple dispensing trays are formed from a single piece of material, the material may be perforated or scored between adjacent packages or at other regular or varying intervals to allow dispensing or single or multiple packages of medication.

In any of the embodiments for dispensing medication, dosage information may be printed on the surfaces of the cover sheet or dispensing tray. This allows the manufacturer or user to label particular doses. For example, with certain medications, a particular dosage must be taken on each day of the week such that the dosages for different days will differ. In this case, a particular dosage can be labelled for "Monday," "Tuesday," and so forth. These embodiments allow the user to see quickly whether the dosage for a particular day has already been dispensed. This may be particularly helpful in the case of forgetful patients.

While the invention has been disclosed with respect to particular embodiments, the applicant does not regard the invention as being limited to such embodiments or applications. It is also understood that this description is not meant to be limiting because further modifications may now suggest themselves to those skilled in the art and is intended to cover such modifications as fall within the scope of the following claims.

CLAIMS:

1. An encased adhesive-coated article combination comprising:

a. a support member;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a second adhesive coating covering at least a portion thereof, said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and said cover member forming a second adhesive bond.

2. The encased adhesive-coated article combination of claim 1, wherein said second adhesive bond is weaker than the first adhesive bond.

3. The encased adhesive-coated article combination of claim 2, wherein said support member further comprises a nonstick mounting pad.

4. The encased adhesive-coated article combination of claim 1 further comprising a means for gripping attached to said cover member.

5. The encased adhesive-coated article combination of claim 4, wherein said adhesive-coated article is an adhesive bandage.

6. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a second adhesive coating covering at least a portion thereof, each said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and each said cover member forming a second adhesive bond.

7. The assemblage of encased adhesive-coated articles of claim 6, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

8. The assemblage of encased adhesive-coated articles of claim 6 wherein the support member further comprises a plurality of nonstick mounting pads.

9. The assemblage of encased adhesive-coated articles of claim 7, wherein said adhesive-coated articles are adhesive bandages.

10. The assemblage of encased adhesive-coated articles of claim 8, wherein said adhesive-coated articles are adhesive bandages.

11. The assemblage of encased adhesive-coated articles of claim 7, wherein said support member is a sheet.

12. The assemblage of encased adhesive-coated articles of claim 11, wherein said sheet is a continuous sheet.

13. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a folded configuration.

14. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a rolled configuration.

15. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated at predetermined intervals.

16. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

17. The assemblage of encased adhesive-coated articles of claim 11, wherein said adhesive coated articles are adhesive bandages.

18. The assemblage of encased adhesive-coated articles of claim 12, wherein said adhesive coated articles are adhesive bandages.

19. The assemblage of encased adhesive-coated articles of claim 6, wherein each said cover member is dimensioned to extend beyond the peripheral edges of a respective adhesive-coated article.

20. An encased adhesive-coated article combination comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-

coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and the first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a third adhesive coating thereon, said cover member being removably attached to said support sheet by contact of said patterned second adhesive coating with said cover member, the contact between said support member and said cover member forming a second adhesive bond, said cover member further being removably attached to said adhesive-coated article by said third adhesive coating, the third adhesive coating forming a third adhesive bond between said cover member and said adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

21. The encased adhesive-coated article combination of claim 20, wherein said second bond is weaker than said first bond.

22. The encased adhesive-coated article combination of claim 20, wherein said support member further comprises a nonstick mounting pad.

23. The encased adhesive-coated article combination of claim 20 further comprising a means for gripping attached to said cover member.

24. The encased adhesive-coated article combination of claim 23, wherein said support member further comprises a nonstick mounting pad.

25. The encased adhesive-coated article combination of claim 23, wherein said adhesive-coated article is an adhesive bandage.

26. The encased adhesive-coated article combination of claim 24, wherein said adhesive-coated article is an adhesive bandage.

27. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, each said adhesive-coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and each said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member being removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a third adhesive coating thereon, each said cover member being removably attached to said support sheet by contact of said second

adhesive coating with said support member, the contact between said support member and each said cover members forming a second adhesive bond, each said cover member further being removably attached to a respective adhesive-coated article by a third adhesive coating, the third adhesive coating forming a third adhesive bond between said each said cover member and a respective adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

28. The assemblage of encased adhesive-coated articles of claim 27, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

29. The assemblage of encased adhesive-coated articles of claim 27, wherein said support member further comprises a plurality of nonstick mounting pads.

30. The assemblage of encased adhesive-coated articles of claim 28, wherein said adhesive-coated articles are adhesive bandages.

31. The assemblage of encased adhesive coated articles of claim 30, wherein said support member further comprises a plurality of nonstick mounting pads.

32. The assemblage of encased adhesive-coated articles of claim 28, wherein said support member is a sheet.

33. The assemblage of encased adhesive-coated articles of claim 32, wherein said sheet is a continuous sheet.

34. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is folded.

35. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is rolled.

36. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated at predetermined intervals.

37. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

38. The assemblage of encased adhesive-coated articles of claim 33, wherein said adhesive coated articles are adhesive bandages.

39. The assemblage of encased adhesive-coated articles of claim 37, wherein said adhesive coated articles are adhesive bandages.

40. The plurality of encased adhesive-coated articles of claim 27, wherein each said cover member is dimensioned to extend beyond the peripheral edges of said adhesive coated articles.

41. An encased sterile article combination comprising:

a. a support member;

b. a sterile article; and

c. a cover member removably attached to said support member to functionally encase said sterile article, said sterile article being removably adhered to said cover member.

42. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator.

43. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator that includes a dispensable medicament.

44. The encased sterile article combination of claim 41 wherein said sterile article is a unit of medicine.

45. The encased sterile article combination of claim 41 wherein said sterile article is a pill, capelet, or capsule.

46. The encased sterile article combination of claim 41 wherein said support member comprises a continuous sheet of molded housings adapted to fittably receive said sterile article.

47. The enclosed sterile article combination of claim 41 wherein said cover member further includes gripping means.

48. The encased sterile article combination of claim 41 further comprising a non-adhesive, burstable film disposed between said support member and said cover member, said film being functionally effective to protect the sterility of said sterile article after the cover member has been removed.

49. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a folded configuration.

50. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a rolled configuration.

51. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit as individual encased units.

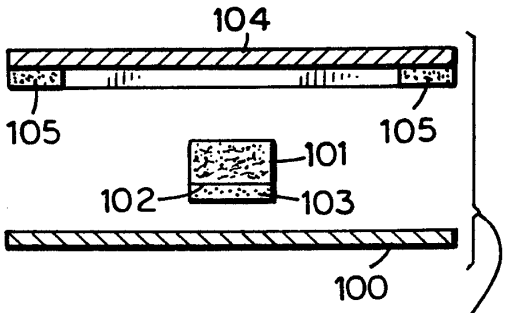


Fig. 1

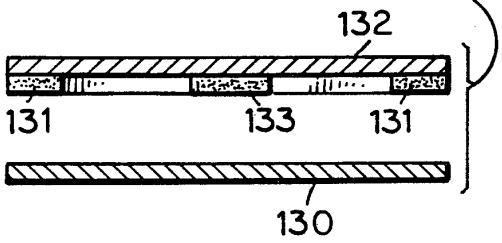


Fig. 4

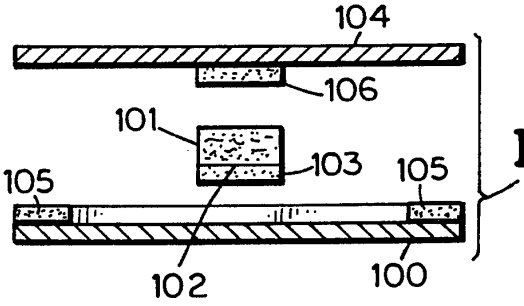


Fig. 2

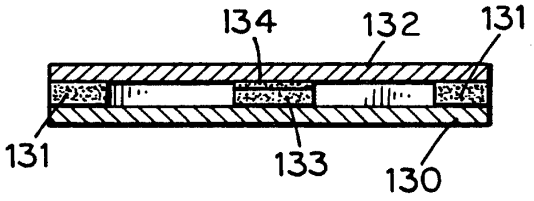


Fig. 5

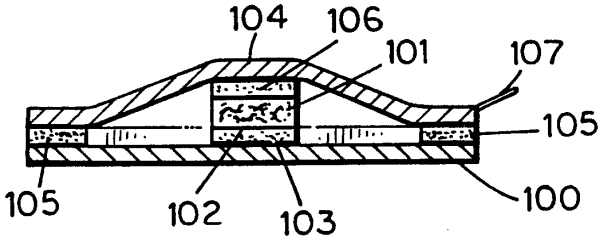


Fig. 3

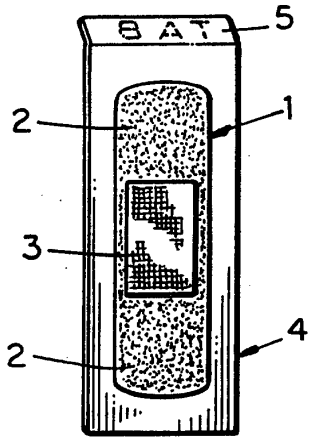


Fig. 6

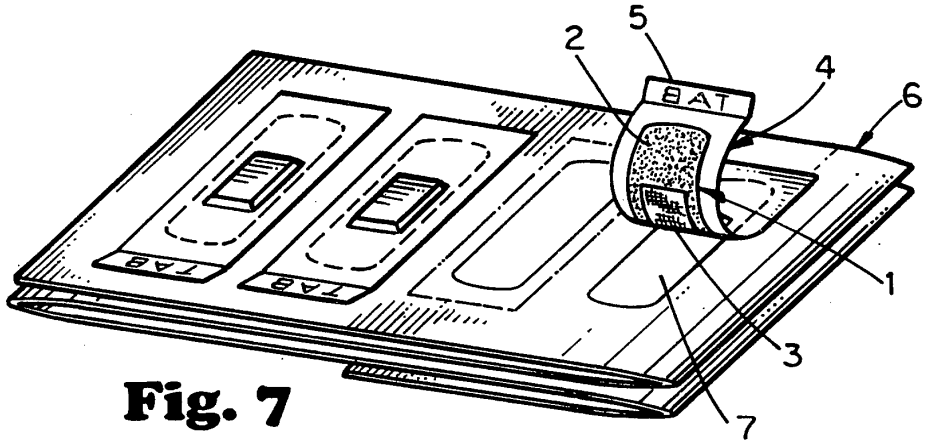


Fig. 7

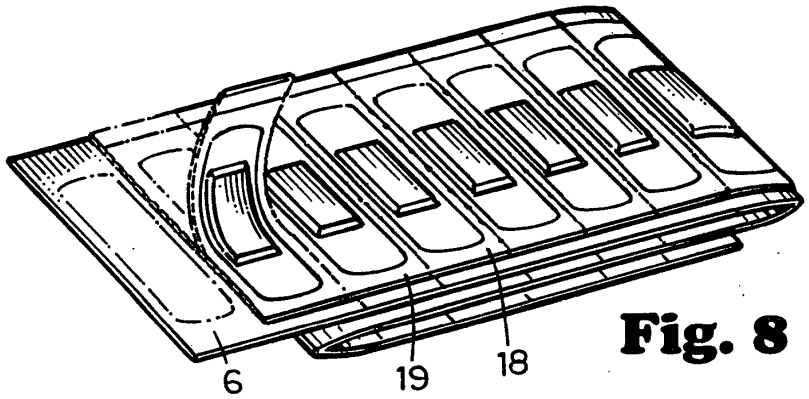


Fig. 8

Fig. 11

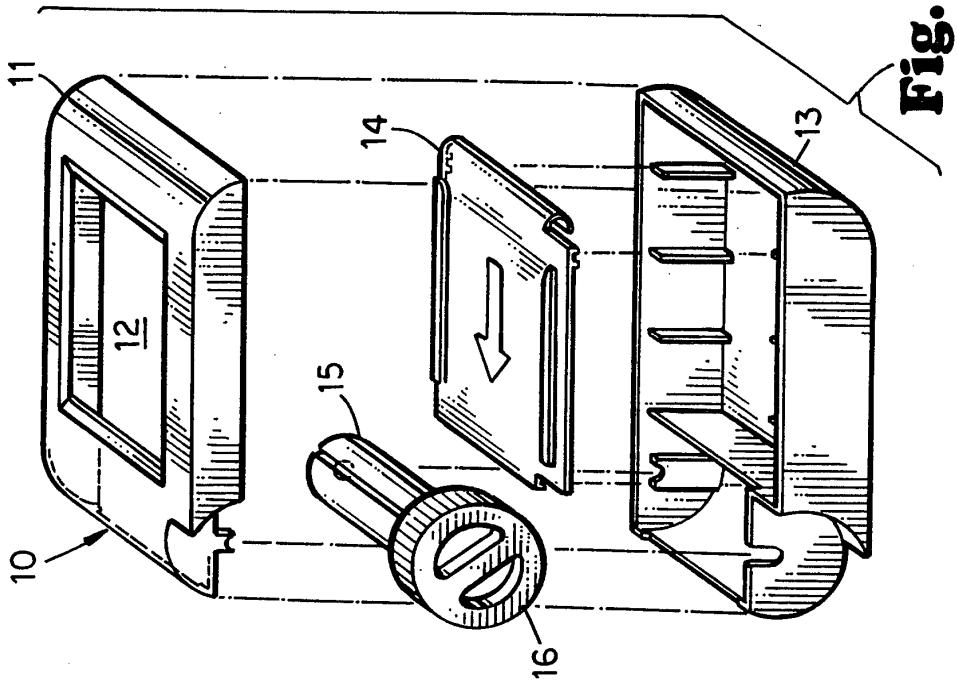


Fig. 9

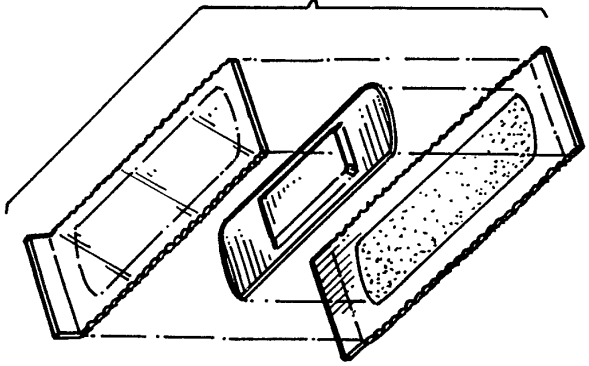
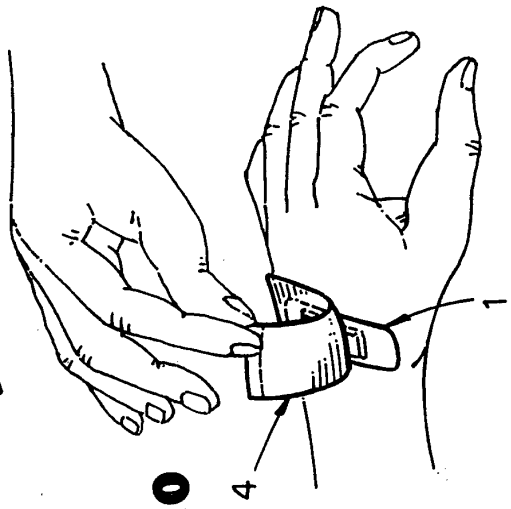


Fig. 10



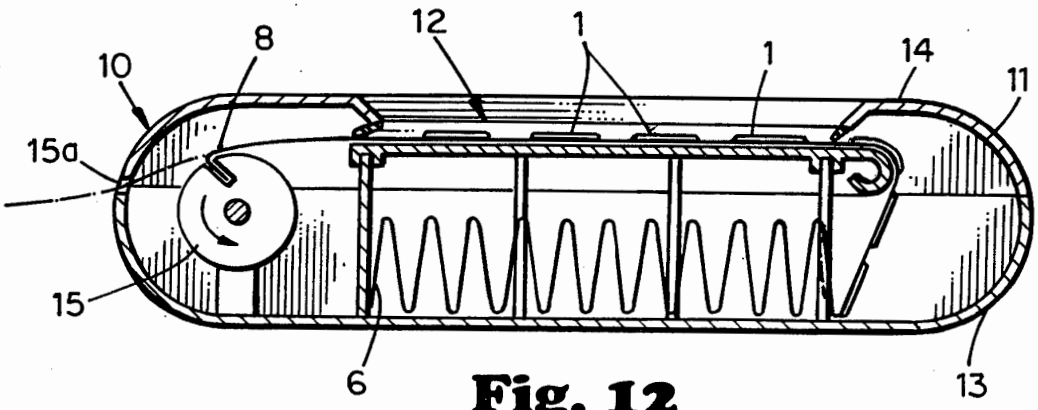


Fig. 12

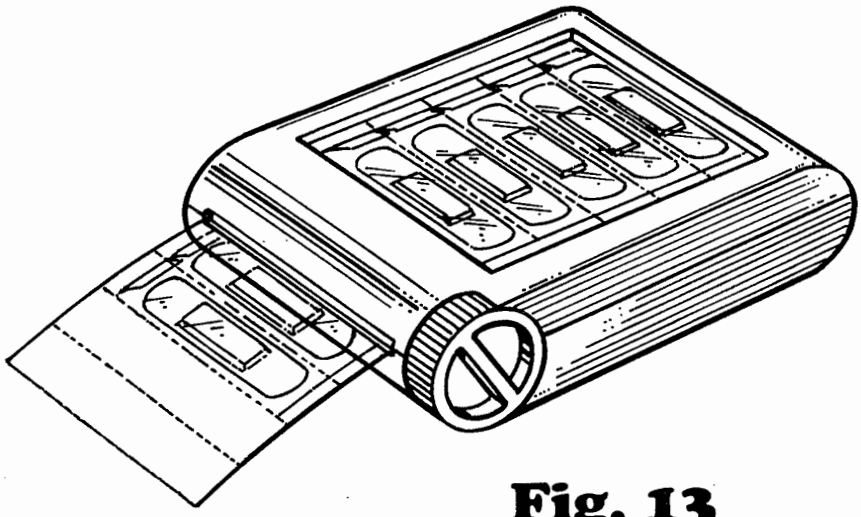


Fig. 13

Fig. 14

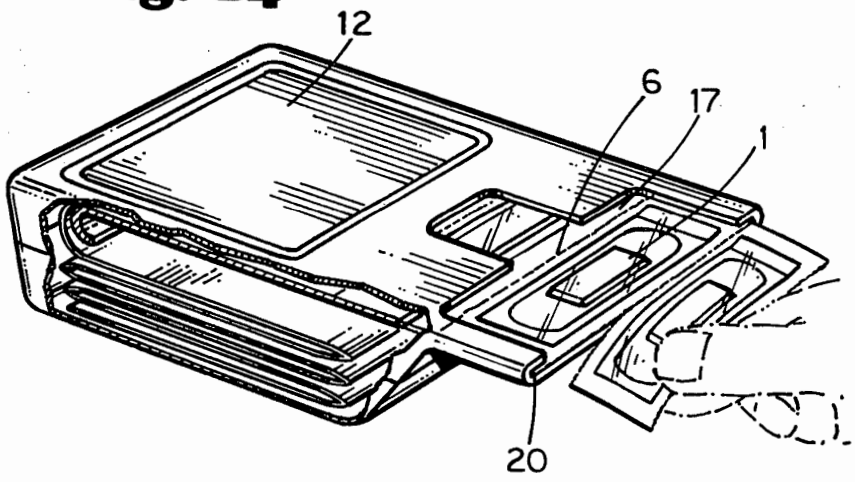


Fig. 15

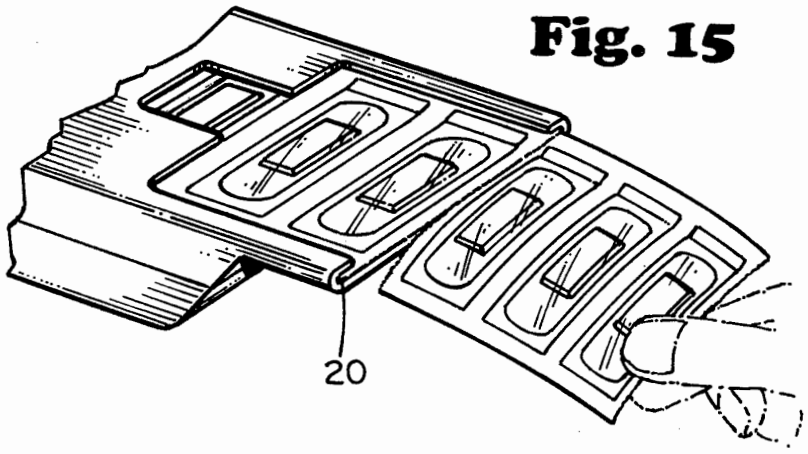
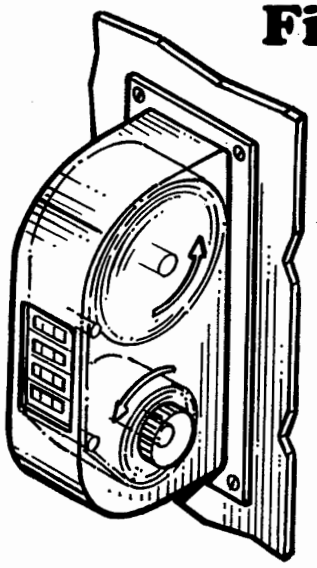


Fig. 16



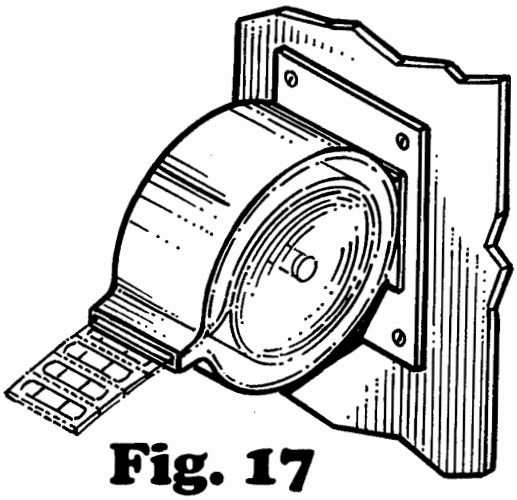


Fig. 17

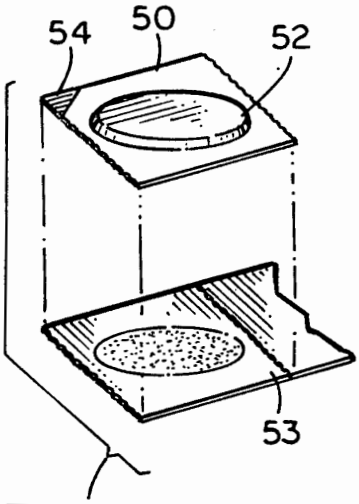


Fig. 18

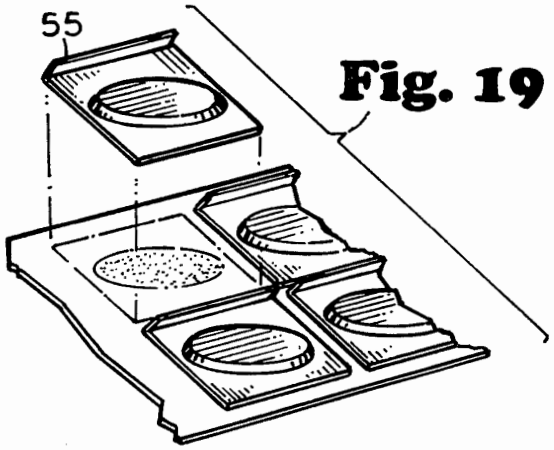


Fig. 19

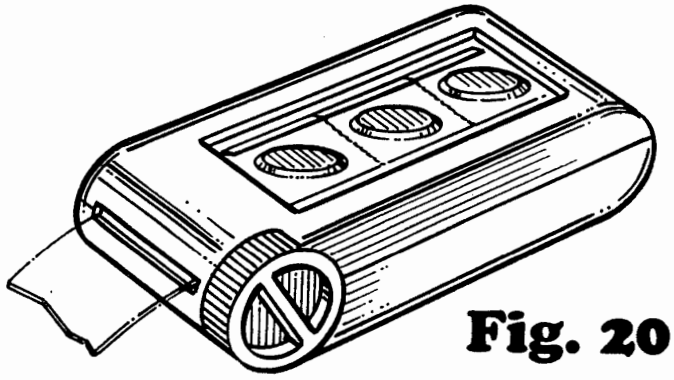


Fig. 20

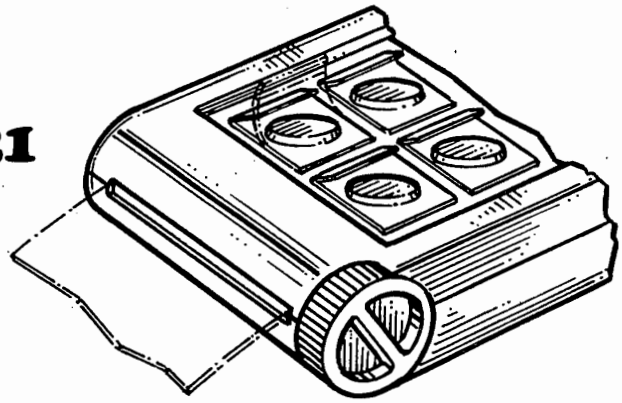


Fig. 21

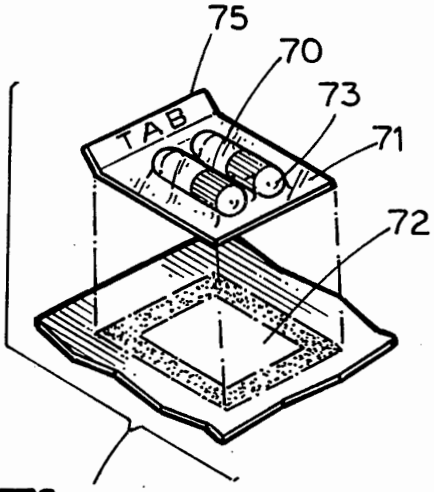


Fig. 22

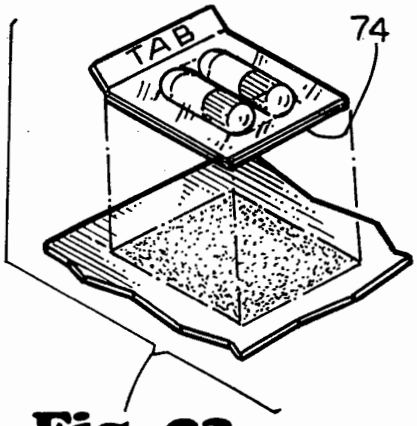


Fig. 23

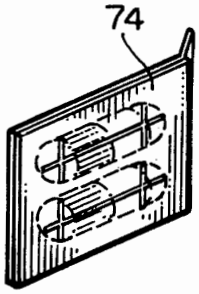


Fig. 24

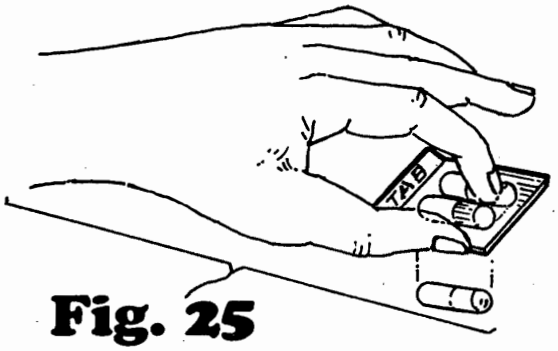


Fig. 25

Fig. 26

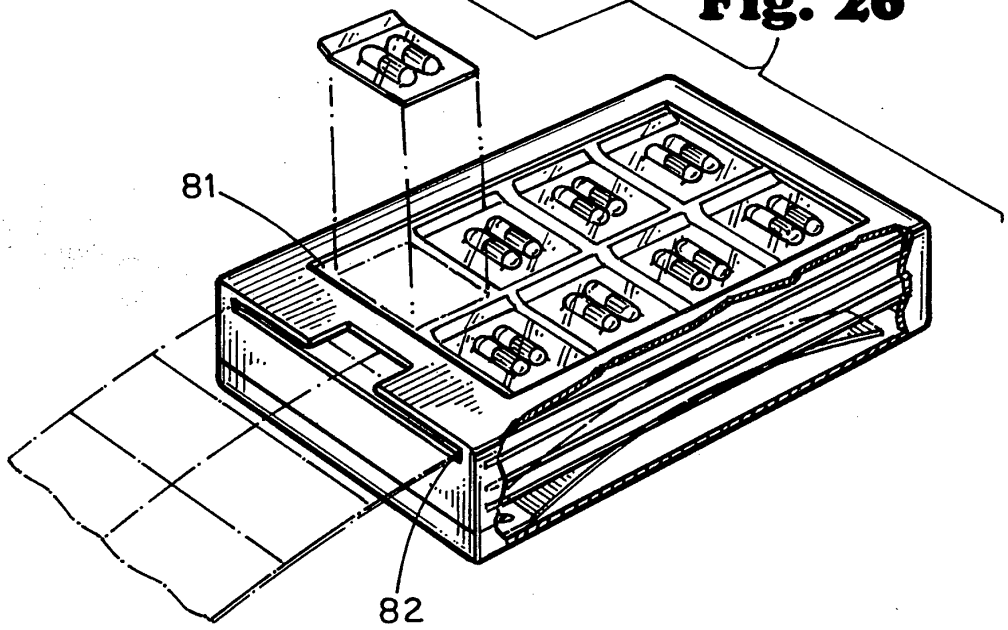
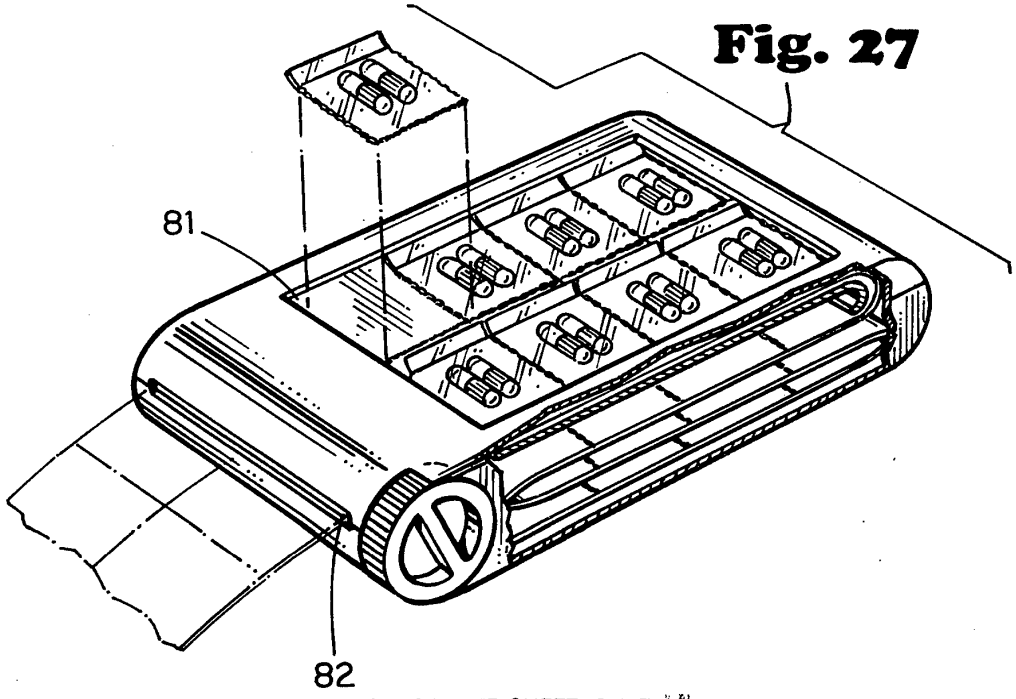


Fig. 27



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OE SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :206/528, 440, 441
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 206/528, 440, 441, 820, 534.1, 538

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 4,265,234 (SCHAAR) 05 May 1991, See the entire document.	1-5, 20-26 ---------- 6-19, 27-41
X ---- Y	US, A, 4,807,753 (GOLDSTEIN) 28 February 1989, See the entire document.	50 ---------- 6-12, 14, 17-19, 27-33, 35, 38, 40

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 MARCH 1995	Date of mailing of the international search report 22 MAR 1995
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 4,993,586 (TANLBEE, DECEASED ET AL.) 19 February 1991, See the entire document.	49 ---- 6-13, 17-19, 27-34, 38, 40
X ---- Y	US, A, 4,666,040 (MURATA) 19 May 1987, See the entire document.	51 ---- 6-12, 15, 16-19, 27-33, 36-40
X	US, A, 3,809,221 (COMPERE) 07 May 1974, See the entire document.	41-48
X	US, A, 3,630,346, (BURNSIDE) 28 December 1971, See the entire document.	41-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

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WO 03/030882 A1

(54) Title: THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFORM

(57) Abstract: The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by controlled drying process, or other process that maintains the required uniformity of the film. Desirably, the films contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

THIN FILM WITH NON-SELF-AGGREGATING UNIFORM HETEROGENEITY, PROCESS FOR THEIR PRODUCTION AND DRUG DELIVERY SYSTEMS MADE THEREFROM

FIELD OF THE INVENTION

The invention relates to rapidly dissolving films and methods of their preparation. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors,

sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Patent No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his

process is a multi-step process that adds expense and complexity and is not practical for commercial use.

Other U.S. Patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Patent 5,629,003 to Horstmann et al. and U.S. Patent 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly

related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-

aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

In one aspect of the present invention, there is provided a film and a method of forming same which can be divided into equally sized dosage units having substantially equal amounts of each compositional component present. This advantage is particularly useful because it permits large area films to be initially formed, and subsequently cut into individual dosage units without concern for whether each unit is compositionally equal. For example, the films of the present invention have particular applicability as pharmaceutical dosage delivery systems because each dosage unit, e.g., each individual dosage film unit, will contain the proper amount of drug. Pharmaceutical film dosage forms to date have not been marketed largely due to the inability to achieve this result.

In a further aspect of the present invention, there is provided a film product that is formed by combining a polymer and a polar solvent, forming the combination into a film, and drying the film in a controlled manner, desirably by initially only applying heat to the bottom side of the film, in order to maintain a non-self-aggregating uniform heterogeneity. Desirably, during the initial bottom drying stage, substantially no convection currents, i.e. hot air currents, are permitted to travel across the tops of the films. Once the visco-elastic properties of the film are such that the film components are "locked" in place and cannot move to cause non-uniformity, other methods of heating may then be employed. The polar solvent may be water, a polar organic solvent, or a combination thereof. An active ingredient may be added to the polymer and water combination prior to the drying step. Alternatively, or in addition to controlling the drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Moreover, the composition desirably is mixed in a manner to minimize the incorporation of air into the mixture and is desirably deaerated, such as by conditioning at room temperature, vacuum treatment or the like, to allow trapped air to escape prior to the drying process. This serves to eliminate bubble and void formation in the final film product, thereby further improving

uniformity. Reverse roll is one particularly useful coating technique may also be used to form the film.

In another aspect of the invention, there is a process for preparing a film with a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto the top side of a substrate surface having top and bottom sides. Heat is applied to the bottom side of the substrate surface in order to dry the film. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to the particular method used to dry the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity. Reverse roll coating technique may also be used to form the film.

A further aspect of the present invention is a method of orally administering an active including the steps of:

(a) preparing a film by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) introducing the film to the oral cavity of a mammal.

An even further aspect of the present invention is method of introducing an active component to liquid including the steps of:

(a) preparing a film by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film; and
  (iii) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity; and
(b) placing the film into a liquid; and
(c) allowing the film to dissolve.

A still further aspect of the present invention provides a dosage form for the administration of an active including:

(a) a first layer including a film formed by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming said material into a film; and
  (iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and
(b) a substantially non-water soluble second layer.

Another aspect of the present invention provides a method of preparing a dosage form for the administration of an active including the steps of:

(a) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
(b) forming the material into a film;
(c) applying the film to a substantially non-water soluble support; and
(d) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity.

In still another aspect of the present invention there is provided another method of administering an active including the steps of:

(a) preparing dosage form by the steps of:
  (i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;
  (ii) forming the material into a film;
  (iii) applying the film to a substantially non-water soluble support; and
  (iv) drying the film in a controlled manner to maintain the non-self-aggregating uniform heterogeneity;
(b) removing the film from said support; and
(c) applying the film to the oral cavity of a mammal.

Another aspect of the invention provides a film product formed by the steps of:

(a) combining a polymer and a liquid carrier to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said non-self-aggregating uniform heterogeneity.

Also provided is a process for making a film having a substantially uniform distribution of components including:

(a) combining a polymer component and liquid carrier to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix; and

(c) removing said liquid carrier, for example, by evaporative methods or by permitting volatilization to occur at selected temperatures, from said film in a manner to maintain said uniform distribution.

A still further aspect of the present invention provides process for making a film having a substantially uniform distribution of components including:

(a) combining a polymer component and a polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution; and

(b) forming a film from said matrix.

The invention also includes films and a process for preparing films having a substantially uniform distribution of components. The process includes the steps of combining a polymer component and water to form a uniformly distributed matrix. This matrix is then formed into a film and fed onto a substrate surface having top and bottom sides where the bottom side is in substantially uniform contact with a bottom drying medium, such as a water bath or heated air space controlled at a temperature sufficient to dry the film. Desirably, no external air currents or heat is applied directly to the exposed top surface of the film during the drying process until the film structure has solidified sufficiently to prevent flow, migration and intermolecular attractive forces from creating aggregates or conglomerates. Desirably the heat is controllably conducted by the substrate surface to the

film to effectuate drying. The matrix from which the film is formed may also include an active ingredient. Also, either alternatively, or in addition to rapidly drying the film, the polymer may be selected in order to provide a viscosity that maintains the non-self-aggregating uniform heterogeneity.

A pharmaceutical and/or cosmetic dosage form is also provided that includes a film having a uniformly dispersed composition including a polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

A still further aspect of the present invention includes a pharmaceutical and/or cosmetic dosage form including a polymeric film having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

The present invention also provides a pharmaceutical composition in the form of a film for external or topical administration, including a composition having a uniformly distributed combination of a polymer, a polar solvent, and a pharmaceutical active, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

A pharmaceutical dispenser is also provided that includes individual unit dosage forms of the pharmaceutical compositions and films of the present invention. The dosage forms may be optionally stacked in a dispenser or in a roll.

Yet another aspect of the present invention provides an ingestible water-soluble delivery system in the form of a film composition that includes a water-soluble polymer and an anti-foaming or defoaming agent, such as simethicone, which includes a combination of a polymethylsiloxane and silicon dioxide. Simethicone can act as either an anti-foaming or defoaming agent, or both, which reduces or eliminates air from the film composition. An anti-foaming agent will aid in preventing the introduction of air into a composition, while a defoaming agent will aid in removing air from the composition. The composition may also include a pharmaceutical and/or cosmetic active ingredient, flavors, sweeteners, plasticizers, surfactants, or other ingredients to alter the film properties to produce the desired product.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

Figure 4 shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

Figure 6 is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial

absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air

currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as

drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o = (2gr^r)(\rho_p - \rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o = 1/(1 + \kappa\varphi)$$

where κ = a constant, and φ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle

sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate

range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_o^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n} (2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n} t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch 22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30, 30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the

mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical

aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent

content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Film-Forming Polymers

The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Delaware and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100L, believed to be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C); lactide/glycolide 100L, believed to be 100% glycolide having a melting point within the range of 437°-455°F (225°-235°C);

lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of 338°-347°F (170°-175° C); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347°F (170°-175°C).

The Biodel materials represent a family of various polyanhydrides which differ chemically.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

Controlled Release Films

The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled release of an active has advantages in

addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. Express Mail Label No.: EU552991605 US of the same title, filed September 27, 2003, attorney docket No. 1199-15P) the entire subject matter of which is incorporated by reference herein.

Actives

When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds,

mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can

be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®,

vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as , but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug

and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-

K), and sodium and calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300mg, desirably up to about 150mg or as low as the microgram range, or any amount therebetween.

The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-foaming and De-foaming Compositions

Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking

unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0. 05 weight percent to about 2.5 weight percent, and most desirably from about 0. 1 weight percent to about 1.0 weight percent.

Optional Components

A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which

assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; and thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components.

The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin, water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcelulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50°C or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids.

The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1mils to about 10mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10'may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films

of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-I:

Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

	Weight (g)								
Ingredient	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99°C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film.

Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:

TABLE 2

Sample	Additive Weight (g)	
	Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

The individual dosages were consistently 0.04gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of

different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.

An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active.

When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L:

Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

	Weight (g)		
Ingredient	**J**	**K**	**L**
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1] Available from ICI Americas
[2] A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

The components of inventive compositions J-L were combined and formed into films using the methods for preparing inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O:

An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

	Weight %		
Ingredient	**M**	**N**	**O**
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1] Available from Dow Chemical Co. as Methocel K35
[2] Available from ICI Americas
[3] Available from Grain Processing Corporation as Pure Cote B792
[4] Available from McCormick
[5] Available from Bestfoods, Inc. as Karo Syrup

The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3nm intervals from 203-1200nm. The frequency of maximum absorption was found to be 530nm. The solution was then re-centrifuged at a higher RPM (for the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

Each of the segments were weighed to 0.1mg and then dissolved in 10ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200nm and later from only 500nm to 550nm at a 1nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530nm.

The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg / % A
1 - 2	1.717
3 - 4	1.700
5 - 6	1.774
7*	1.701
9 - 10	1.721
11 - 12	1.729
13 - 14	1.725
15 - 16	1.713

* segment 8 was lost

The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W:

Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Ingredient	**P**	**Q**	**R**	**S**	**T**	**U**	**V**	**W**
Hydroxypropylmethyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/Ethanol(60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (°C)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

[1] First Heater Section (3m)
[2] Second Heater Section (3m)

TABLE 7 (continued)

	Bot.[2] v (m/sec)	T[2] (°C)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1] First Heater Section (3m)
[2] Second Heater Section (3m)

In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA:

TABLE 8

	Weight (g)			
Ingredient	**X**	**Y**	**Z**	**AA**
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate polymer as the coating. The coating was spray coated at a 20% level. Therefore 10mg of drug 12.5 mg of the final dry product must be weighed.

The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

The process bottom temperature was set at 90°C with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1" x .75" piece weighed 70 mg and contained 10 mg of Loratadine.

The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

The products were sweet without any noticeable drug aftertaste.

The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90°C to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film was 0.005 inch. thick (5 mil) and was cut into 1 in. x 0.75 in. pieces weighing 70 mg +/- 0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples BA-BI:

The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable

organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Ingredient	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

Examples CA-CC:

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

Ingredient	(parts by wt.) CA
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Ethoxylated caster oil, Cremophor® EL available from BASF
[3] Propylene Glycol
[4] Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

Ingredient	(parts by wt.) CB
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Propylene Glycol
[3] Polydimethyl Siloxane Emulsion
[4] Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

Ingredient	(parts by wt.) CC
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1] Polydimethyl Siloxane Emulsion
[2] Prosweet from Virginia Dave
[3] Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD:

The following example of the present invention describe films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredients that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Ingredient	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1] Sucralose, available from McNeil Nutritionals
[2] Magna Sweet, available from Mafco Worldwide Corp.
[3] Gutte Enteric, coated acetaminophen, Gatte, LLC

The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20

min. Food coloring (7 drops of red food coloring and 1 drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C for about 11 minutes until about 3% moisture remained.

The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

2. The film product of claim 1, wherein said film includes a top side and a bottom side and said drying includes drying said bottom side first.

3. The film product of claim 1, wherein said drying includes applying heat to said bottom side.

4. The film product of claim 1, wherein said polar solvent is a combination of water and a polar organic solvent.

5. The film product of claim 1, wherein said polar solvent is water.

6. The film product of claim 1 further comprising an active component.

7. The film product of claim 1, wherein said polar solvent added in step (a) has a weight percent of at least about 30%.

8. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 10% or less.

9. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 8% or less.

10. The film product of claim 1, wherein said drying of said film reduces the weight percent of said polar solvent to about 6% or less.

11. The film product of claim 6, wherein said active component is a member selected from the group consisting of medicaments, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins, and combinations thereof.

12. The film product of claim 1, wherein said drying occurs within about 10 minutes or fewer.

13. The film product of claim 1, wherein said polymer is a member selected from the group consisting of water soluble polymers, water insoluble polymers, and combinations thereof.

14. The film product of claim 1, wherein said polymer is a cellulose derivative.

15. The film product of claim 13, wherein said water soluble polymer is a member selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinylpyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch and combinations thereof.

16. The film product of claim 13, wherein said water insoluble polymer is a member selected from the group consisting of ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate, and combinations thereof.

17. The film product of claim 1, wherein said film product has a thickness of greater than about 0.1 mils.

18. The film product of claim 1, wherein said film product has a thickness of about 10 mils or fewer.

19. The film product of claim 1, wherein said film product has a substantially uniform thickness.

20. The film product of claim 6, wherein said film product is divided into dosage forms of substantially equal dimensions.

21. The film product of claim 20, wherein each of said dosage forms contains a substantially equal amount of said active.

22. The film product of claim 20, wherein said dosage forms contain an amount of said active that varies about 10% or less among said dosage forms.

23. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

24. The process of claim 23, further comprising the step of adding an active component to said matrix of step (a).

25. The process of claim 23, wherein said film is ingestible.

26. The process of claim 23, wherein said drying step maintains a non-self-aggregating uniform heterogeneity of said components throughout said film.

27. The process of claim 23, wherein said film is flexible when dried.

28. The process of claim 23, wherein said film is self-supporting.

29. The process of claim 24, wherein uniform distribution determines the amount of active material component per area.

30. The process of claim 24, wherein a specific amount of the active material component may be obtained from said film by cutting said film to a predetermined size.

31. The process of claim 23, wherein said drying of said film occurs within about 10 minutes or fewer.

32. A method of orally administering an active comprising the steps of:

(a) preparing a film by the steps of:

(i) combining a polymer, an active component, and water to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) introducing said film to the oral cavity of a mammal.

33. A method of introducing an active component to liquid comprising the steps of:

(a) preparing a film by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) placing said film into a liquid; and

(c) allowing said film to dissolve.

34. The method of claim 33, wherein said active ingredient is a flavoring.

35. The method of claim 34, wherein said flavoring is selected from the group consisting of hot and cold beverage flavorings and soup flavoring.

36. The method of claim 33, wherein said liquid is ingestible.

37. A dosage form for the administration of an active comprising:

(a) a first layer comprising a film formed by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film; and

(iii) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity; and

(b) a substantially non-water soluble second layer.

38. The dosage form of claim 37, wherein said first layer is removable from said second layer.

39. The dosage form of claim 37, wherein said film may be applied to the tongue of a mammal.

40. The dosage form of claim 37, wherein said film has a shape comprising first and second opposing bases wherein first base is longer than said second base.

41. The dosage form of claim 37, wherein said film has a shape selected from the group consisting of trapezoid and triangle.

42. The dosage form of claim 37, wherein said film adheres to an oral cavity.

43. The dosage form of claim 37, wherein said film includes an adhesive to adhere said film to an oral cavity.

44. A method of preparing a dosage form for the administration of an active comprising the steps of:

a. combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

b. forming said material into a film;

c. applying said film to a substantially non-water soluble support; and

d. drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

45. A method of administering an active comprising the steps of:

(a) preparing dosage form by the steps of:

(i) combining a polymer, an active component, and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(ii) forming said material into a film;

(iii) applying said film to a substantially non-water soluble support; and

(iv) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity;

(b) removing said film from said support; and

(c) applying said film to the oral cavity of a mammal.

46. The method of claim 45, wherein said active is released as said film dissolves.

47. A film product formed by the steps of:

(a) combining a water soluble polymer and water to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

48. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity, said polymer selected to provide a viscosity sufficient to maintain said non-self aggregating heterogeneity;

(b) forming said material into a film; and

(c) drying said film.

49. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity;

(b) forming said material into a film by reverse roll coating; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

50. A film product formed by the steps of:

(a) combining a polymer and a polar solvent to form a material with a non-self-aggregating uniform heterogeneity, said polymer selected to provide a viscosity sufficient to maintain said non-self aggregating heterogeneity;

(b) forming said material into a film by reverse roll coating; and

(c) drying said film in a controlled manner to maintain said non-self-aggregating uniform heterogeneity.

51. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution;

(b) forming a film from said matrix;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

52. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix by reverse roll coating;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

53. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component, and polar solvent to form a matrix with a uniform distribution of said components, said polymer selected to provide a viscosity sufficient to maintain said uniform distribution;

(b) forming a film from said matrix by reverse roll coating;

(c) providing a surface having top and bottom sides;

(d) feeding said film onto said top side of said surface; and

(e) drying said film by applying heat to said bottom side of said surface.

54. A process for making a film having a substantially uniform distribution of components comprising:

(a) combining a polymer component and polar solvent to form a matrix with a uniform distribution of said components;

(b) forming a film from said matrix; and

(c) drying said film by feeding said film onto a surface having top and bottom sides; said bottom side being in substantially uniform contact with a water bath at a temperature sufficient to dry said film.

55. The process of claim 54, wherein said water bath is temperature controlled.

56. A pharmaceutical and/or cosmetic dosage form comprising a film having a uniformly dispersed composition comprising a polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate

surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

57. A pharmaceutical and/or cosmetic dosage form comprising a polymeric film having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

58. A pharmaceutical composition in the form of a film for enteral or topical administration, comprising a composition having a uniformly distributed combination of a polymer, a polar solvent, and a pharmaceutical active, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

59. The pharmaceutical composition of claim 58 in unit dosage form sealed in a pouch.

60. A pharmaceutical dispenser comprising individual unit dosage forms of the pharmaceutical composition of claim 58.

61. The dispenser of claim 60 wherein said individual unit dosage forms are in a roll or stacked in a dispenser.

62. The pharmaceutical composition of claim 58, further including simethicone.

63. The pharmaceutical and/or cosmetic dosage form of claim 56 or 57, further including simethicone.

64. The film product of claim 1, further including simethicone.

65. An edible water-soluble delivery system in the form of a film composition comprising a water-soluble polymer and simethicone.

66. The pharmaceutical composition of claim 58, wherein the pharmaceutical composition is essentially free of a surfactant.

67. The pharmaceutical and/or cosmetic dosage form of claims 56 or 57, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a surfactant.

68. The film product of claim 1, wherein the film product is essentially free of a surfactant.

69. The pharmaceutical composition of claims 58 or 66, wherein the pharmaceutical composition is essentially free of a plasticizer.

70. The pharmaceutical and/or cosmetic dosage form of claims 56, 57 or 67, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a plasticizer.

71. The film product of claims 1 or 68, wherein the film product is essentially free of a plasticizer.

72. The pharmaceutical composition of claims 58, 66 or 69, wherein the pharmaceutical composition is essentially free of a polyalcohol.

73. The pharmaceutical and/or cosmetic dosage form of claims 56, 57, 67 or 70, wherein the pharmaceutical and/or cosmetic dosage form is essentially free of a polyalcohol.

74. The film product of claims 1, 68 or 71, wherein the film product is essentially free of a polyalcohol.

75. An edible water-soluble delivery system in the form of a film composition comprising:

a water-soluble polymer comprising hydroxypropylmethyl cellulose, hydroxypropyl cellulose, and combinations thereof; and

an active component selected from the group consisting of cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof;

wherein the delivery system is essentially free of plasticizers, surfactants and polyalcohols.

76. The edible water-soluble delivery system of claim 75, wherein said active component is present in amounts of up to about 0.1% to about 60% by weight of the total delivery system.

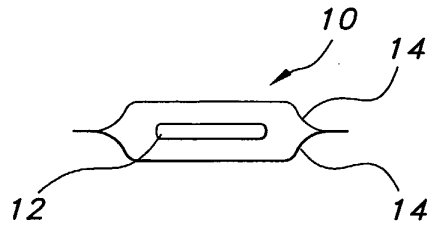

FIG. 1

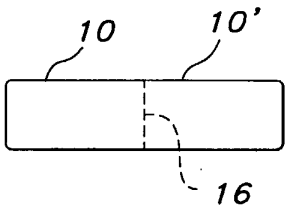

FIG. 2

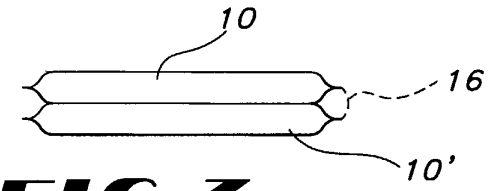

FIG. 3

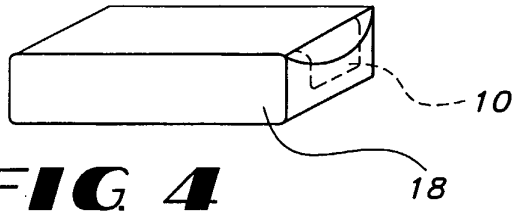

FIG. 4

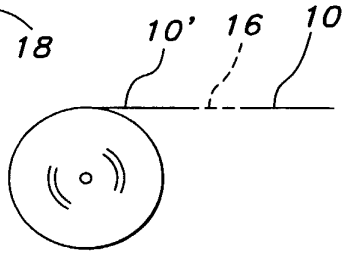

FIG. 5

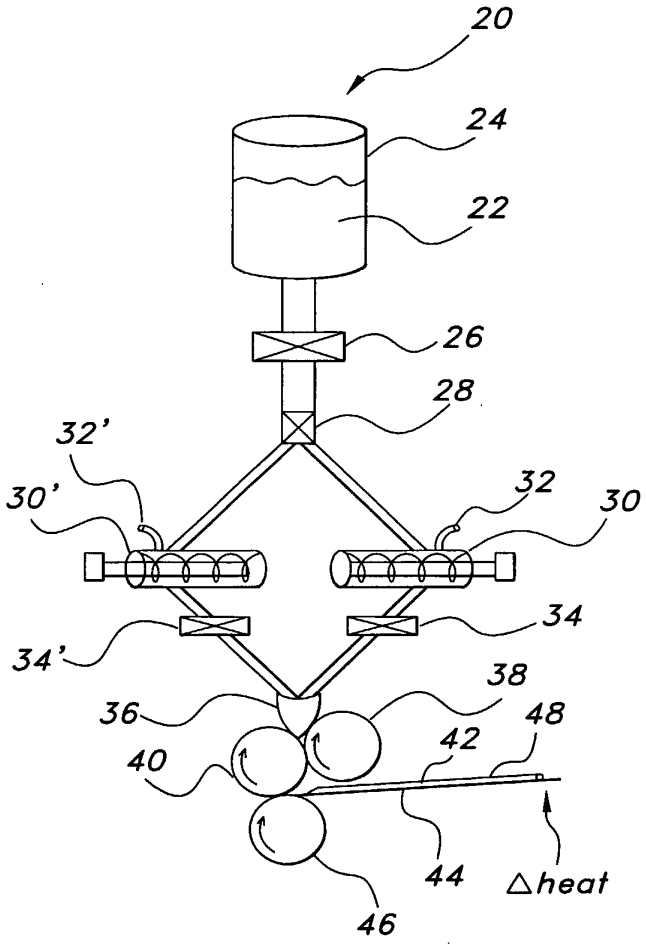

FIG 6

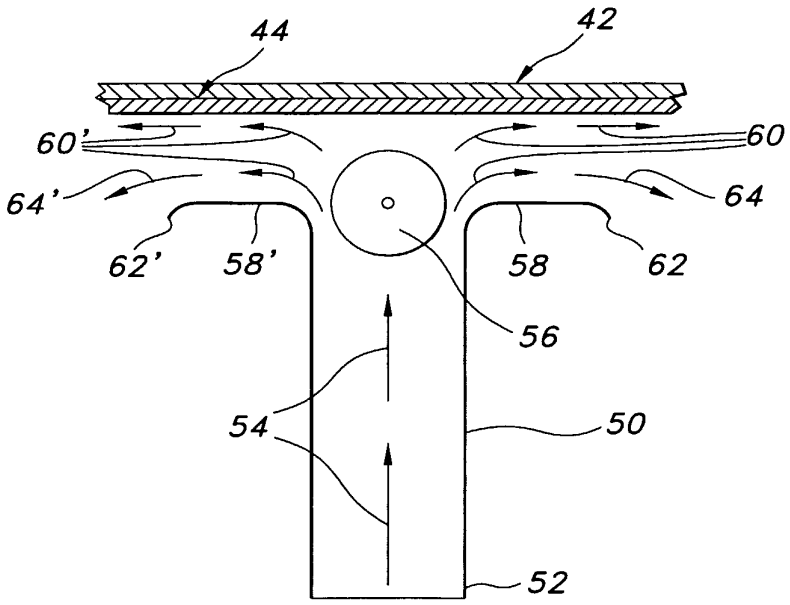

FIG. 7

INTERNATIONAL SEARCH REPORT

Internati pplication No
PCT/US 02/32575

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, FSTA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 01 91721 A (STALEY MFG CO A E) 6 December 2001 (2001-12-06) example 8 ---	1-76
X	US 6 284 264 B1 (ZERBE HORST GEORG ET AL) 4 September 2001 (2001-09-04) cited in the application column 4, line 7-11 example 1 ---	1-76
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X	EP 1 110 546 A (JOHNSON & JOHNSON CONSUMER) 27 June 2001 (2001-06-27) page 4, line 32-37 --- -/--	1-76

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2003	06/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/US 02/32575

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 849 246 A (SCHMIDT WOLFGANG) 18 July 1989 (1989-07-18) cited in the application the whole document	1-76
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/32575

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 32, 44 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-75 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-75 (in part)

There is an abundancy of independent claims with (partly) overlapping subject-matter. The current set of claims therefore lack clarity and conciseness (Art. 6 PCT).
The following independent claims in the respective categories were identified:
Product-by-process claims 1, 37, 47, 48, 49, 50.
Process/method claims 23, 33, 44, 51, 52, 53, 54,
Method of administration claims 32, 45
Product claims 56, 57 (pharm./cosmetic dosage form) 58 (pharm. composition), 65, 75 (delivery system).

In view of the large number of independent claims presently on file, it is difficult, if not impossible, to determine the matter for which protection is sought, the present set of claims fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search for all these claims is impossible.

Although each respective category of independent claims contain somewhat different technical features, they appear to relate to the same invention. The following features seems however common to all the process claims:
A process for the production of a film with a uniform distribution of components, comprising:
a) combining a polymer with a polar solvent to form a matrix with a uniform distribution of said components
b)forming a film of the matrix
c) providing a surface having top and bottom sides
d) feeding the film to the surface
e) drying the film by applying heat to the bottom side of said surface

The feature "drying the film in a controlled manner" in some independent claims is vague and unclear and comprise basically all ways of drying. Consequently, the search has been carried out for the technical features a)-e) common to all independent process claims, as well as products formed by this process and a method of administering the product.

Moreover, the terms "polymer" and a "polar solvent" are so broad that they relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds used in the process claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the polymers in the present claim 15 and 16 and to the polar solvents used in the examples (water, ethanol).

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Moreover, the independent process claims relate to subject-matter defined by reference to a desirable characteristic or property, namely the uniform distribution of the components in the film. An attempt is made to define the process by reference to a result to be achieved. Said claims therefore lack clarity (Article 6 PCT). The claims should be drafted in such a way that the essential technical features necessary to achieve this desirable property are described.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat pplication No
PCT/US 02/32575

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Form PCT/ISA/210 (patent family annex) (July 1992)

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(54) Title: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

(57) Abstract: A thin film drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein. The combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for the preparation and use of a uniform rapid dissolve dosage form in the form of a film that includes a pharmaceutically active or bioeffecting agent and a taste-masking agent for masking the taste of the pharmaceutically active agent.

BACKGROUND OF RELATED TECHNOLOGY

While active ingredients such as pharmaceutical preparations may be included in a tablet or similar form to provide an accurate and consistent dose, including medicaments in such a form has several disadvantages in both the administration and preparation of the drug. Moreover, in such oral dosage forms, such as tablets or emulsions, pharmaceuticals have been coated to provide control release or taste-masking. Particle sizes of particulate pharmaceuticals are not critical in such dosage forms and generally large particle sizes, i.e., greater than 200 microns have been used.

There have been several attempts to provide an alternate dosage form, such as a film that would include a pharmaceutical active. However, such attempts have not been successful in providing a film that incorporates a drug with sufficient uniformity to provide accurate dosing.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not specifically disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent governmental or agency standards relating to the variation of active in dosage forms. Currently, by law, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

Moreover, the problems of self-aggregation leading to non-uniformity of a film can result in an unpleasant tasting film when the film contains an unpleasant tasting pharmaceutical agent. Agglomerates of unpleasant tasting pharmaceutical agents may not be adequately masked by flavoring agents and sweeteners that are simply mixed into a film because the non-uniformity of the agglomerates may result in segregation of the unpleasant tasting agents from the flavoring agents and sweeteners. Fuchs merely mixes flavors and sweeteners into a film forming mix and fails to address the problem of aggregation or segregation of these materials.

Similarly, WO 00/42,992 also discloses the use of taste-modifying agents in a film dosage form. This international application also merely mixes taste-modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents.

Furthermore, WO 01/70,194 discloses the use of ion exchange resins to for covalently binding pharmaceutical agents thereto. The resins have particle sizes from 20 microns to 200 microns and are described as being taste masking agents. The ion exchange resins are described as being bound with pharmaceutical agents and being mixed into consumerable films having thicknesses from 7 to 11 mils, or 180 microns to 280 microns. Such ion exchange resins, however, have limitations in the binding of pharmaceutical agents to the ion exchange resins, making the process for producing taste-masked comsumerable films complicated and expensive. Moreover, the use of ion exchange resins, which are water insoluble, limits the selection of useful pharmaceutical agents in water soluble films to only certain water soluble pharmaceutical agents that can covalently bond to the ionic resin.

Therefore, there is a need for a rapid dissolve dosage form, presented as a uniform film that addresses and corrects the problems associated with non-uniformity of a drug in film such as agglomeration or separation of particles within the film and the unpleasant tasting effects of the same. Moreover, there is a need for taste-masked, pharmaceutically active agents suitably contained within such a uniform film.

SUMMARY OF THE INVENTION

The present invention seeks to attain low adjuvant content, high taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and uniformity. The present invention also provides for a unique method of producing the inventive compositions such that the compositional components are evenly distributed throughout the film. This process is described in detail in co-pending U.S. Patent Application No. 10/074,272, entitled "Thin Film with Non-Self-Aggregating Uniform Heterogeneity and Drug Delivery Systems Made Therefrom", the subject matter of which is herein incorporated by its entirety.

In one aspect of the present invention, a drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the

stationing of the particulate bioeffecting agent therein. The importance of such particle sizes has not been recognized in the prior art, especially in prior art dosage forms, such as tablets and emulsions. Moreover, the importance of particle size is heightened in orally ingestible thin films, where uniformity is also of particular importance, and the prior art has failed to recognize such critically important features.

Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness. Desirably, such particle sizes are contained within these dry films. In other words the dry films of the present invention desirably have smooth surfaces free of exposed agents that could impart grittiness or maldistribution of the active. Thus, in one aspect of the invention there is provided a film vehicle which contains a uniform distribution of actives, as defined herein, being suitably free of particles which accumulate on the film surface when dried.

Desirably, taste-masking agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymers may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

The matrix may be a cellulosic material; a gum; a protein; a starch; a glucan; and combinations thereof; such as but not limited to carboxymethyl cellulose; methyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

The bioeffecting agent may be present in amounts of up to about 0.1% to about 60% by weight of the total composition. Useful bioeffecting agents include, but are not limited to, antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, anti-pyretics, psychopharmacological drugs and combinations thereof. The delivery vehicle composition may further include an organoleptic agent.

In another aspect of the present invention, a drug delivery vehicle includes (i) a water-soluble film matrix; and (ii) a particulate bioeffecting agent uniformly suspended within the matrix and having associated with it a taste-masking agent. The uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns. Useful taste-masking agents include water-soluble polymers. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Non-limiting water-soluble polymers include acrylic polymers, cellulosic polymers, and combinations thereof. The taste-masking agents may also include vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof. The drug delivery vehicle of claim may further include an organoleptic agent with the bioeffecting agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000. Water-soluble polymers having an average molecular weight of equal to or greater than about 40,000 are also useful. Useful water-soluble polymers include of acrylic polymers, cellulosic polymers, and combinations thereof. Desirably, the pharmaceutically active particles are embedded within the film. Additionally, the film includes sections of substantially equal size and the particles are distributed in an amount that varies less than about 10% among the sections. Desirably,

the size of the particles are about 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. Moreover, the drug delivery vehicle may further include an organoleptic agent with the water-soluble polymer.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle having a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 20-60% by weight of the particle. More desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The pharmaceutically active particle is desirably embedded within the film, and the film includes sections of substantially equal size where the particles are distributed in an amount that varies less than about 10% among the sections. Useful sizes of the pharmaceutically active particles include particle sizes of 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. The drug delivery vehicle may further include an organoleptic agent with the taste-masking agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The active particle has a particle size of less than about 200 microns. Desirably, the thickness of the film is less than about 380 microns.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The particle desirably has a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-

60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent. The active particle is taste-masked with a taste-masking agent. Useful organoleptic agents include flavors, sweeteners and combinations thereof.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

In another aspect of the present invention, a method of preparing a thin film drug delivery vehicle is provided. The method includes the steps of (a) providing a pharmaceutically active agent / taste-masking agent complex; (b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein; (c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and (d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film. The step of providing the pharmaceutically active agent with the taste-masking agent includes a treatment for coating the taste masking agent onto portions of the pharmaceutically active agent. The drying includes applying heat the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Useful methods for providing the pharmaceutically active agent with the taste-masking agent include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating the taste masking agent onto portions of the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

Figure 4 shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

Figure 6 is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition in the form of a film for external or topical administration, including a composition having a uniformly distributed combination of a polymer, a polar solvent, and a taste-masked pharmaceutically active or bioeffecting agent. The composition in its dried film form maintains the uniform distribution of components through the application of controlled bottom drying of the film.

Water-soluble polymers useful in the present invention include cellulosic materials, gums, proteins, starches, and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Examples of cellulosic materials include, without limitation, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof.

Examples of water-soluble gums include gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

Examples of other polymeric materials which may be incorporated include polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

Useful starches include gelatinized, modified or unmodified starches. The source of the starches may vary and include pullulan, tapioca, rice, corn, potato, wheat and combinations thereof.

Useful water-soluble protein polymers include gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof. Additional water-soluble polymers include dextrin, dextran and combinations thereof, as well as chitin, chitosin and combinations thereof, polydextrose and fructose oligomers.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The edible water-soluble delivery system of the present invention further include glucans, such as pullulan and elsinan. The ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Glucans are generally desirable materials for edible film because of their high water solubility, rapid dissolution and excellent mouth-feel.

The edible water-soluble delivery system of the present invention further include an anti-foaming or defoaming agent, such as simethicone, which is a combination of a polymethylsiloxane and silicon dioxide. Simethicone acts as either an anti-foaming or defoaming agent which reduces or eliminates air from the film composition. An anti-foaming agent will aid in preventing the introduction of air into a composition, while a defoaming agent will aid in removing air from the composition.

The edible water-soluble delivery system of the present invention further include an active component selected from cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof. The active component may be present in any amount effective for the intended treatment. It is particularly desirable and an advantage of the present invention that the active component can be included in high loads. For example, the active component may be present in amounts up to about 60% by weight of the total composition and desirably in amounts of 0.01% to about 50% by weight of total composition.

The pharmaceutically or bioeffecting active components that may be incorporated into the films of the present invention include a wide variety of medicaments and pharmaceutical compositions. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmátics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines,

anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium

hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as , but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

The pharmaceutically active agents employed in the present invention may be incorporated into the film compositions of the present invention in a taste-masked form. For example, particles of drug may be coated with taste-masking agents, for example polymers, oils and waxes. Additionally, organoleptic agents, such as, but not limited to sweeteners and/or flavors, may also be employed in such taste-masked compositions, including in the coating layer of the taste masking agent.

Suitable sweeteners include both natural and artificial sweeteners. Non-limiting examples of suitable sweeteners include, e.g.:

a. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

b. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt

of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin and the like;

c. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame), L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

d. water-soluble sweeteners derived from naturally occurring water-soluble sweeteners, such as a chlorinated derivatives of ordinary sugar(sucrose), known, for example, under the product description of sucralose; and

e. protein based sweeteners such as thaumatoccous danielli(Thaumatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

Useful flavors or flavoring agents include natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Non-limiting flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and the like. These flavorings can be used individually or in combination. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in combination. Flavorings such as aldehydes and esters including cinnamylacetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and the like may also be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamicaldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral,

i.e. beta citral(lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream);heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese);valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal(citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits);aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);12,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2 dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference, subject to such factors as flavor type, individual flavor, and strength desired. The amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useful with the practice of the present invention.

A variety of polymeric and non-polymeric materials can be employed for taste masking pharmaceutically active agents. Non-limiting examples of polymers include acrylic polymers, cellulosic polymers or vinyl polymers. Non-limiting examples of non-polymeric materials include crown ethers, fully hydrogenated oils and waxes. Moreover, the taste masking agents may be water soluble, water insoluble or partially water soluble.

Useful non-limiting acrylic polymers include those available under the trade name Eudragit® from Röhm America, LLC, such as methacrylic acid co-polymers sold under the trade names Eudragit E®, Eudragit L®, Eudragit RD® and Eudragit S®, and polyethylacrylate-methylmethacrylate sold under the trade name, Eudragit NE®. These acrylic polymers are generally water soluble materials.

Useful non-limiting cellulosic polymers include, alkylcelluloses, such as, methyl or ethyl cellulose and, hydroxyalkylcelluloses, such as hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof. Useful alkylcelluloses include those sold under the trade names Methocel E™ by Dow Chemicals. Additionally, useful ethylcelluloses are commercially available commercially available from FMC Corporation under brand name Aquacoat ECD. These acrylic polymers are generally water soluble materials.

Moreover, the pharmaceutically active agents may be sprayed and congealed with fully hydrogenated oils or waxes considered safe for human consumption and are relatively stable. Useful, but non-limiting, pharmaceutically acceptable oils include mineral oil, peanut oil, soybean oil, sunflower oil, corn oil, olive oil, hard palm oil and rapeseed oil.

Furthermore, crown ether compounds, such as cyclodextrins, are also useful for coating the pharmaceutically active agents. The pharmaceutically active agents are taste masked with crown ethers through entrapment or coaccervation methods. Useful cyclodextrins are commercially available under the trade name of Trappsol® from CTD, Inc.

Pharmaceutically active agents may be taste masked with the above-described taste-masking agents by a variety of techniques. The techniques coat the pharmaceutically active agents or portions of the pharmaceutically active agents with taste masking agents to avoid the unpleasant taste effects, such as bitterness, often associates with the pharmaceutically active agents or drugs. Useful coating techniques include, but are not limited to, fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating and the like.

The fluidized bed coating method is commonly used in pharmaceutical industries for taste masking pharmaceutically active agents. Fluidized bed coaters achieve fluidization of the pharmaceutically active agents by introducing a continuous stream of process gas into a chamber. The coating material is deposited onto the suspended agent as it passes through the spray path of the coating material. The coated agents is dried. A relative low water solubility polymer is typically used to coat the active particles' surface. Minimum limits on particle sizes are about 100 to 120 microns. Smaller particle sizes are difficult to achieve due to process limitation and product loss. Water insoluble pharmaceutically active agents may be suitable coated with water soluble taste masking agents with this method.

In the spray congealing method both the pharmaceutically active agents and the coating materials are sprayed simultaneously into a chamber supplied with process gas to create a uniformly coated active. This method typically involves the coating of the actives with material that could be melted at reasonable temperatures, for example fatty materials or polymers such as certain Eudragit® polymers. The mix of materials are sprayed through a

fine nozzle and cooled through a temperature-control air stream or a cold surface. Consideration of mixture temperature is important. The melting temperature of the coating agent selected should not exceed a degradation temperature of the pharmaceutically active agent.

In the agglomeration or granulation method, the pharmaceutically active agents are mixed with the taste-masking agents and a solvent by mechanical means or by spray drying. The solvent is gradually removed by vacuum or heating, or both. Particles are then agglomerated. The agglomerated particles are not typically coated entirely with the taste masking agent and some bitterness may result accordingly. The bitterness, however, may be further reduced by incorporating such coated particles in the films of the present invention.

In typical entrapment coating methods, certain compounds having specific properties that can trap pharmaceutically active agents into its molecule cages must first be selected. Compounds, like certain specifically made starches and crown ether type molecules, such as cyclodextrins and zeolites, are useful with this method. The compounds and the agents are entrapped by ionic attraction. The entrapped agents are then precipitated from solution.

The coaccervation coating method uses two polymers with opposite charges in solution. When the solution is neutralized an insoluble matrix will precipitate from solution and trap the pharmaceutically active agents therein. Examples include interactions of gum arabic and gelatin solutions and interactions of cyclodextrins and protein solutions.

In the infusion method pharmaceutically active agents and flavors or sweeteners are dissolved and infused into a polymer matrix to form a dry powder. In spin coating methods, pharmaceutically active agents are combined with sugars or fats and spun into coated particles. Details of the method are disclosed in U.S. Patent No. 5,028,632, the contents of which is incorporated herein by reference. In ion exchange coating, ionic bonding of pharmaceutically active agents to ion exchange resins masks the tastes of the agents.

Extrusion and spheronization methods may also be used of taste-masking pharmaceutically active particulates. Ratios of active(s) and polymer(s) (such as, starch, cellulose, gum and/or combinations thereof) are first mixed and thicken by adding a small amount of water. The thickened mixture is then extruded through a single or double nozzle

screw. Small spherical particles are formed by a Marumerization® process. Desirable particle sizes are obtained through process control and particulate sieving.

Lyophilization (Freeze-Drying) methods may also be used with the practice of the present invention A combination of polymer(s) (such as, starch, gum, cellulose and/or combinations thereof) with active(s) are mixed and dissolved (or dispersed) in aqueous medium. This mixture is then freeze-dried on a pre-form substrate. Desirable particles sizes can be obtained by process control and product sieving.

In some instances, taste-masking may amount to the addition of two components together, neither of which are particularly pleasing to the taste, but which, due to their chemical makeup, counteract each other or allow for a third substance or more of one of the substances to be added without a concomitant reduction in pleasantness of the taste.

The edible water-soluble delivery system of the present invention further includes one or more members selected from antifoaming agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents, antigens and combinations thereof.

In one aspect of the present invention, a drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein.

Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles. Furthermore, the flowable

water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

Desirably, taste-masking agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymers have an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymer may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

The matrix may be a cellulosic material; a gum; a protein; a starch; a glucan; and combinations thereof; such as but not limited to carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

The bioeffecting agent may be present in amounts of up to about 0.1% to about 60% by weight of the total composition. Useful bioeffecting agents include, but are not limited to, antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof. The delivery vehicle composition may further include an organoleptic agent.

In another aspect of the present invention, a drug delivery vehicle includes (i) a water-soluble film matrix; and (ii) a particulate bioeffecting agent uniformly suspended within the matrix and having associated with it a taste-masking agent. The uniformity is determined by

the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns.

Useful taste-masking agents include water-soluble polymers. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Non-limiting water-soluble polymers include acrylic polymers, cellulosic polymers, and combinations thereof. The taste-masking agents may also include vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof. The drug delivery vehicle of claim may further include an organoleptic agent with the bioeffecting agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000. Water-soluble polymers having an average molecular weight of equal to or greater than about 40,000 are also useful. Useful water-soluble polymers include of acrylic polymers, cellulosic polymers, and combinations thereof. Desirably, the pharmaceutically active particles are embedded within the film. Additionally, the film includes sections of substantially equal size and the particles are distributed in an amount that varies less than about 10% among the sections. Desirably, the size of the particles are about 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. Moreover, the drug delivery vehicle may further include an organoleptic agent with the water-soluble polymer.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle having a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 20-60% by weight of the particle. More desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The pharmaceutically active particle is desirably

embedded within the film, and the film includes sections of substantially equal size where the particles are distributed in an amount that varies less than about 10% among the sections. Useful sizes of the pharmaceutically active particles include particle sizes of 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. The drug delivery vehicle may further include an organoleptic agent with the taste-masking agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The active particle has a particle size of less than about 200 microns. Desirably, the thickness of the film is less than about 380 microns.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The particle desirably has a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent. The active particle is taste-masked with a taste-masking agent. Useful organoleptic agents include flavors, sweeteners and combinations thereof.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a

water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

In another aspect of the present invention, a method of preparing a thin film drug delivery vehicle is provided. The method includes the steps of (a) providing a pharmaceutically active agent / taste-masking agent complex; (b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein; (c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and (d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film. The step of providing the pharmaceutically active agent with the taste-masking agent includes a treatment for coating the taste masking agent onto portions of the pharmaceutically active agent.

The drying includes applying heat to the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Such microwave drying is useful because drying initiates in the middle portions of the film. The present invention, however, is not limited to these drying methods. Any drying method may suitably be used as long as the drying does not initiate at the top surface of the casted mixture. Such top surface drying does not typically provide desirable film uniformity.

Useful methods for providing the pharmaceutically active agent with the taste-masking agent include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating the taste masking agent onto portions of the pharmaceutically active agent.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate

that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or

plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10'may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

Rheology and Films Properties

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform

heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of

the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o = (2gr^r)(\rho_p - \rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o = 1/(1 + \kappa\varphi)$$

where κ = a constant, and φ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated

from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_o^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n} (2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n} t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps ("cps" or "centipoise") to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the

selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

Film Component Mixing:

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which

includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch 22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30, 30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility

of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known

as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first ½ minute to about the first 4 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its

surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1mils to about 10mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical

aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent

content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

The following non-limiting examples are intended to further illustrate the present invention.

EXAMPLES

Preparation Of Taste-Masked Pharmaceutically Active Agents:

The following drugs were coated with taste masking components and were used in the films of the present invention.

a. Fluidized Bed Coating: A taste-masked particle was prepared having a core material of northindrone (Norlutin®). Northindrone was first sieved through a 60 mesh screen having a 250 micron sieve opening. The resulting particles, i.e., having particles sizes of less than 250 microns, were then coated by the fluidized bed coating procedure in a Verse Glatt Fluidized Bed using a Wurster Column. Accordingly, a 625 grams of 5 % methylcellulose and 0.5 % Acesulfame® K (a non-caloric sweetener) solution was prepared. The solution was then applied onto 500 grams of the sieved northindrone powder at an air pressure of 40 psi through a Gustav Schlick nozzle model 941. The fluidized bed temperature was heated and maintained at 115°F during the spraying process. At the end of coating, the resulting particles were further dried therein for 3 minutes. A total of 530 grams taste masked northindrone was obtained.

b. Agglomeration Process: A sweetener solution of 94 grams of 2.5 % sodium saccharin and 2.5 % Acesulfame® K was prepared. A dry blend of 60 grams of hydroxypropylmethyl cellulose and 40 grams of silica dioxide with 20 grams polythiazide (Renese®) was made. The sweetener solution was then sprayed a little at a time onto the dry blend powder during low-shear mixing. The dry powder was, at this point, being agglomerated through the granulation/absorption process. The wet mixture was then dried in a convection oven at 105°F for 17 hours. The resulting dried product was ground in a Fitz Hammer Mill grinder and sieved through a 100 mesh screen having a 149 micron sieve opening.

c. Pelletization Process: The following product was made using a model RV02 Mix Pelletizer (made by Eirich Machines Ltd.) at maximum mixing speed. A small of crashed ice was added, slowly through a funnel, to the 40 grams Loratidine®, 40 grams Aspartame®, 10 grams hydroxypropyl cellulose and 5 grams gum arabic powder mix in the mixer while mixing at low settings of both pan rotation and mixing motor. It took 1 to 2 minutes to add the ice. Once the ice addition was completed, both the pan and the rotor mix were turned to high speed to form spherical particles. The end point was determined by examining the particles using a low power microscope. When the end point is not reached after 2 minutes of intense mixing, additional 1 to 2 minutes mixing with or without adding more ice is tried. This procedure is repeated until the end point is reach, i.e., the spherical particles are formed. The wet samples obtained were dried in a tray dryer at 55°C for about 5 hours. The resulting particles size ranged from 20 to 200 mesh. The particles were then sieved to obtain the desired particle size.

d. Infusion Method: A dry blend of 3.7 grams of Sucralose®, 10 grams fluoxetine HCl (Prozac®), and 1.25 grams polyvinylpyrrolidone were mixed uniformly. Water of 5.0 grams and 2.74 grams of propylene glycol were then added to the mixture and mixed thoroughly. To this mixture, 22 grams of hydroxypropylmethyl cellulose was added and blended under a high shear Stephan Mixer for at least 3 minutes. The resulting particles were sieved through a 100 mesh screen and were ready to be used in film matrix solution.

e. Triglyceride Reduction Formula™ microspheres from Southwest Research Institute were coated with ethylcellulose by a spinning and congealing particle producing process. The coated particles had a particle size of less than 100 microns. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

f. Tamoxifen was produced by spray coating 50 to 100 micron sized particles of Eudragit® E100 (cationic methacrylate with dimethylamino ethyl ammonium groups). During fluidized coating, coated particles were isolated using a fractional separation device which insured particles having a size of less than 150 microns. The estimated level of coating was about 15%. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent.

g. Torsemide was coated by a critical fluid process by dissolving torsemide in polyethylene glycol (400 molecular weight) which was added to a flowing stream of supercritical CO_2 by using a sonic spray nozzle. The resulting droplet size was controlled to produce approximated 150 micron sized spherical particles. The particles were then moved to an apparatus used for spraying a polymer coating. The polymer condensed on the drug particles thereby imparting a taste-masked pharmaceutically active agent. The polymer coating used was Eudragit® E100 dissolved in ethanol at 15% solids. The coated product was isolated by lowering the pressure and removal of the CO2 and the ethanol.

h. Felodipine was coated via an emulsion solvent evaporation method using acrylate methacrylate copolymers (Eudragit® RL or Eudragit® PO and Eudragit® RS or Eudragit® PO) as the coating materials. The mean sphere diameter was 12 microns with a drug loading of about 50%.

i. Digoxin was coated with Trappsol® cyclodextrin. A 50% (wt/vol) solution of chemically modified cyclodextrin was produced by mixing it with water at room temperature. A finely ground digoxtin (less than 15 microns) was suspended in the solution with mild stirring. The mix was stirred for 60 minutes and any undissolved drug was removed by

centrifugation through a 0.45 micron sized membrane. Spray drying of the solution yielded a dry powder with a 10% drug loading.

Preparation Of The Film Forming Composition:

A film-forming composition, Composition A in Table 1, was prepared and mixed under vacuum to remove air bubbles. In further detail, a polymer mix of hydroxypropylmethyl cellulose (Methocel™ E15), polyvinylpyrrolidone and starch and xanthan were added to water with stirring over a short period of time of about 15 minutes. The stirring was set at 350 to 1500 rpm using an axial impeller. Stirring continued for another 45 minutes after combining the components to form a viscous, uniform mix.

To this viscous mix plasticizer (propylene glycol), flavor, antifoam and sweetener were sequentially added. The mixture was stirred for an additional 10 minutes at 500 rpm before the addition of a taste-masked drug.

TABLE 1

Film Forming Polymer Composition	Composition
Ingredient	**A**
Hydroxypropylmethyl cellulose	8.5
Polyvinylpyrrolidone	5.5
Starch	5.5
Sweetener	2.4
Flavor (Mint Mix)	3.3
Xanthan Gum	0.3
Plasticizer	3.4
Antifoam agent	0.8
Water	70.4
Total:	100

A taste-masked drug was added to the mixture in about a 5 minute time period. After the addition of the drug the mixture was placed under a vacuum from about 0.1 to about 0.7 torr for about 45 minutes.

Film Compositions With Taste-Masked Pharmaceutically Active Agents:

After removing the vacuum, the product mix was added to a coating pan and filmed using a three-roll coater. The suspension was coated at 250 microns onto siliconized paper

substrate and moved through a drying oven heated at 90°C. The composition was dried in accordance with the process set forth in co-pending U.S. Application No. 10/074,272.

The dried product was examined for physical appearance, dissolution in the mouth and bitterness.

The resultant uncut films of inventive composition A with the above-described taste-masked drugs exhibited uniformity in content particularly with respect to the tasted-masked drugs, as well as unit doses of ¾" by 1" by 5-6 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The films had minimal taste when ingested. All films dissolved in the mouth in less than 15 seconds.

The film produced with the less than 100 micron sized taste-masked triglyceride had a loading of 20 mg per 25 mm^2 piece of film. The film produced with the less than 150 micron sized taste-masked tamoxifen had a loading of 10 mg per 20 mm^2 of film (assuming 85% active). The film produced with the less than 150 micron sized taste-masked torsemide had a loading of 10 mg per 25 mm^2 of film (assuming 90% active). The film produced with the taste-masked digoxin had a loading of 0.5 mg per 15 mm^2 of film (assuming 90% active).

Film Compositions Free of Surfactants and/or Plasticizers

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 2

Ingredient	(parts by wt.) B
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Ethoxylated caster oil, Cremophor® EL available from BASF
[3] Propylene Glycol
[4] Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 3

Ingredient	(parts by wt.) C
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Propylene Glycol
[3] Polydimethyl Siloxane Emulsion
[4] Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 4

Ingredient	(parts by wt.) D
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1] Polydimethyl Siloxane Emulsion
[2] Prosweet from Virginia Dave
[3] Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

While there have been described what are presently believed to be the certain desirable embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. A drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein.

2. The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. The drug delivery composition of claim 1, wherein said flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness.

5. The drug delivery composition of claim 1, wherein said flowable water-soluble film forming matrix is formable into a dry film of less than about 250 microns in thickness.

6. The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

7. The drug delivery composition of claim 1, wherein said taste-masking agent is a polymer.

8. The drug delivery composition of claim 7, wherein said taste-masking agent is a water-soluble polymer.

9. The drug delivery composition of claim 8, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

10. The drug delivery composition of claim 8, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

11. The drug delivery composition of claim 1, wherein said taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

12. The drug delivery composition of claim 1, wherein said matrix is a cellulosic material, a gum, a protein, a starch, a glucan, and combinations thereof.

13. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof.

14. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

15. The delivery vehicle composition of claim 1, wherein said matrix is a starch selected from the group consisting of tapioca, rice, corn, potato, wheat and combinations thereof.

16. The delivery vehicle composition of claim 15, wherein said starch is gelatinized, modified or unmodified.

17. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

18. The delivery vehicle composition of claim 1, wherein said matrix is a protein selected from the group consisting of gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof.

19. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of dextrin, dextran and combinations thereof.

20. The delivery vehicle composition of claim 1, wherein said matrix is selected from the group consisting of chitin, chitosin or combinations thereof.

21. The delivery vehicle composition of claim 1, wherein said matrix is polydextrose, fructose oligomers, or combinations thereof.

22. The delivery vehicle composition of claim 1, wherein said bioeffecting agent is present in amounts of up to about 0.1% to about 60% by weight of the total composition.

23. The delivery vehicle composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

24. The delivery vehicle composition of claim 1, further including organoleptic agent.

25. A drug delivery vehicle comprising:

(i) a water-soluble film matrix; and

(ii) a particulate bioeffecting agent uniformly suspended within said matrix and having associated with it a taste-masking agent;

wherein the uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout said matrix.

26. The drug delivery vehicle of claim 25, wherein said drug variance is less than 5% by weight.

27. The drug delivery vehicle of claim 25, wherein said drug variance is less than 2% by weight.

28. The drug delivery vehicle of claim 25, wherein said drug variance is less than 1% by weight.

29. The drug delivery vehicle of claim 25, wherein said drug variance is less than 0.5% by weight.

30. The drug delivery vehicle of claim 25, wherein the size of particulate has a particle size of 200 microns or less.

31. The drug delivery vehicle of claim 25, wherein said film matrix has a thickness of less than about 380 microns.

32. The drug delivery vehicle of claim 1, wherein said taste-masking agent is a water-soluble polymer.

33. The drug delivery vehicle of claim 32, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

34. The drug delivery vehicle of claim 32, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

35. The drug delivery vehicle of claim 25, wherein said taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

36. The drug delivery vehicle of claim 25, further including organoleptic agent with said bioeffecting agent.

37. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000.

38. The drug delivery vehicle of claim 37, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

39. The drug delivery vehicle of claim 37, wherein said water-soluble polymer is selected from the group consisting of acrylic polymers, cellulosic polymers, and combinations thereof.

40. The drug delivery vehicle of claim 37, wherein said pharmaceutically active particle are embedded within said film and further wherein said film includes sections of substantially equal size and said particles are distributed in an amount that varies less than about 10% among said sections.

41. The drug delivery vehicle of claim 37, wherein the size of said particle is about 200 microns or less.

42. The drug delivery vehicle of claim 37, wherein said film has a thickness of less than about 380 microns.

43. The drug delivery vehicle of claim 25, further including organoleptic agent with said water-soluble polymer.

44. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle.

45. The drug delivery vehicle of claim 44, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

46. The drug delivery vehicle of claim 44, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

47. The drug delivery vehicle of claim 44, wherein said pharmaceutically active particle is embedded within said film and further wherein said film includes sections of substantially equal size and said particles are distributed in an amount that varies less than about 10% among said sections.

48. The drug delivery vehicle of claim 44, wherein the size of said pharmaceutically active particle has a particle size of 200 microns or less.

49. The drug delivery vehicle of claim 44, wherein said film has a thickness of less than about 380 microns.

50. The drug delivery vehicle of claim 44, further including an organoleptic agent with said taste-masking agent.

51. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent;

wherein said active particle having a particle size of less than about 200 microns.

52. The delivery vehicle of claim 51, wherein said thickness of said film is less than about 380 microns.

53. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

54. The drug delivery vehicle of claim 53, wherein the particle size of said particle is about 150 microns or less.

55. The drug delivery vehicle of claim 53, wherein the particle size of said particle is about 100 microns or less.

56. The delivery vehicle of claim 53, wherein said thickness of said film is less than about 380 microns.

57. The delivery vehicle of claim 53, wherein said thickness of said film is less than about 250 microns.

58. The drug delivery vehicle of claim 53, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle

59. The drug delivery vehicle of claim 53, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle

60. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent; said active particle being taste-masked with a taste-masking agent.

61. The delivery vehicle of claim 60, wherein said organoleptic agent is selected from the group consisting of flavors, sweeteners and combinations thereof.

62. A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer; and

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

63. A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining said complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

64. The method of claim 63, wherein said providing said pharmaceutically active agent with said taste-masking agent includes a treatment for coating said taste masking agent onto portions of said pharmaceutically active agent.

65. The method of claim 64, wherein said treatment for coating said taste masking agent onto said portions of said pharmaceutically active agent. is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers and oils.

66. The method of claim 63, wherein said drying includes applying heat to the bottom of said carrier surface.

67. The method of claim 63, wherein said drying includes applying microwave energy to said film.

68. The method of claim 63, wherein said pharmaceutically active agent comprises particles that are less than about 300 microns.

69. The method of claim 63, wherein said pharmaceutically active agent comprises particles that are less than about 250 microns.

70. The method of claim 63, wherein said providing said pharmaceutically active agent with said taste-masking agent is selected from the group consisting of fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating said taste masking agent onto portions of said pharmaceutically active agent.

71. The drug delivery composition of claim 1, wherein said combined particulate and taste-masking agent have a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

72. The drug delivery of claim 25, wherein said particulates have a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

73. The drug delivery vehicle of claim 37, wherein said particle has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

74. The drug delivery composition of claim 1, wherein the composition is essentially free of a surfactant.

75. The drug delivery composition of claims 1 or 74, wherein the composition is essentially free of a plasticizer.

76. The drug delivery composition of claims 1, 74 or 75, wherein the composition is essentially free of a polyalcohol.

77. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60 or 62, wherein the vehicle is essentially free of a surfactant.

78. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60, 62 or 77, wherein the vehicle is essentially free of a plasticizer.

79. The drug delivery vehicle of claims 25, 37, 44, 51, 53, 60, 62, 77 or 78, wherein the vehicle is essentially free of a polyalcohol.

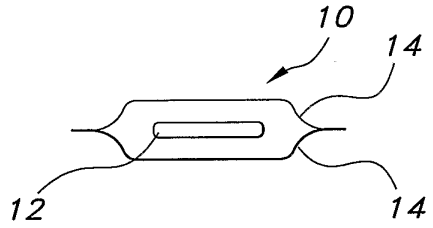

FIG. 1

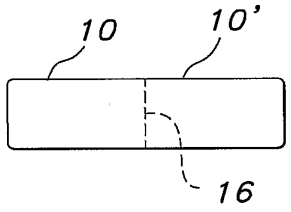

FIG. 2

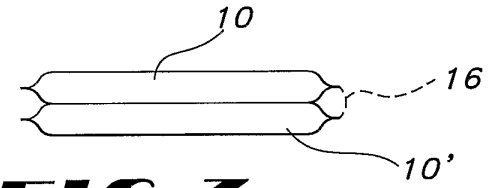

FIG. 3

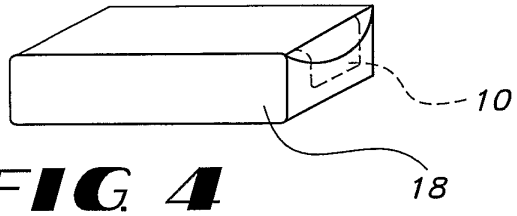

FIG. 4

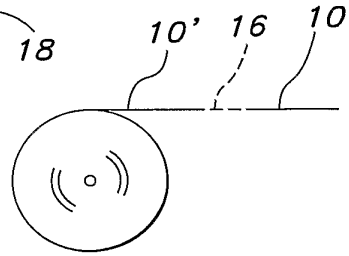

FIG. 5

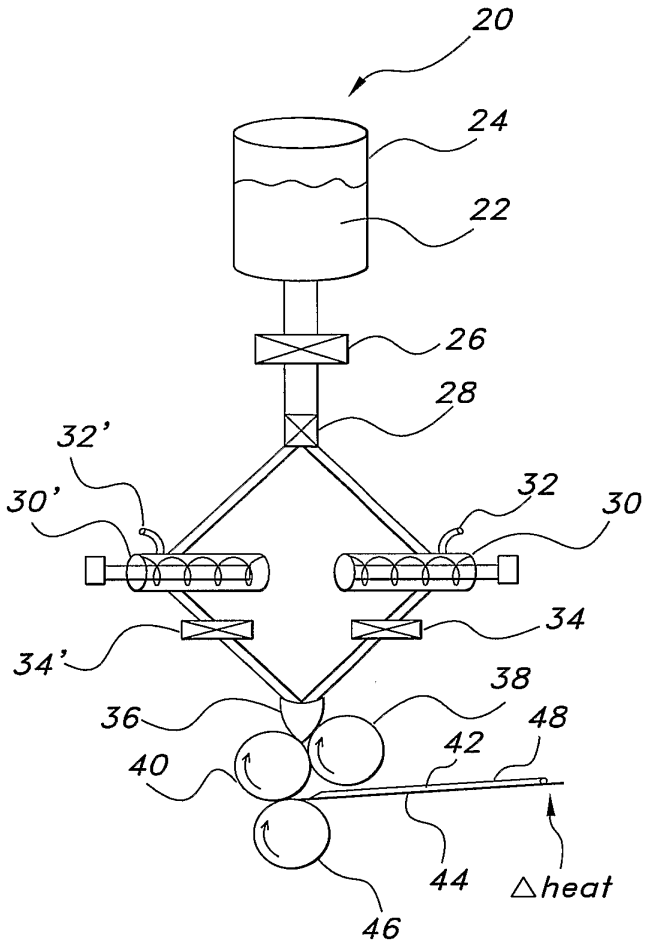

FIG. 6

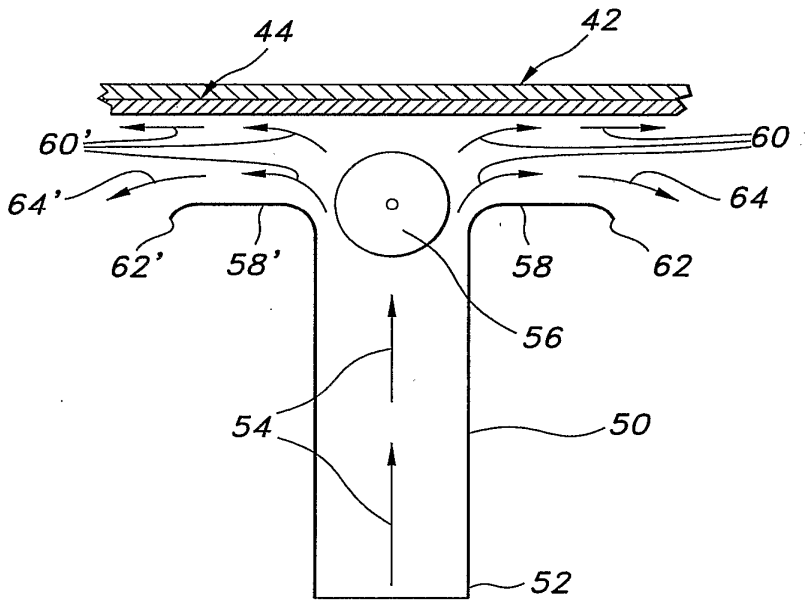

FIG. 7

INTERNATIONAL SEARCH REPORT

Inter ıal Application No
PCT/US 02/32594

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K9/00 A61K9/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, FSTA, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 42992 A (LAVIPHARM LAB INC) 27 July 2000 (2000-07-27) cited in the application page 8, line 10,11 page 19, line 17 -page 20, line 12 claims 2,25 ---	1-79
X	WO 01 70194 A (WARNER LAMBERT CO) 27 September 2001 (2001-09-27) cited in the application abstract page 7, line 19-21 page 10, line 7,8 figure 2 --- -/--	1-79

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2003	06/02/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Skjöldebrand, C

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 136 145 A (FUCHS PETER ET AL) 23 January 1979 (1979-01-23) cited in the application the whole document	1-62, 71-79
X	EP 0 241 178 A (ROHTO PHARMA) 14 October 1987 (1987-10-14) abstract claims 3,4 column 5, line 31-33	1-62, 71-79
X	US 2001/006677 A1 (ROBINSON JOSEPH R ET AL) 5 July 2001 (2001-07-05) abstract claims paragraph '0051!	1-62, 71-79
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A	US 6 153 210 A (SPACCIAPOLI PETER ET AL) 28 November 2000 (2000-11-28) abstract; example 1	1-79
A	US 5 567 431 A (VERT MICHEL ET AL) 22 October 1996 (1996-10-22) abstract; example 2	1-79

INTERNATIONAL SEARCH REPORT

ıational application No.
PCT/US 02/32594

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-79 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-79 (in part)

There is an abundance of independent product claims with (partly) overlapping subject-matter. The current set of claims therefore lacks clarity and conciseness (Art. 6 PCT).

Independent product claims 1, 25, 37, 44, 51, 53, 60, 62 appear to relate to the same invention. Said claims however contain somewhat differing technical features. The following features seems however common to all these drug delivery devices: a water soluble film, a particulate bioactive agent associated with a taste masking agent. In view of the large number independent product claims presently on file, it is difficult, if not impossible, to determine the matter for which protection is sought, the present set of product claims 1-62 and 71- fails to comply with the clarity and conciseness requirements of Article 6 PCT (see also Rule 6.1(a) PCT) to such an extent that a meaningful search for all these claims is impossible. Consequently, the search has been carried out for those parts of the said product claims which do appear to be clear and concise, namely the technical features common to all independent product claims, namely: a water soluble film, a particulate bioactive agent associated with a taste masking agent.

Moreover, independent product claims 1, 25 and method claim 63 relate to subject-matter defined by reference to a desirable characteristic or property, namely the uniform distribution of the active agent in the film. An attempt is made to define the product/method by reference to a result to be achieved. Said claims therefore lack clarity (Article 6 PCT). The claims should be drafted in such a way that the essential technical features necessary to achieve this desirable property are described. As the unifom distribution of the drug is not mentioned in independent product claims 37, 44, 51, 53, 60 and 62, this feature appears to be optional, and the search was performed for devices as described above.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte al Application No
PCT/US 02/32594

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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(54) **Title:** Pharmaceutical compositions for acute glucocorticoid therapy

(57) **Abstract:** The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid

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Pharmaceutical compositions for acute glucocorticoid therapy

Field of the invention

The present invention relates to glucocorticoid-containing pharmaceutical compositions or kits for use in acute emergency situations where acute glucocorticoid therapy is required. Notably, the invention relates to pharmaceutical compositions and kits that are designed to be administered by non-medically trained persons outside a hospital or another medical or clinical setting. The invention also relates to a method for treating a disorder requiring acute glucocorticoid therapy by providing a fast onset of action of a glucocorticoid.

Background of the invention

Glucocorticoids are important steroids for intermediary metabolism, immune function, musculoskeletal and connective tissue as well as the brain. The importance of the glucocorticoids is best understood in patients with glucocorticoid deficiency. In such patients, the one-year survival rate was only 20% in the 1950s before the availability of glucocorticoid replacement therapy. The major use of glucocorticoids in clinical practice began, however, with their use in the treatment of rheumatoid arthritis in the 1940s. Both natural and synthetic glucocorticoids have been employed in the management of a wide variety of conditions and they play a crucial part of many emergency treatments involving allergic and inflammatory disorders.

The endogenous glucocorticoids are steroids predominantly produced in the adrenal cortex. The main glucocorticoid in the body is cortisol. The production and secretion of cortisol is governed by a complex and highly efficient system that includes the hypothalamus, pituitary and the adrenal glands i.e. hypothalamic-pituitary-adrenal axis (HPA). Cortisol secretion has a circadian release rhythm with peak values in early morning and trough values at midnight. The HPA axis is also activated by several physical and psychological stressors. Thus, under stress conditions, such as physical activity, fever, surgery or mental stress, the serum cortisol concentration is increased.

Adrenocortical deficiency results in a number of complex symptoms that results from deficiency of adrenocortical hormone activity. It may be of a primary type as a result of a disease in the adrenal cortex, a secondary (central) type due to the specific pathology in the hypothalamus and/or the pituitary gland, or a tertiary type due to a suppressed HPA axis after long-term high dose glucocorticoid treatment.

The onset of adrenocortical insufficiency may vary from insidious to an acute life-threatening situation with severe salt and water deficit, which leads to shock and death if not treated fast and adequately.

Therapy of e.g. acute adrenal crisis requires that the one or more glucocorticoids quickly enter (are absorbed) into the systemic circulation at a therapeutically effective concentration interval (therapeutic window). Although a number of various glucocorticoid-containing pharmaceutical compositions already are on the market, most of these are not suitable for the treatment of a disorder requiring acute glucocorticoid therapy as they either result in a too slow appearance in the systemic circulation (e.g. conventional tablets) or in a too low, if any, glucocorticoid serum level (many glucocorticoid-containing pharmaceutical compositions are intended for local treatment e.g. in the nose or on the skin).

There are today two ways of administering glucocorticoids in medical emergencies. One is the parenteral route where an intravenous (IV) infusion has to be set up or a deep intramuscular (IM) injection has to be given. However, one disadvantage of this administration is that an IV route can be challenging to establish particularly in patients with compromised peripheral circulation. Furthermore, parenteral administration requires qualified personnel and is therefore limited to well-crewed ambulances and in-hospital settings.

The other administration route is traditionally by oral administration using a dissolvable betamethasone tablet in water. This route is mainly used in outpatient clinics and for patient self-medication. However, the disadvantages are the considerable lag-time when preparing the solution and the time from intake until a significant serum level of the drug is obtained. The maximum plasma concentration (C_{max}) is usually reached within 1 to 3 hours after administration (T_{max}) It is also well known that the onset of intestinal absorption cannot be earlier than 0.5 hour for these oral immediate release products of a rapidly dissolved and rapidly absorbed drug (a class I drug according to the FDA's Biopharmaceutics Classification System), the gastric emptying being very variable both in the fasted and fed state. Furthermore, it is mandatory that the patient is conscious and has unaffected ability to swallow the solution since a weak gastrointestinal motility results in a further delay in gastric emptying and reduced intestinal absorption (both rate and extent).

Examples of such cumbersome oral administrations are obtained in patients with acute laryngitis, patients with severe distress due to breathlessness, children with croup or severe angiooedema, and in patients with gastroenteritis where gastrointestinal absorption is uncertain.

Accordingly, it would be of great therapeutic advantage to develop pharmaceutical compositions that enable self-administration by patients and administration to patients by non-medically trained persons outside of a hospital, clinic, ambulance, paramedical or similar medical settings and at the same time result in a sufficient treatment of a disorder requiring acute glucocorticoid therapy (e.g. acute adrenal crises) by providing a fast onset of action after administration. Moreover, there is also a need for pharmaceutical compositions that can be administered to a patient who e.g. is unconscious or otherwise unable to swallow a composition (e.g. a tablet or solution) and that does not require medically trained personnel or need be done in a medical setting.

Detailed disclosure of the invention

The present invention meets the above-described needs by providing a pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium such as, e.g., water, simulated saliva or simulated intestinal fluid without enzymes, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

The dissolution medium can be chosen depending on the type of composition in question. Accordingly, water or simulated saliva can be used for compositions intended for administration to the oral cavity. A person skilled in the art will know how to chose the right dissolution medium depending on the formulation in question. Normally a dissolution medium based on water and adjusted to a pH in the range of from pH 4.5 to about 8 is suitable irrespective of whether the compositions are intended for administration via nasal, rectal, vaginal mucosa.

In the present context the term "substantially immediate release" is intended to include all types of release which differ from the release obtained from plain tables and provide a release, which is faster than that obtained from plain tablets. In particular, the term is related to a rapid release of the one or more glucocorticoids in an *in vitro* dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and simulated intestinal fluid without enzymes as dissolution medium.

The term "C_{max}" denotes the average maximum serum//plasma/blood concentration or serum//plasma/blood level obtained after administration of the composition to at least six normal healthy human subjects.

The term "via a mucosa" indicates that the one or more glucocorticoids must enter into the systemic circulation in order to obtain the desired effect and that the administration route is different from that of topical, intravenous and intramuscular administration.

In another aspect, the invention relates to a kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to the invention and instructions for use thereof. In a specific embodiment, the one or more containers are in the form of blisters or blister packs.

In a further aspect, the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

In a still further aspect, the invention relates to the use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined herein for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

As mentioned above, in order to obtain a fast onset of action it is required that a fast rise of glucocorticoid serum level is obtained after administration of a composition of the invention. Accordingly, in specific embodiments least 40% of C_{max} is reached within

30 min and/or at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

Normally, T_{max} (i.e. the time it takes to obtain the maximum serum/plasma/blood concentration in the serum/plasma/blood concentration time profile) is reached within 60 min after administration of the composition via a mucosa of the subject. T_{max} is typically within a range of from about 30 to about 75 min such as in a range of from about 45 to about 60 min.

As mentioned above, the pharmaceutical compositions and kits of the present invention are suitable for use in the treatment of a disorder requiring acute glucocorticoid therapy. Examples of such disorders are acute adrenal crises relating to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, acute kidney transplant rejection, systemic lupus erythematosus or a severe allergic reaction. Other examples include inflammatory disorders, autoimmune disorders, or medical disorders in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment. Specific examples of disorders that can be treated according to the present invention are given in the following.

Active substance, dosage and administration routes

In the present context, the term "glucocorticoid" or "glucocorticosteroid" is intended to denote a therapeutically, prophylactically and/or diagnostically active glucocorticoid or a glucocorticoid that has physiologic effect. The term is intended to include the glucocorticoid in any suitable form such as e.g. a pharmaceutically acceptable salt, complex, solvate, ester, active metabolites or prodrug thereof of in any physical form such as, e.g., in the form of crystals, amorphous or a polymorphous form or, if relevant, in any stereoisomer form including any enantiomeric or racemic form, or a combination of any of the above. The glucocorticoid may be a synthetic glucocorticoid.

The one or more glucocorticoids used according to the invention are selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone including pharmaceutically acceptable esters, salts, complexes and mixtures thereof. In a preferred embodiment of the invention, the glucocorticoid is betamethasone.

Specific examples of pharmaceutically acceptable salt suitable for use according to the invention are phosphates, succinates, lysinates, acetates, cypionates, valerates, hemisuccinates, butyrates and trometamole salts.

As the glucocorticoid is intended for immediate release, the release and/or absorption into the systemic circulation takes place already in the oral cavity in the case the composition is administered orally. In such cases, the glucocorticoid of choice for the first part may be any other than hydrocortisone (as such) or cortisone as these two active substances have a bitter taste. However, these substances may be employed provided that a sufficient taste masking is obtained. In the paragraph relating to "Pharmaceutically acceptable excipients" taste-masking is discussed in more detail. Accordingly, the one or more glucocorticoids of the first part may have an acceptable taste, may be tasteless or it may be effectively taste-masked.

Furthermore, in specific embodiments of the invention, the glucocorticoid used may be a readily water-soluble glucocorticoid (e.g. a water-soluble salt of the glucocorticoid) in order to ensure a fast dissolution of the glucocorticoid from the composition.

In a preferred embodiment of the invention the glucocorticoid is hydrocortisone trometamole (or succinate) due to its high solubility in water, which in turn leads to a rapid absorption into the systemic circulation.

Dosage

In general, the dosage of the glucocorticoids present in a composition according to the invention depends *inter alia* on the specific drug substance, the age and condition of the patient and of the disease to be treated.

The term "hydrocortisone equivalents" is used herein to define the amount in mg of a specific glucocorticoid that corresponds to 1 mg of hydrocortisone for the purpose of glucocorticoid therapy as generally understood by medical practitioners. The term is based on the fact that the individual glucocorticoids have different potency and in order to achieve a desired therapeutic effect different doses of the individual glucocorticoids are required. Equivalent doses of the glucocorticoids can be calculated based on the following table.

Glucocorticoid	Equivalent amount (mg)	Hydrocortisone equivalent (1 mg of the glucocorticoid corresponds to the listed amount in mg of hydrocortisone)
Cortisone acetate	25	0.8
Hydrocortisone	20	1
Prednisolone	5	4
Prednisone	5	4
Methylprednisolone	4	5
Triamcinolone	4	5
Paramethasone	2	10
Betamethasone	0.75	26.66
Dexamethasone	0.75	26.66
Fludrocortisone	0.05	400

In general, a pharmaceutical composition according to the invention contains a total amount of the one or more glucocorticoids expressed as hydrocortisone of from about 1 to about 200 mg. In specific embodiments, the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

More specifically, normal dose ranges are given below for acute glucocorticoid therapy

Hydrocortisone	1-200 mg; in acute adrenal crises about 100 mg
Cortisone	1-200 mg such as about 100 mg
Betamethasone	1-20 mg; in increased intracranial pressure e.g. brain oedema about 4 mg daily In chemotherapy or radiation induced nausea 4-8 mg
Prednisolon	1-100 mg; such as from 1 to 30 mg daily; in severe cases 50-60 mg/day

Dexamethasone	0.1-6 mg such as 0.5-2 mg or 1.5-3 mg; in severe cases up to 6 mg/day
Fludrocortisone	0.05-5 mg; in Addison disease to correct inadequate electrolyte balance 0-05-0.2 mg daily; Cortical adrenal hyperplasia ("salt losing adrenogental syndrome") 0.1-0.2 mg
Prednisone	10-100 mg such as 50 mg
Methylprednisolone	2-40 mg such as 2-20 mg

In the following are given suitable doses of the individual glucocorticoids in various treatment regimens.

Acute asthma – adults

betamethasone	4-8 mg
prednisolone	30-60mg
methylprednisolone	40 mg

Acute anaphylaxia - adults

betamethasone	5 mg up to 20 mg
hydrocortisone	200 mg
dexamethasone	4-20mg –80mg

Acute anaphylaxia - children

hydrocortisone	100-200 mg

Septic shock - adults

hydrocortisone	200-300 mg/day
methylprednisone	30 mg/kg

Acute bacterial meningitis

dexamethasone	0.3 mg/kg/dose (max 10 mg) x 4 times daily for 2-4 days
betamethasone	8 mg x 4 times daily

Acute RSV (respiratory syncytial virus) infection with bronchiolitis in children

betamethasone 4-6 mg

Acute croup-children
betamethasone 4-6 mg

Mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia)
betamethasone 5-6 mg

Tonsillitis/peritonsillitis – children with airway obstruction
betamethasone 4-6 mg

A composition according to the invention is designed to provide a fast onset of action and upon administration a fast rise in glucocorticoid serum/plasma/blood level is obtained. In the case hydrocortisone is used as the glucocorticoid a serum level of at least about 200 nmol/l is obtained within 20 min after administration. In the case that another glucocorticoid than hydrocortisone is used, a person skilled in the art will know how to determine suitable equivalent serum/plasma/blood concentrations.

For example, hydrocortisone can be rapidly released from a composition during a time period of from about 0 to abut 30 minutes after administration and 5-10 mg of hydrocortisone can be rapidly administered as an extra dose in conjunction with fever etc in patients with adrenal insufficiency. Likewise, 5-20 mg of betamethasone can be rapidly released for most indications in which a rapid glucocorticoid effect is of value.

Administration routes

As mentioned above, the one or more glucocorticoids used according to the invention are administered to the subject (preferably a human) via a mucosa into the systemic circulation. In particular, in specific embodiments of the invention, the mucosa is the mucosa in the oral cavity, the nose, the rectum or in the vagina or via pulmonary, bronchial or respiratory mucosa and ephithelia. Preferably, the mucosa is the oral mucosa.

Figures 11 and 12 show sites of oral mucosal administration suitable for use. Four well-defined sites may be used, namely

"buccal" administration that includes the term "labial" administration and is used for administration of a pharmaceutical composition to a mucosa between the gums (gingiva) and the inside of the cheeks;
"sublingual" administration that refers to administration of a pharmaceutical composition under the tongue;
"palatal" administration that refers to administration of a pharmaceutical composition to the hard and/or soft palate; and
"gingival" administration that refers to administration of a pharmaceutical composition to the upper and/or lower gingiva.

All the above-mentioned sites are suitable for use to obtain a very fast onset of action due to a rapid absorption (transport of active drug) into the systemic circulation. In specific embodiments of the invention the buccal administration route is preferred, i.e. administration of a composition to the oral mucosa between the gums and the inside of the cheeks and thus enabling the absorption to take place from two sites, namely the gingival mucosa and the buccal mucosa.

Pharmaceutical compositions

In the following is given a description of pharmaceutical compositions according to the invention.

Release of the one or more glucocorticoids

A rapid release of the one or more glucocorticoids is necessary in order to obtain a fast onset of action after administration via a mucosa where the glucocorticoid is rapidly absorbed (transported) into the systemic circulation. Accordingly a general requirement is that at least 60% of the one or more glucocorticoids contained in the composition must be released within 30 min when tested in an *in vitro* dissolution test as defined herein. Specific embodiments of the composition fulfil one or more of the requirements given in the following table. In general, it is preferred that the requirement stated within 30 min after start of the dissolution test is fulfilled. In preferred embodiments, at least 70% or at least 80% of the one or more glucocorticoids contained in the composition are released within the first 20 min of the dissolution test.

time after start of the dissolution test	% hydrocortisone equivalents released (based on the content in the

	composition)
within 30 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or more preferably at least about 90%
within 20 min	at least about 60%, preferably at least about 70%, at least about 80% or even more preferred at least about 90%
within 15 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80%or at least about 90%
within 10 min	at least about 60% such as, e.g., at least about 70%, preferably at least about 80% or at least about 90%
within 5 min	at least about 60%

In specific embodiments (cf. the examples herein) more than 50 % of the one or more glucocorticoids can be released within 2 min, between 50 and 90 % can be released within 5-8 min, and more than 90 % of the dose can be released within 15 min.

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A pharmaceutical composition according to the invention is designed for systemic administration via a mucosa. In a preferred embodiment the mucosa is the mucosa in the oral cavity.

The pharmaceutical composition may be in any suitable form including liquid, semi-solid or solid form.

In a preferred aspect of the invention the pharmaceutical composition is in the form of a dosage form such as a unit dosage form.

Examples of compositions according to the invention suitable for administration via the oral mucosa into the systemic circulation are typically solid or semi-solid dosage forms. The solid dosage form is typically selected from the group consisting of granules, beads, pellets and powders and - when presented in unit dosage form - it may be in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet, melt tablets, lozenges, pastilles or it may be presented in a more candy-like form, or the like.

A pharmaceutical composition for administration via the oral mucosa into the systemic circulation may also be in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a solution, an inhaler or the like.

Examples of compositions according to the invention suitable for administration via the mucosa in the nose into the systemic circulation are typically in the form of nasal sprays, nasal aerosols, nasal solutions including nasal drops and the like.

Examples of compositions according to the invention suitable for administration via the pulmonary, bronchial and respiratory mucosa and epithelia into the systemic circulation are inhalers including powder inhalers.

Examples of compositions according to the invention suitable for administration via the mucosa in the rectum or the vagina into the systemic circulation include suppositories, vagitories, clysmas etc.

A pharmaceutical composition according to the invention may also have bio/mucoadhesive properties. The absorption of drugs into the systemic circulation from a mucosal drug delivery system is significantly improved if a mucosal bioadhesive component is added in the formulation. It will prevent both swallowing and create a high local concentration of the glucocorticoid adjacent to the absorption site. The mucoadhesive component will be mixed in an appropriate way together with the glucocorticoid and other ingredients in the dosage form. The term "bio/mucoadhesive is used to denote that the composition is able to reversible adhere to a biological mucosa. In some cases a bio/mucoadhesion promoting agent is included in the composition to promote adherence to the mucosa.

In the term bio/mucoadhesion promoting agent mucoadhesion and bioadhesion are used interchangeable even if bioadhesion may have a wider definition meaning that an adhesion to any biological feature available at the mucosa takes place. If present, the bio/mucoadhesion promoting agent may be a polymeric substance, preferable a substance having an average molecular weight above 5 kD. The hydration property is crucial for the bio/mucoadhesion forces and therefore a rapid swelling of the polymer will initiate the bio/mucoadhesion process. A swelling factor by volume when brought into contact with the saliva fluid should be between 10 and 20.

A pharmaceutical composition according to the invention typically contains one or more pharmaceutically acceptable excipients. A general description of pharmaceutically acceptable excipients suitable for use in a composition according to the present invention is given in the paragraph under the heading "Pharmaceutically acceptable excipients". Depending on the specific kind of dosage form a person skilled in the art will know which kinds of excipients to choose, if necessary guided by the teaching in handbooks like Remington's Pharmaceutical Science and Handbook of Pharmaceutical Excipients. In the following is given a description of specific kinds of excipients suitable for use in the formulation of compositions in the form of film or patches especially for administration to the oral cavity.

When the pharmaceutical composition is in the form of a film, patch, wafer, gel, sachet, gingival patch or the like it may contain a pharmaceutically acceptable excipient selected from the group consisting of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof. The cellulose derivative may be selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

A pharmaceutical composition according to the invention may also contain the one or more bio/mucoadhesion promoting agents. Normally such bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w. Examples of bio/mucoadhesion promoting agents include polymers including synthetic polymers, natural polymers and derivatives thereof, and mixtures thereof. The polymer

may be selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof; or it may be a polysaccharide. The polysaccharide may be selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

A pharmaceutical composition according to the invention may also containg a dissolution promoting agent. If present, a dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w of the total weight of the composition. The dissolution promoting agent may be selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

In specific embodiment the one or more glucocorticoids in a composition of the invention are present as microparticles or nanoparticles. In general, he mean particle size of such particles is 10 μm or less. Furthermore, the micro- or nanoparticles may be encapsulated such as coated with a coating comprising a lechitin or a lechitin based compound.

When the glucocorticoid is present in the form of micro- or nanoparticles, a pharmaceutical composition according to the invention may also comprise a disintegrating agent. Such agents promote the dispersion of microparticles of the glucucorticoid over the administration site in for example the labial and gingival mucosa. Examples of pharmaceutically acceptable disintegrating agents are cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum. If present, it is normally used in a concentration of from 0.5 to 10 w/w based on the total weigh of the composition Different pharmaceutical excipients, such as mannitol and lactose, have been found to be particularly suitable as excipients.

As mentioned above, the pharmaceutical composition according to the invention may further comprise a taste-masking agent. Examples of a taste-masking agent are e.g. menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener. In a specific embodiment, the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

In general, the composition of the invention contains from 0.05 up to 50 weight percent such as, e.g., from 0.05 up to 40 weight percent, 0.05 up to 30 weight percent or from about 0.05 up to 20 weight percent of glucocorticoid. More preferably, the compositions contains from 0.05 to 10 weight per cent of glucocorticoid, and especially from 0.1 to 5 weight per cent. The contents can also be expressed as the amount of glucocorticoid in a dose unit of the composition, such as a tablet. In this connection a dose refers to the therapeutically amount of the at least one glucocorticoid, or its derivative, which is to be administered at one time. When the glucocorticoid is used in the form of a pharmaceutically acceptable salt, these percentages and amounts should be recalculated accordingly.

Pharmaceutically acceptable excipients

In the present context the terms "pharmaceutically acceptable excipients" are intended to denote any material, which is inert in the sense that it substantially does not have any therapeutic and/or prophylactic effect *per se*. Such an excipient may be added with the purpose of making it possible to obtain a pharmaceutical, which have acceptable technical properties.

Examples of suitable excipients for use in a solid dosage form according to the invention include fillers, diluents, disintegrants, binders, lubricants etc. or mixture thereof. As the individual parts of a composition or kit according to the invention are used for different purposes (e.g. immediate and extended release), the choice of excipients is normally made taken such different uses into considerations. A person skilled in the art will know which kinds of pharmaceutically acceptable excipients that are suitable choices depending on the specific dosage form in question. Other pharmaceutically acceptable excipients for suitable use are e.g. acidifying agents, alkalising agents, preservatives, antioxidants, buffering agents, chelating agents, colouring agents, complexing agents, emulsifying and/or solubilizing agents, flavours and perfumes, humectants, sweetening agents, wetting agents etc.

Examples of suitable fillers, diluents and/or binders include lactose (e.g. spray-dried lactose, α-lactose, β-lactose, Tabletose®, various grades of Pharmatose®, Microtose® or Fast-Floc®), microcrystalline cellulose (various grades of Avicel®, Elcema®, Vivacel®, Ming Tai® or Solka-Floc®), hydroxypropylcellulose, L-hydroxypropylcellulose (low substituted), hydroxypropyl methylcellulose (HPMC) (e.g. Methocel E, F and K, Metolose SH of Shin-Etsu, Ltd, such as, e.g. the 4,000 cps grades of Methocel E and Metolose 60 SH, the 4,000 cps grades of Methocel F and Metolose 65 SH, the 4,000, 15,000 and 100,000 cps grades of Methocel K; and the 4,000, 15,000, 39,000 and 100,000 grades of Metolose 90 SH), methylcellulose polymers (such as, e.g., Methocel A, Methocel A4C, Methocel A15C, Methocel A4M), hydroxyethylcellulose, sodium carboxymethylcellulose, carboxymethylene, carboxymethylhydroxyethylcellulose and other cellulose derivatives, sucrose, agarose, sorbitol, mannitol, dextrins, maltodextrins, starches or modified starches (including potato starch, maize starch and rice starch), calcium phosphate (e.g. basic calcium phosphate, calcium hydrogen phosphate, dicalcium phosphate hydrate), calcium sulfate, calcium carbonate, sodium alginate, collagen etc.

Specific examples of diluents are e.g. calcium carbonate, dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate, microcrystalline cellulose, powdered cellulose, dextrans, dextrin, dextrose, fructose, kaolin, lactose, mannitol, sorbitol, starch, pregelatinized starch, sucrose, sugar etc.

Specific examples of disintegrants are e.g. alginic acid or alginates, microcrystalline cellulose, hydroxypropyl cellulose and other cellulose derivatives, croscarmellose sodium, crospovidone, polacrillin potassium, sodium starch glycolate, starch, pregelatinized starch, carboxymethyl starch (e.g. Primogel® and Explotab®) etc.

Specific examples of binders are e.g. acacia, alginic acid, agar, calcium carrageenan, sodium carboxymethylcellulose, microcrystalline cellulose, dextrin, ethylcellulose, gelatin, liquid glucose, guar gum, hydroxypropyl methylcellulose, methylcellulose, pectin, PEG, povidone, pregelatinized starch etc.

Glidants and lubricants may also be included in the composition. Examples include stearic acid, magnesium stearate, calcium stearate or other metallic stearate, talc, waxes and glycerides, light mineral oil, PEG, glyceryl behenate, colloidal silica,

hydrogenated vegetable oils, corn starch, sodium stearyl fumarate, polyethylene glycols, alkyl sulfates, sodium benzoate, sodium acetate etc.

Other excipients which may be included in a composition of the invention are e.g. flavoring agents, coloring agents, taste-masking agents, pH-adjusting agents, buffering agents, preservatives, stabilizing agents, anti-oxidants, wetting agents, humidity-adjusting agents, surface-active agents, suspending agents, absorption enhancing agents, agents for modified release etc.

The composition or kit components according to the invention may also be coated with a film coating, a protective coating, an anti-adhesive coating etc.

A composition according to the invention may also be coated in order to obtain suitable properties e.g. with respect to taste-masking of the one or more glucocorticoids. The coating may also be applied as a readily soluble film. The coating may be applied on single unit dosage forms (e.g. tablets) or it may be applied on a multiple-unit dosage form or on its individual units.

Suitable coating materials are e.g. methylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, acrylic polymers, ethylcellulose, cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, polyvinylalcohol, sodium carboxymethylcellulose, cellulose acetate, cellulose acetate phthalate, gelatin, methacrylic acid copolymer, polyethylene glycol, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, glyceryl monostearate, zein.

Plasticizers and other ingredients may be added in the coating material. The same or different active substance may also be added in the coating material.

Taste masking

In general, it is difficult in most cases to prepare a formulation for oral mucosa or nasal administration with satisfactory safety and stability from a drug having irritating properties or capable of forming molecular aggregates, although it depends on the kind of the drug used. In the case of hydrocortisone, the base has a distinctively bitter taste and a formulation has to be taste masked in order to be applicable for repeated use.

The taste masking agent can be a menthol, a peppermint, a vanillin, or a terpene based compound. In addition, the taste masking agent can be an artificial sweetener, e.g. sorbitol, xylitol or aspartame. Taste masking can also be achieved by microencapsulation of the glucocorticoid as particles. This is for example accomplished with lecithin based compounds. The taste masking agent is carefully mixed with the active drug in order to be present both at the surface and within the administration formulation. Taste masking can also be achieved by formation of inclusion complexes with cyclodextrins.

Typical examples of the cyclodextrin compound are alpha.-cyclodextrin, .beta.-cyclodextrin, .gamma.-cyclodextrin, hydroxypropyl .beta.-cyclodextrin, dimethyl .beta.-cyclodextrin, maltosyl .beta.-cyclodextrin and .beta.-cyclodextrin sulfate. Particularly preferred are .alpha.-cyclodextrin, .beta.-cyclodextrin and .gamma.-cyclodextrin. These cyclodextrin compounds may be used alone or in combination.

The amount of cyclodextrin compound to be used may vary with its solubility and the concentration of hydrocortisone. It is, however, desirable that the amount of cyclodextrin compound is 0.5 to 4.0 moles, preferably 2.0 to 4.0 moles, as much as the mole of hydrocortisone.

Method aspect

A pharmaceutical composition or a kit according to the invention is suitable for use in the treatment of a subject such as a mammal including a human suffering from a disorder requiring acute glucocorticoid therapy.

Accordingly, in a separate aspect the invention relates to a method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

Normally, it is preferred that at least 40% of C_{max} is reached within 30 min after administration in order to obtain a fast onset of action. In specific preferred embodimentd, at least 75% of C_{max} is reached within 45 min after administration and/or T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

Details concerning other aspects of the invention are described hereinbefore and apply also to the method aspect of the invention.

The method according to the invention can be carried out by the patient itself or by non-medically trained persons due to the fact that the one or more glucocorticoids are not presented in the form of a composition for injection or infusion. Normally, medically trained personnel can only administer such compositions. Accordingly, the present invention provides a method that compared to the known treatment methods requiring acute glucocorticoids is much more simple to handle without the necessity of specialized equipment. It is therefore contemplated that the present invention provides a method that enables a treatment when the condition of the patient requires it, i.e. there is no need for bringing the patient to a hospital or a medical clinic in order to be able to give the necessary treatment.

Moreover, due to the development of compositions that enable a fast onset of action after administration and that can be administered without the need of the patient to swallow the composition (e.g. compositions of the invention in the form of films, bio/mucoadhesive compositions, patches, gingival patches, sprays etc.), the patient may be unconscious or otherwise unable to swallow normal tablets and still be correctly treated with glucocorticoids in acute situations.

Use of a composition or a kit according to the invention

In another separate aspect, the invention relates to the use one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined hereinbefore for the treatment of a disorder requiring acute glucocorticoid therapy and to provide a serum level as defined herein.

In the above is given a detailed description of the invention relating one or more aspects of the invention, in particular relating to pharmaceutical compositions. However, all details and particulars disclosed under this aspect of the invention apply *mutatis mutandis* to the other aspects of the invention.

Legends to figures

Figure 1 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject.

Figure 2 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition B to a human subject.

Figure 3 shows results from Example 11. The plasma concentration-time profile of cortisol following a single dose administration of composition C to a human subject.

Figure 4 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film A to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 5 shows results from Example 12. The plasma concentration-time profile of cortisol following a single dose administration of film B to a human subject. Non-mucoadhesive thin-layer film, 6 cm^2, 11.2 mg hydrocortisone acetate, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids.

Figure 6 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. In vivo plasma profile. Muocadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 7 shows results from Example 13. The plasma concentration-time profile of cortisol following a single dose administration of composition A to a human subject. Mucoadhesive thin-layer film, 10 mg hydrocortisone, buccal administration. Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 8 shows results from Example 14. The plasma concentration-time profile of cortisol following a single dose administration of composition C. In vivo plasma profile. Mucoadhesive rapid-release tablet, 10 mg hydrocortisone, buccal administration.

Subject has the endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids

Figure 9 shows results from Example 15 (Composition C from Example 14).

Figure 10 shows results from Example 15 (Composition A from Example 13).

Figures 11 and 12 illustrates different administration sites within the oral cavity

The invention is further illustrated in the following non-limiting examples.

Materials

The materials used in the following examples were

Trade name	*Chemical substance*	*Manufacturer*
Betamethasone	USP/NF	
Carboxymetylcellulose	USP/NF	
Chitosan glutamate	USP/NF	
Crospovidone	USP/NF	
Hydrocortisone	Ph. Eur., Qual. D	Aventis, Switzerland (by Apoteksbolaget)
Hydrocortisone acetate	USP/NF	
Hydrocortisone 21-hemisuccinate sodium	Ph. Eur	Aventis, Switzerland (by Apoteksbolaget)
2-OH-propyl-β-cyclodextrin		
Hydroxypropylmethylcellulose	USP/NF	
Levomenthol	USP/NF	
Menthol	USP/NF	
Methocel E5	Hydroxypropyl-methyl cellulose	Dow Chemicals, USA (by Colorcon)
Methocel® KV 100 LV	USP/NF	Dow Chemicals, USA (by Colorcon)
Metolose®		
Microcrystalline cellulose, Avicel® PH-102	USP/NF	FMC Corporation

Paraffin powder	USP/NF	
PEG 300	USP/NF	
PEG 6000	Polyethylene glycol	Svenska Hoechst AB
PEG 400	Polyethylene glycol	Fluka, Switzerland
Prednisolone	USP/NF	
Polyox WSR 301	Polyethylene oxide	Dow Chemicals, USA
Na-alginate PH157		
Sodium dihydrogen phosphate	$NaH_2PO_4 \cdot 2\ H_2O$	
Sodium stearyl fumarate	USP/NF	
Sorbitol	USP/NF	
Sugar	USP/NF	
Sugar/starch seeds	USP/NF	
Talc	USP/NF	
Triethyl citrate	USP/NF	
Xylitab 300 Xylisorb 300		Xyrofin Kotka, Finland (Danisco Sweeteners Ltd, UK
Xylitol	USP/NF	Roquette, France

Methods

The in vivo experiments reported herein were carried out on healthy volunteers. At 6 pm and 11 pm the day before administration of the test composition, the endogenous cortisol secretion was suppressed by oral administration of 2 mg of betamethasone. The test composition was administered to healthy volunteers. The volunteers were in fasted state and were not allowed to take any food until noon. In the case a tablet is administered, it is ingested together with 200 ml of water. The test composition is administered between 8 am and 10 am on the day following the suppression of endogenous glucocorticoid secretion.

Examples

Example 1

Capsules containing an immediate release pellets (IR pellets)

IR pellets

Sugar/starch seeds, diameter 0.25-0.35 mm	1 kg

are coated in a fluidised bed equipped with a Wurster column with a water suspension containing

Hydrocortisone 21-hemisuccinate sodium	10 %
Hydroxypropyl methylcellulose, 6 cps	3 %
Talc	10 %

to a weight gain of approximately 75 %.

An amount of IR pellets containing 13.4 mg of hydrocortisone 21-hemisuccinate sodium (approximately 70 mg) are filled into hard gelatine capsules size No 3 in a capsule-filling machine.

70 mg pellets will easily fit into a capsule size No. 3 (or even size No. 4) and can be filled in a normal capsule filling machine.

Example 2

Immediate release (IR) tablet

IR tablets for oral or sublingual use:

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a]	40
Lactose anhydrous USP/NF	5
Microcrystalline cellulose USP/NF	10
Crospovidone USP/NF	4
Sodium stearyl fumarate	1
Water	qs

[a] Direct compression xylitol from Danisco Sweeteners Ltd UK

Dry mix lactose and microcrystalline cellulose. Dissolve betamethasone in a small amount of water and disperse the solution over the powder blend. Mix and dry. Add Xylitab and crospovidone and dry mix until the blend is homogeneous.

Add sodium stearyl fumarate and continue blending for another 2 minutes.
Compress the blend to tablets in a tablet press using 6 mm round concave punches.

Example 3

Immediate release (IR) film

Thin films for administration to the oral cavity:

	% by weight
Prednisolone	0.75
PEG 400 USP/NF	2
Methocel E5, Dow Chemical	4
Xylitol, Roquette France	1
Water	up to 100

Methocel was added to approximately 90% of the total amount of distilled water and stirred with a magnetic stirrer until Methocel was completely dissolved. PEG 400 was added under continued stirring, followed by xylitol and prednisolone. Water was added to final weight and stirring was continued during four hours.

330 µl of the solution was pipetted into 16 mm diameter flat-bottomed PVC blisters. The solutions were allowed to dry at room temperature over night and the blister packs were sealed with heat-seal lacquered aluminium foil.

Example 4

Immediate release (IR) oral solution

Oral solution:

Prednisolone acetate	0.9 mg
Sorbitol	60 mg
Menthol	1.2 mg
Sterile water	5 ml

Make a solution and fill into a moisture tight aluminium foliated sachet.

Example 5

Immediate release (IR) sublingual spray

Sublingual spray of hydrocortisone:

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0.08%)
2-OH-propyl-β-cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
$NaH_2PO_4 \cdot 2\ H_2O$	2
Water	qs

Dissolve hydrocortisone acetate in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and $NaH_2PO_4 \cdot 2\ H_2O$. Add water up to final volume. Dispense into a spray package that delivers 0.58 ml per dose (5 mg of hydrocortisone).

Example 6

Betamethasone IR tablet for peroral or buccal administration

	Mg per tablet
Betamethasone	0.4
Xylitab®300[a)]	45
Microcrystalline cellulose NF	10
Crospovidone NF	4
Water	qs
Sodium stearyl fumarate NF	1

[a)] Direct compression xylitol from Danisco Sweeteners Ltd, UK

Dissolve betamethasone in a small amount of water.
Disperse the solution over the microcrystalline cellulose. Mix and dry.

Add Xylitab and crospovidone and dry mix in a suitable mixer until a homogeneous blend is achieved.
Then add sodium stearyl fumarate and continue mixing another two minutes.
Compress the powder blend in a suitable tablet press using 6 mm round concave punches.

Example 7
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Carboxymetylcellulose	0.8 (0.08%)
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 8
Sublingual spray of betamethasone

	mg/ml
Betamethasone	0.4
Chitosan glutamate	10
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve betamethasone in a small amount of water. Add chitosan glutamate and mix. Filter through 0.2µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 9

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Carboxymetylcellulose	0.8 (0,08%)
2-OH-propyl-β- cyclodextrin	40
PEG 300	5
Menthol	0.3
Sorbitol	12
Levomenthol	2.0
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add carboxymetylcellulose and mix. Add PEG 300, menthol, sorbitol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 10

Sublingual spray of hydrocortisone

	mg/ml
Hydrocortisone acetate	10
Chitosan glutamate	10
2-OH-propyl-β- cyclodextrin	40
Menthol	0.1
Levomenthol	1.5
NaH_2PO_4*2 H_2O	2
Water	qs

Dissolve hydrocortisone in a small amount of water. Mix with 2-OH-propyl-β-cyclodextrin, let stand for 1 hour. Add chitosan glutamate and mix. Filter through 0.2

µm membrane filter. Add menthol, levomenthol and NaH_2PO_4*2 H_2O. Add water up to final volume.

Example 11

Thin-layer film of hydrocortisone

Composition A:

	% w/w
Hydrocortisone	3%
Na-alginate PH157	2%
Water	95%

Composition B:

Hydrocortisone acetate	3.4%
Na-alginate PH157	2%
Water	94.6%

Composition C:

Hydrocortisone	3%
Metolose 60SH-50	2%
Water	95%

The films were made as described in the following:

1. Amount polymer, glucocorticoid and H_2O were weighed.
2. The glucocorticoid was added to the water during stirring.
3. The formulation was kept on stirring until a suspension was obtained.
4. The polymer was added to the suspension.
5. The formulation was kept on stirring until a uniform gel was obtained (minimum 2h).
6. 0.5g gel was weighed in empty blisters and placed in a heating cupboard (Drying: 25°C for 22h).

Table. In vitro dissolution (rotating basket 100 rpm, phosphate buffer pH=7.0, one unit per 500 ml medium) after 1, 3 ,5, 10 and 15 min as a percentage of 10 mg

hydrocortisone. Units with 10 mg hydrocortisone in polymers of sodium alginate (Na-alg), hypromellose (HPMC) and approx. 7 mg/unit. Two units were tested with Na-alg and HPMC. The mean value is tabulated. The results in the following table reflect the rank order regarding viscosity, i.e. HPMC has the lowest viscosity and Na-alg the highest.

Composition	Polymer	1 min,%	3 min,%	5 min,%	10 min,%	15 min,%
A	Na-alg	15	25	38	65	84
B	Na-alg	15	25	38	65	84
C	HPMC	18	48	67	88	92

In vivo plasma profiles in humans, N=1 per composition
Dexamethasone suppression test, fasting state, otherwise as described in the paragraph denoted "Method".

The results show that the use of hydrocortisone acetate does not seem to be suitable for an immediate release composition. This was further investigated in the following example.

Example 12
Non-mucoadhesive immediate release films

Two films were prepared essentially similar to Example 13 – composition A. Film A contains 10 mg of hydrocortisone and film B contains 11.2 mg of hydrocortisone acetate. The results from in vivo testing after buccal administration are shown in Figures 4 and 5. The results show that even if the films are not bioadhesive, a fast onset of the absorption into the systemic circulation after single dose administration of Film A is obtained. In contrast, the results obtained with the film containing hydrocortisone acetate indicate that this compound does not seem to be suitable when a fast onset of the absorption into the systemic circulation of the glucocorticoid is required.

Example 13
Thin-layer films for immediate release

Batches of glucocorticoid films were prepared from the following compositions A and B:

Rapid-release composition A:

Component	*% w/w*
PEG 400	2.0
Hydrocortisone	3.0
Methocel E5	4.0
Xylitol	1.0
Water	90

Slower release composition B:

Component	*w/w %*
PEG 400	1.3
Hydrocortisone	3.0
Methocel E5	5.7
Water	90

To distilled water (18 ml) in 50 ml round-bottomed glass flask provided with a magnetic stirred was added Methocel E5. After the Methocel had dissolved completely PEG 400 was added under continued stirring, followed by xylitol (Composition A only) and hydrocortisone. Stirring was continued for 4 h.

Into flat-bottomed PVC-blisters (Inpack AB, Lund, Sweden) 16 mm in diameter was pipetted (Finnpipette; automatic) 330 µl of solution A or B into each blister trough. The solutions were allowed to dry at room temperature over night. The next day 10 films were removed for dose analysis. Each film was dissolved in 100 ml of water/ethanol (95%) 9:1 (w/w). The solutions were analysed by UV spectroscopy at 242 nm. Mean contents of 10.19 mg and 9.83 mg hydrocortisone per blister (SD 0.29 and 0.14, respectively) were found for Compositions A and B, respectively.

The hydrocortisone compositions were tested in two human subjects after labial administration. The subjects had their endogenous glucocorticoid secretion suppressed by synthetic glucocorticoids. The plasma concentration of cortisol was monitored during 360 min after the labial administration, and the serum concentration time profiles from these two subjects are shown in Figures 6 and 7.

It is clearly seen that the rate and extent of mucosal uptake of hydrocortisone is high and the appearance of cortisol in serum is rapid, as the first measured plasma concentration was attained already at 10-15 min.

These serum pharmacokinetic data illustrate that a formulation of the invention for oral mucosa administration results in a high rate and extent of mucosal absorption of the active drug, even though a small volume of fluid is available for dissolution at the site of administration and absorption in this route drug delivery.

Example 14

Glucocorticoid tablets for immediate release

Glucocorticoid tablets were manufactured by direct compression of the dry-mixed powderous components to the following composition C:

Rapid-release composition C:	*Component*	*Per Batch*
	PEG 6000	8.7 g
	Hydrocortisone	2.5 g
	Xylitab 300	8.7 g
	Mg stearate	0.16 g

Batch size 100 tablets

The powderous components were sieved (mesh size 0.7 mm) and dry-mixed by shaking by hand in a small tin can for five min. The homogeneity of the mixture was analyzed by the same method as used for analysis of the tablets. Tabletting was carried out with a DIAF tabletting machine using a flat circular punch 7 mm in diameter (with a dividing score). The hydrocortisone dose in 10 tablets was assessed by the same method as used for the films. Mean contents of 9.53 mg hydrocortisone per tablet (SD 0.15) were found for composition C.

Tablet thickness (10 tablets): 1.72-1.76 mm (C);
Friability (20 tablets): 0.6% (C);
Tablet hardness (10 tablets): 23.7 N (C).

The compositions were tested after oral administration to two human subjects (see Figure 8).

The rate of absorption of the glucocorticoid into the systemic circulation from the solid dosage forms of Example 14 was somewhat slower than that of compositions from Example 13, which means that it is possible to adjust the absorption rate of hydrocortisone into the systemic circulation by introducing changes in the composition and function of the labial pharmaceutical formulation.

Example 15

In vitro dissolution profile

The *in vitro* dissolution profiles of hydrocortisone from drug formulations according to Example 20 and 21 were followed over time in a standardized controlled *in vitro* environment. A United States Pharmacopoeia dissolution apparatus II (paddle) coupled to automatic sampling devices and software was used for acquiring release profiles of the drug formulations in a neutral pH environment. The dissolution profile was acquired at 37 °C, 50 rpm of the paddles, in a total of 300 ml of water. Sampling was performed at 0, 1, 3, 5, 7, 10 and 15 minutes following the insertion of the pharmaceutical composition in the example in the dissolution medium.

The dissolution profile from each formulation was monitored in two experiments up to 360 min after administration, and the corresponding dissolution time profiles are shown in Figs. 9 and 10, respectively. The release rate is given as the per cent of dose over time.

The release rate from the solid dosage forms of Example 21 was somewhat slower (Fig. 10). This means that it is possible to adjust the release rate of hydrocortisone by introducing changes in the composition and function of the oronasopharyngeal pharmaceutical preparation.

Claims

1. A pharmaceutical composition comprising one or more glucocorticoids for substantially immediate release, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 30 min after start of an in vitro dissolution test according to USP employing USP Dissolution Apparatus No. 2 (paddle), 50 rpm and a suitable dissolution medium, and wherein a glucocorticoid serum level of a subject of at least 20% of C_{max} is reached within 20 min after administration of the composition via a mucosa of the subject.

2. A pharmaceutical composition according to claim 1, wherein at least 40% of C_{max} is reached within 30 min after administration of the composition via a mucosa of the subject.

3. A pharmaceutical composition according to claim 1 or 2, wherein at least 75% of C_{max} is reached within 45 min after administration of the composition via a mucosa of the subject.

4. A pharmaceutical composition according to any of the preceding claims, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

5. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 20 min or 15 min of the dissolution test defined in claim 1.

6. A pharmaceutical composition according to any of the preceding claims, wherein at least about 60% of the one or more glucocorticoids are released from the composition within the first 10 min or 5 min of the dissolution test defined in claim 1.

7. A pharmaceutical composition according to any of the preceding claims, wherein at least about 70% of the one or more glucocorticoids are released from the composition within the first 15 min such as, e.g., within the first 10 min or 5 min of the dissolution test defined in claim 1.

8. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 15 min of the dissolution test defined in claim 1.

9. A pharmaceutical composition according to any of the preceding claims, wherein at least about 80% of the one or more glucocorticoids are released from the composition within the first 10 min of the dissolution test defined in claim 1.

10. A pharmaceutical composition according to any of the preceding claims, wherein at least about 90% of the one or more glucocorticoids are released from the composition within the first 15 min or within the first 10 min of the dissolution test defined in claim 1.

11. A pharmaceutical composition according to any of the preceding claims for administration to the systemic circulation via a mucosa.

12. A pharmaceutical composition according to claim 11, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum, and the vagina.

13. A pharmaceutical composition according to claim 12, wherein the mucosa is the mucosa in the oral cavity.

14. A pharmaceutical composition according to any of the preceding claims designed for administration to the oral cavity.

15. A pharmaceutical composition according to any of the preceding claims in liquid, semi-solid or solid form.

16. A pharmaceutical composition according to any of the preceding claims in the form of a solid dosage form.

17. A pharmaceutical composition according to claim 35, wherein the solid dosage form is selected from the group consisting of granules, beads, pellets and powders.

18. A pharmaceutical composition according to any of the preceding claims in unit dosage form.

19. A pharmaceutical composition according to claim 18, wherein the unit dosage form is in the form of a tablet including a chewable tablet, a suckable tablet, an effervescent tablet, a sublingual tablet, a rapid-burst tablet, an immediate release tablet, a rapidly dissolvable tablet or the like.

20. A pharmaceutical composition according to any of claims 142-15 in the form of a spray, a wafer, a film, a gel, a hydrogel, a patch, a gingival patch, a bioadhesive patch, a sachet, a pulmonary, bronchial or respiratory inhaler including a powder inhaler, a suppository, a vagitory, a clysma, a solution or the like.

21. A pharmaceutical composition according to any of the preceding claims, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

22. A pharmaceutical composition according to claim 21, wherein the total amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 100, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1 to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

23. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

24. A pharmaceutical composition according to claim 23, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

25. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1-200.

26. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 20 mg.

27. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 1 to about 10 mg.

28. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.1 to about 2 mg.

29. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 0.05 to about 5 mg.

30. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 10 to about 50 mg.

31. A pharmaceutical composition according to claim 23 in unit dosage form, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof in an amount corresponding to from about 2 to about 20 mg.

32. A pharmaceutical composition according to any of the preceding claims in the form of a film, patch, wafer, gel, sachet, gingival patch, lozenge or the like.

33. A pharmaceutical composition according to claim 32, wherein the composition comprises a pharmaceutically acceptable excipient selected from the group consisting

of an acrylic polymer including a derivative thereof, a cellulose derivative, modified starch, polyethylene oxide, chitosan, gelatin, sodium alginate, pectin, scleroglucan, xanthan gum, guar gum, or poly-co-(methyl vinyl ether-maleic anhydride), alone or in combinations thereof.

34. A pharmaceutical composition according to claim 33, wherein the cellulose derivative is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, sodium carboxymethyl cellulose, methyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, microcrystalline cellulose, modified cellulose gum, or crosscaramellose.

35. A pharmaceutical composition according to any of the preceding claims further comprising one or more bio/mucoadhesion promoting agents.

36. A pharmaceutical composition according to claim 35, wherein the one or more bio/mucoadhesion promoting agents are present in concentration of from about 0.1 to about 25% w/w.

37. A pharmaceutical composition according to claim 35 or 36, wherein the one or more bio/mucoadhesion promoting agents are a polymer including a synthetic polymer, a natural polymer and a derivative thereof, and mixtures thereof.

38. A pharmaceutical composition according to claim 37, wherein the polymer is selected from a carbomer, a polyethylene oxide, a poly co-(methylvinyl ether/maleic anhydride, and mixtures thereof.

39. A pharmaceutical composition according to claim 37, wherein the polymer is a polysaccharide.

40. A pharmaceutical composition according to claim 40, wherein the polysaccharide is selected from the group consisting of gelatin, sodium alginate, pectin, scleroglucan, xanthan gum; guar gum, microcrystalline cellulose, crosscaramellose, hydroxypropyl cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, ethyl hydroxyethyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, moderately cross-linked starch, and chitosan.

41. A pharmaceutical composition according to any of the preceding claims further comprising a dissolution promoting agent.

42. A pharmaceutical composition according to claim 41, wherein the dissolution promoting agent is present in a concentration of from about 0.05 to about 5% w/w.

43. A pharmaceutical composition according to claim 41 or 42, wherein the dissolution promoting agent is selected from the group consisting of sodium lauryl sulphate, a polysorbate, a bile acid, a bile salt, a salt of cholic acid or cholanic acid, isopropyl myristate, methyl laurate, oleic acid, oleyl alcohol, glycerol monoleate, glycerol dioleate, glycerol trioleate, glycerol monostearate, glycerol monolaurate, propylene glycol monolaurate, sodium dodecyl sulfate, and a sorbitan ester.

44. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are present as microparticles or nanoparticles.

45. A pharmaceutical composition according to claim 44, wherein the mean particle size is 10 μm or less.

46. A pharmaceutical composition according to claim 44 or 45, wherein the micro- or nanoparticles are encapsulated.

47. A pharmaceutical composition according to claim 46, wherein the micro- or nanoparticles are encapsulated with a coating comprising a lechitin or a lechitin based compound.

48. A pharmaceutical composition according to any of the preceding claims further comprising a disintegrating agent.

49. A pharmaceutical composition according to claim 48, wherein the disintegrating agent is selected from the group consisting of cross-linked polyvinylpyrrolidone, carboxymethyl starch, natural starch, microcrystalline cellulose, and cellulose gum.

50. A pharmaceutical composition according to claim 48 or 49, wherein the disintegrating agent is present in a concentration of from about 0.5 to about 10% w/w.

51. A pharmaceutical composition according to any of the preceding claims further comprising a taste-masking agent.

52. A pharmaceutical composition according to claim 51, wherein the taste-masking agent is selected from the group consisting of menthol, peppermint, vanillin, a terpene based compound, or an artificial sweetener.

53. A pharmaceutical composition according to any of the preceding claims, wherein the one or more glucocorticoids are taste masked by incorporation into an inclusion complex by means of alpha-, beta-, or gamma-cyclodextrins, preferably by beta-cyclodextrins.

54. A pharmaceutical composition according to any of the preceding claims for buccal administration.

55. A pharmaceutical composition according to claim 54 in the form of a gel, a gum, a wafer, a thin-layer film, a patch, a gingival patch, a tablet, a sachet, a lozenge, a fast-dissolving tablet, a cream or an ointment.

56. A kit for treating a subject suffering from a disorder requiring acute glucocorticoid therapy comprising one or more containers for housing a pharmaceutical composition according to any of claims 1-55, and instructions for use thereof.

57. A kit according to claim 56, wherein the one or more containers are in the form of blisters or blister packs.

58. A method for treating a subject suffering from a disorder requiring acute glucocorticoid therapy, the method comprises administering via a mucosa of the subject an effective amount of one or more glucocorticoids to obtain a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration.

59. A method according to claim 58, wherein at least 40% of C_{max} is reached within 30 min after administration.

60. A method according to claim 58 or 59, wherein at least 75% of C_{max} is reached within 45 min after administration.

61. A method according to any of claims 58-60, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

62. A method according to any of claims 58-61, wherein the disorder requiring acute glucocorticoid therapy is an acute adrenal crisis.

63. A method according to claim 62, wherein the acute adrenal crisis relates to a primary, secondary or tertiary adrenal insufficiency, an anaphylactic reaction, an Addison crisis, a status asthmaticus, a blood transfusion reaction, a brain edema, a severe allergic reaction, acute asthma, acute anaphylaxia, septic shock, acute bacterial meningitis, acute RSV (respiratory syncytial virus) infection with bronchiolitis in children, acute croup-children, mononucleosis with complications (airway obstruction, thrombocytopenia or haemolytical anaemia), or tonsillitis/peritonsillitis e.g. in children with airway obstruction.

64. A method according to any of claims 58-62, wherein the disorder requiring acute glucocorticoid therapy relates to an inflammatory disorder, an autoimmune disorder, or a medical disorder in which a glucocorticoid forms a part of the first line emergency medical treatment or intense short-time medical treatment.

65. A method according to any of claims 58-64, wherein the mucosa is selected from the mucosa in the oral cavity, the nasal cavity, the lung, the bronchia, the rectum and the vagina.

66. A method according to any of claims 58-65, wherein the mucosa is the mucosa in the oral cavity.

67. A method according to any of claims 58-66, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 200 mg.

68. A method according to claim 67, wherein the effective amount of the one or more glucocorticoids expressed as hydrocortisone is from about 1 to about 175 mg such as, e.g., from about 1 to about 150 mg, from about 1 to about 125 mg, from about 1 to about 100 mg, from about 1 to about 75 mg, from about 1 to about 70 mg, from about 1

to about 60 mg, from about 5 to about 50 mg, from about 5 to about 40 mg or from about 10 to about 30 mg.

69. A method according to any of claims 58-68, wherein the one or more glucocorticoids is selected from the group consisting of hydrocortisone, cortisone, prednisolone, prednisone, methylprednisone, triamcinolone, paramethasone, betamethasone, dexamethasone and fludrocortisone or mixtures thereof, including pharmaceutically acceptable esters, salts and complexes thereof.

70. A method according to claim 69, wherein the pharmaceutically acceptable salt is a phosphate, a succinate, a lysinate, an acetate, a cypionate, a valerate, a hemisuccinate, a butyrate or a trometamole salt.

71. A method according to any of claims 58-70, wherein the effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

72. A method according to claim 71, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

73. A method according to claim 71 or 72, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

74. A method according to any of claims 58-73, wherein the one or more glucocorticoids are cortisone or hydrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 100 mg.

75. A method according to any of claims 58-73 wherein the one or more glucocorticoids are betamethasone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 1 to about 20 mg.

76. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisolone including pharmaceutically acceptable esters, salts

and complexes thereof and wherein the effective amount is in a range of from about 1 to about 10 mg.

77. A method according to any of claims 58-73, wherein the one or more glucocorticoids are dexamethsone including pharmaceutically acceptable esters, salts and complexes and wherein the effective amount is in a range of from about 0.1 to about 2 mg.

78. A method according to any of claims 58-73, wherein the one or more glucocorticoids are fludrocortisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 0.05 to about 5 mg.

79. A method according to any of claims 58-73, wherein the one or more glucocorticoids are prednisone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 10 to about 50 mg.

80. A method according to any of claims 58-73, wherein the one or more glucocorticoids are methylprednisolone including pharmaceutically acceptable esters, salts and complexes thereof and wherein the effective amount is in a range of from about 2 to about 20 mg.

81. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical composition as defined in any of claims 1-55.

82. A method according to any of claims 58-80, wherein the effective amount is administered in the form of a pharmaceutical kit as defined in claims 56 or 57.

83. Use of an amount of one or more glucocorticoids for the preparation of a pharmaceutical composition or kit as defined in any of claims 1-58 for the treatment of a disorder requiring acute glucocorticoid therapy by providing a fast rise in the glucocorticoid serum level to at least 20% of C_{max} within 20 min after administration via a mucosa.

84. Use according to claim 83, wherein at least 40% of C_{max} is reached within 30 min after administration.

85. Use according to claim 83 or 84, wherein at least 75% of C_{max} is reached within 45 min after administration.

86. Use according to any of claims 83-85, wherein T_{max} is reached within 60 min after administration of the composition via a mucosa of the subject.

87. Use according to any of claims 83-86, wherein an effective amount of the one or more glucocorticoid is contained in a pharmaceutical composition suitable for administration by the subject itself or by non-medically trained persons.

88. Use according to any of claims 83-87, wherein the composition is in a form that can be administered to the subject even if he is unconscious.

89. Use according to claim 87 or 88, wherein the composition is in a form that can be administered to the subject and have effect even if he is unable to swallow the composition.

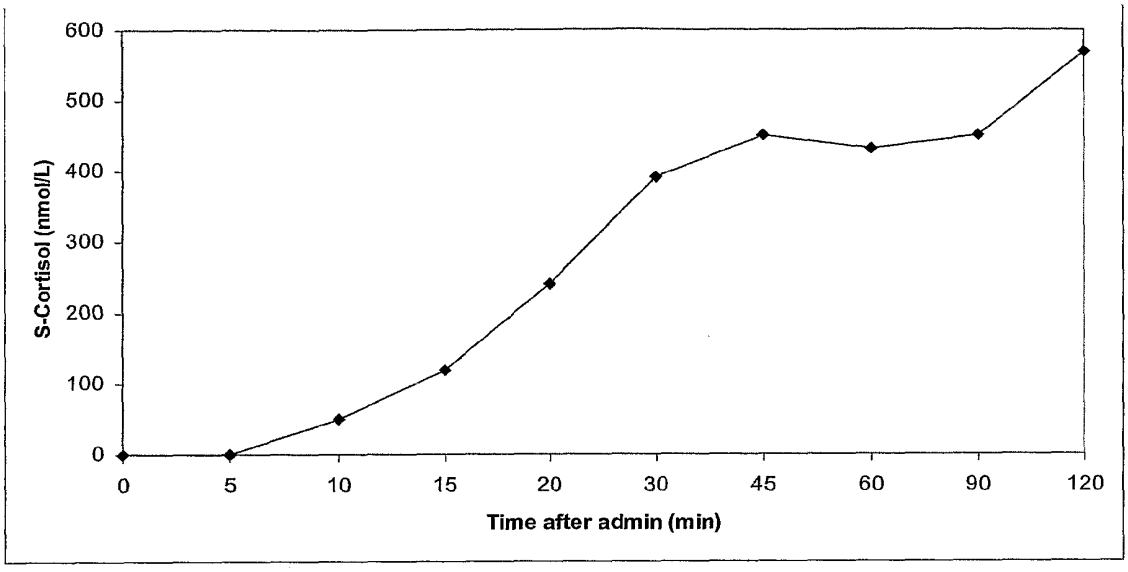

600
500
400
300
200
100
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
Time after admin (min)

Fig. 1

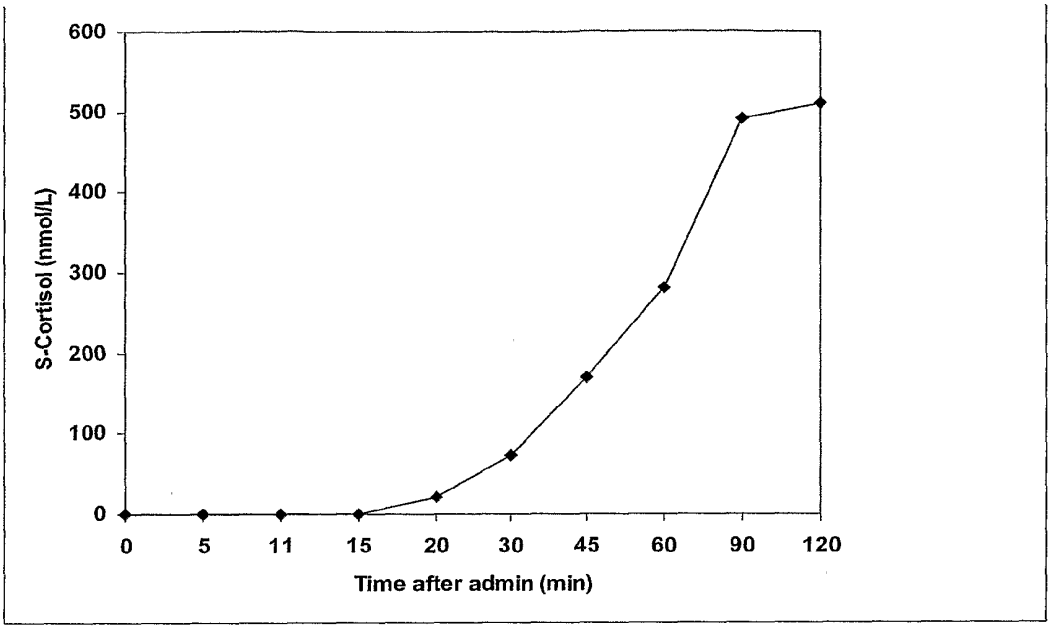

600
500
400
300
200
100
0
S-Cortisol (nmol/L)
0
5
11
15
20
30
45
60
90
120
Time after admin (min)

Fig. 2

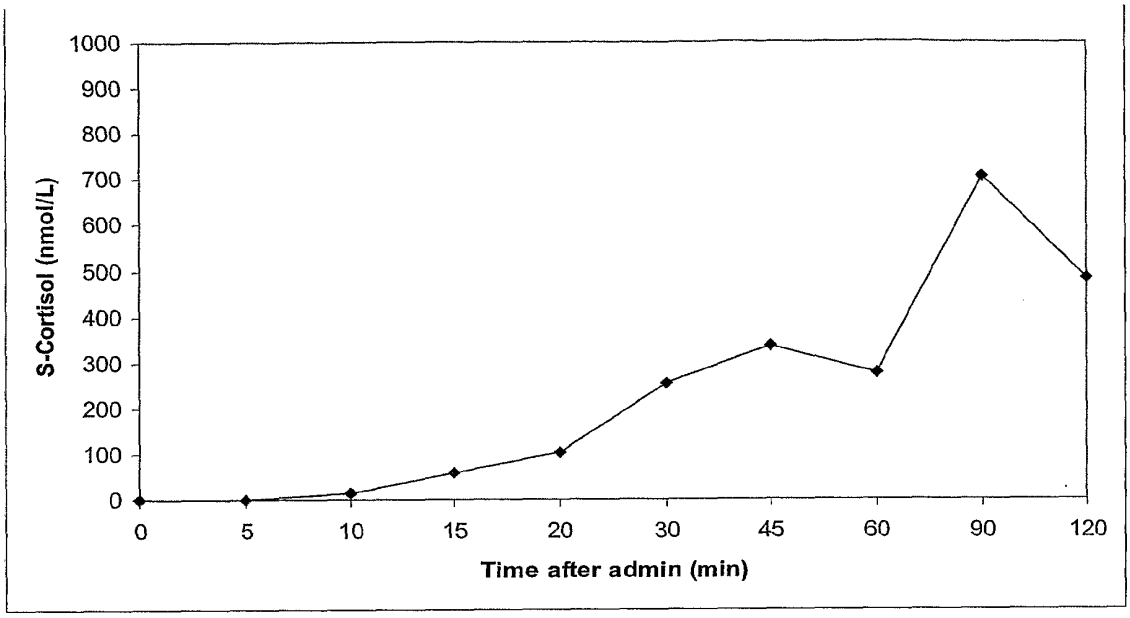
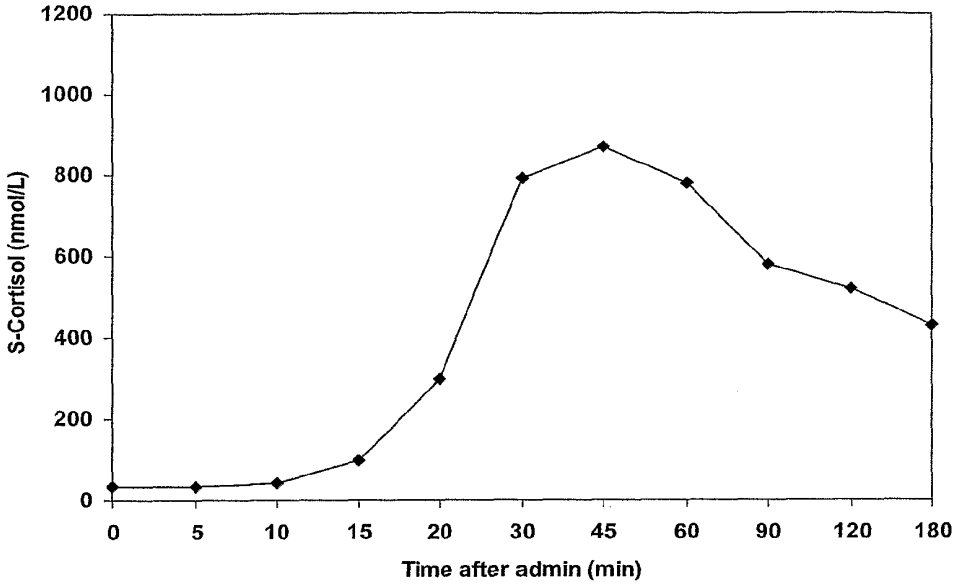

S-Cortisol (nmol/L)
1000
900
800
700
600
500
400
300
200
100
0
0
5
10
15
20
30
45
60
90
120
Time after admin (min)

Fig. 3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1000
800
600
400
200
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 4

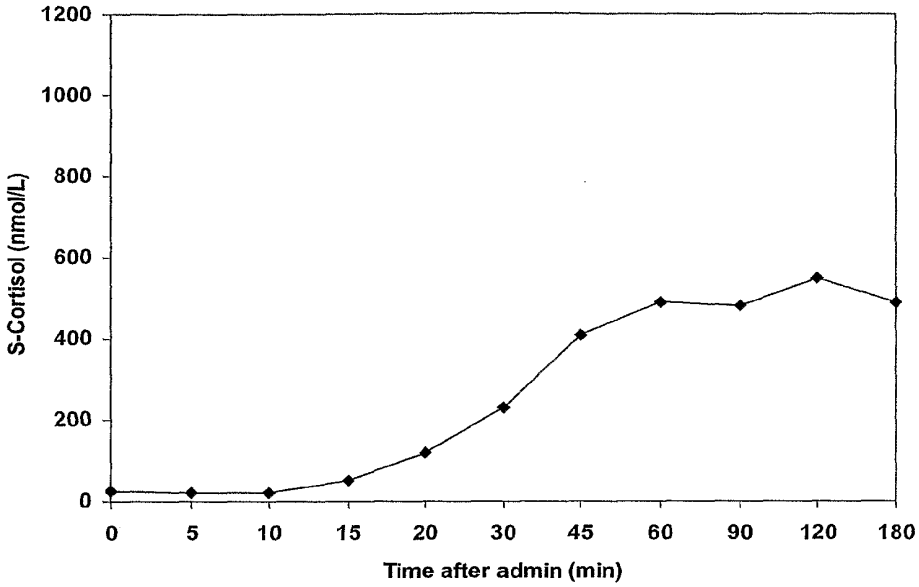
1200
1000
800
600
400
200
0
S-Cortisol (nmol/L)
0
5
10
15
20
30
45
60
90
120
180
Time after admin (min)

Fig. 5

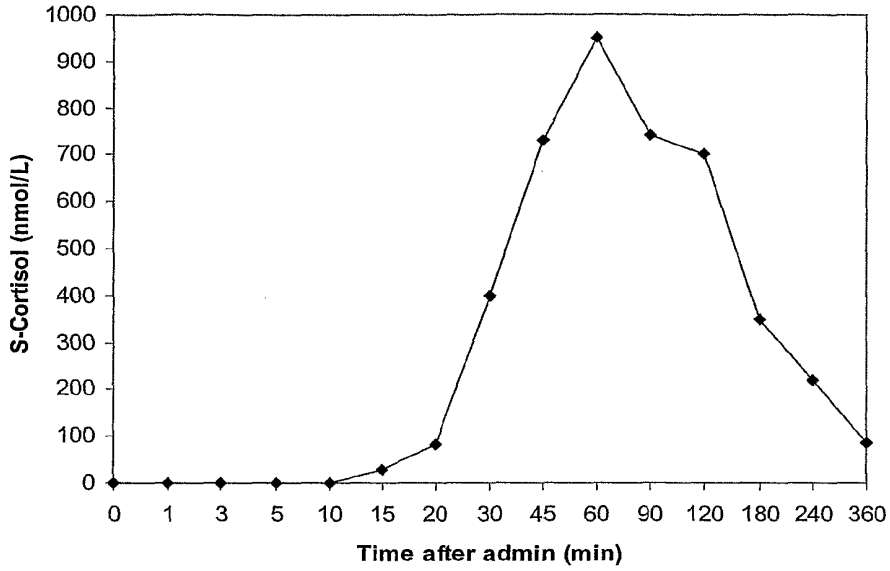
S-Cortisol (nmol/L)
1000
900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 6

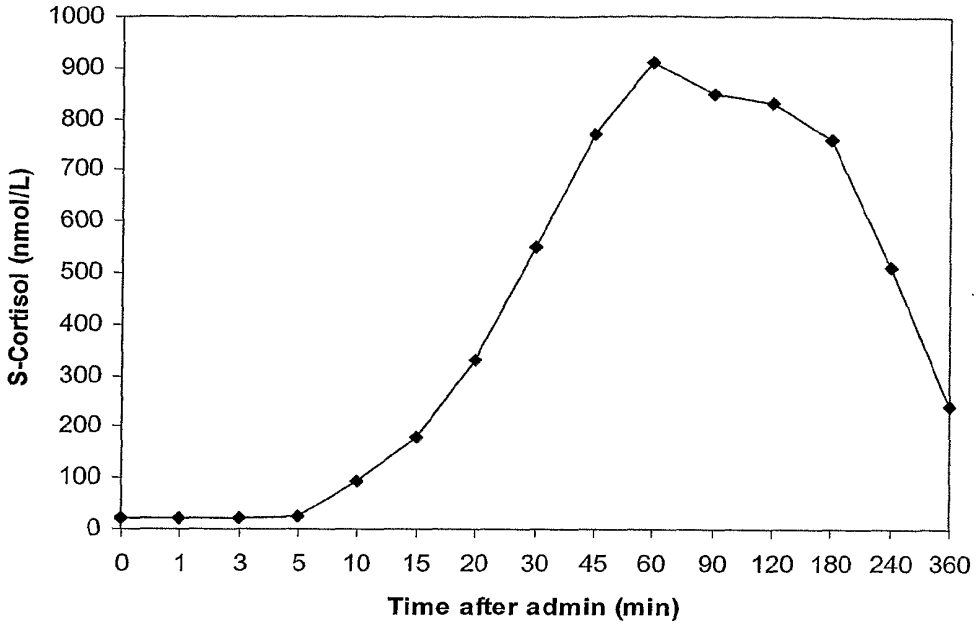
1000
900
800
700
600
500
400
300
200
100
0
S-Cortisol (nmol/L)
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 7

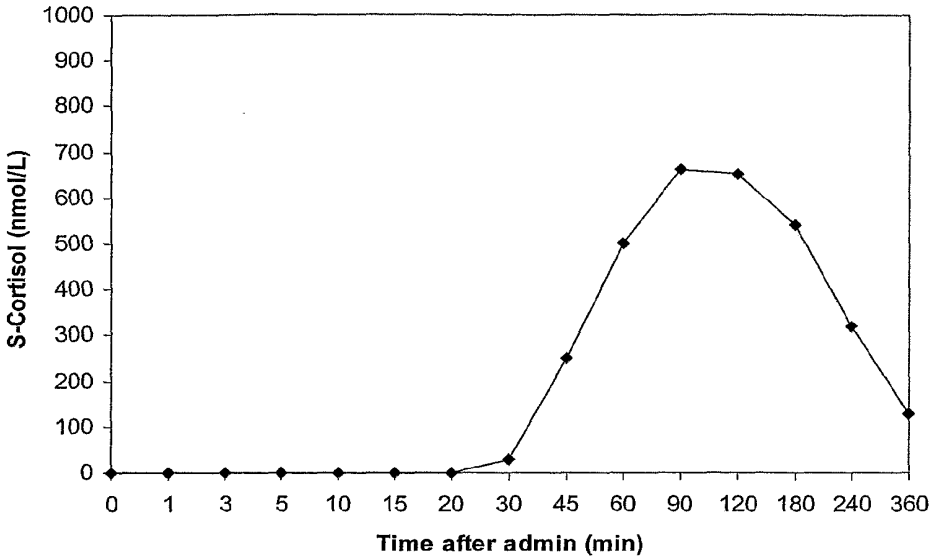
S-Cortisol (nmol/L)
1000
900
800
700
600
500
400
300
200
100
0
0 1 3 5 10 15 20 30 45 60 90 120 180 240 360
Time after admin (min)

Fig. 8

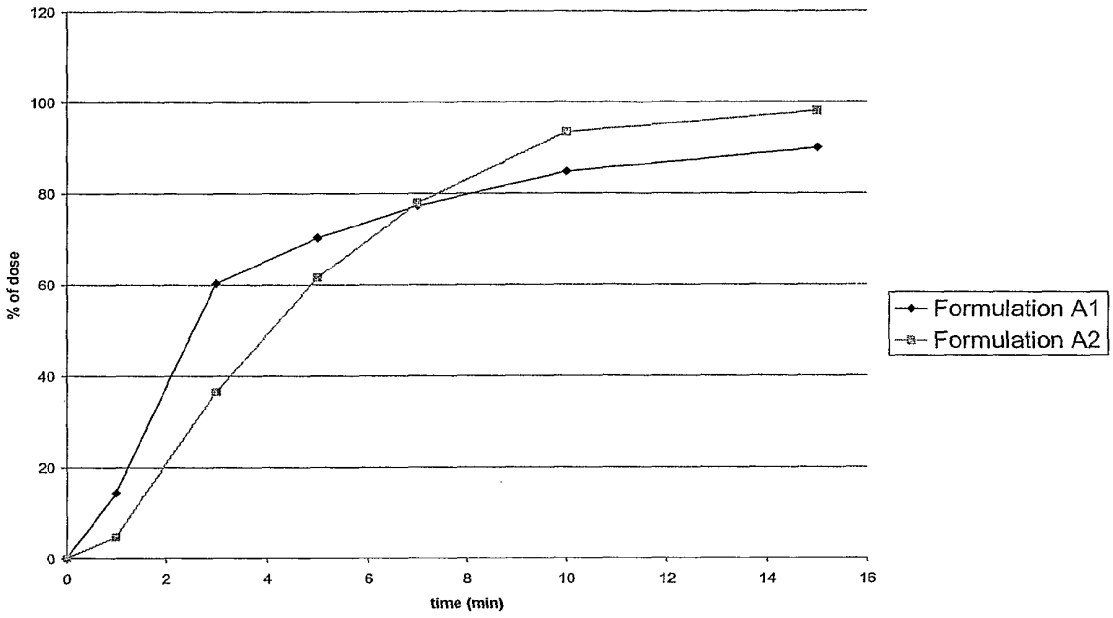
120
100
80
60
40
20
0
% of dose
0
2
4
6
8
10
12
14
16
time (min)
Formulation A1
Formulation A2

Fig. 9

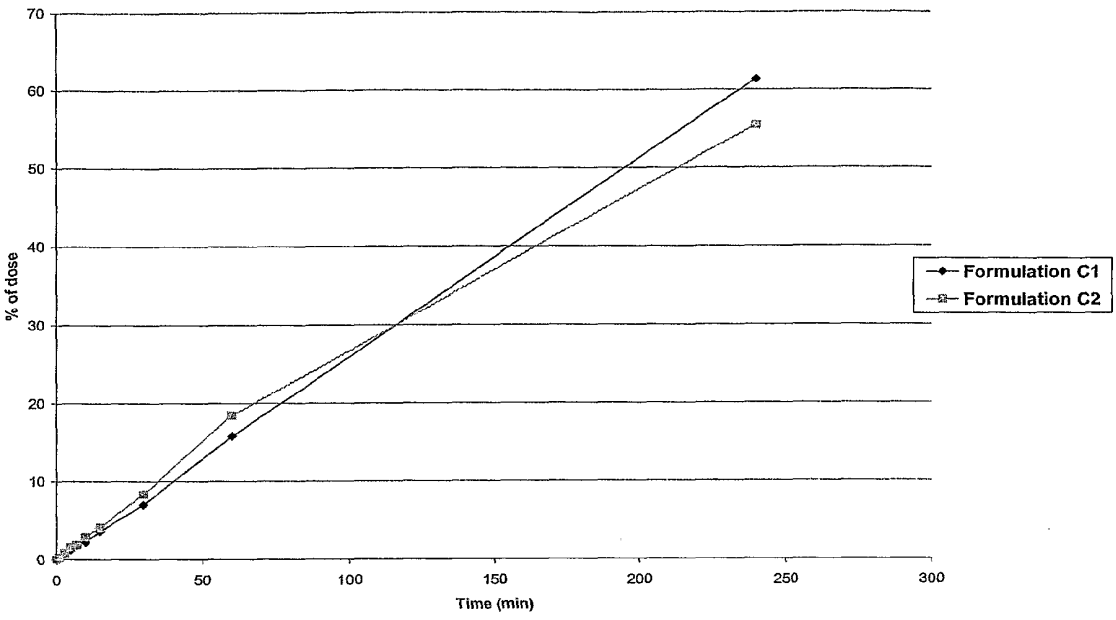
70
60
50
40
30
20
10
0
% of dose
0
50
100
150
200
250
300
Time (min)
Formulation C1
Formulation C2

Fig. 10

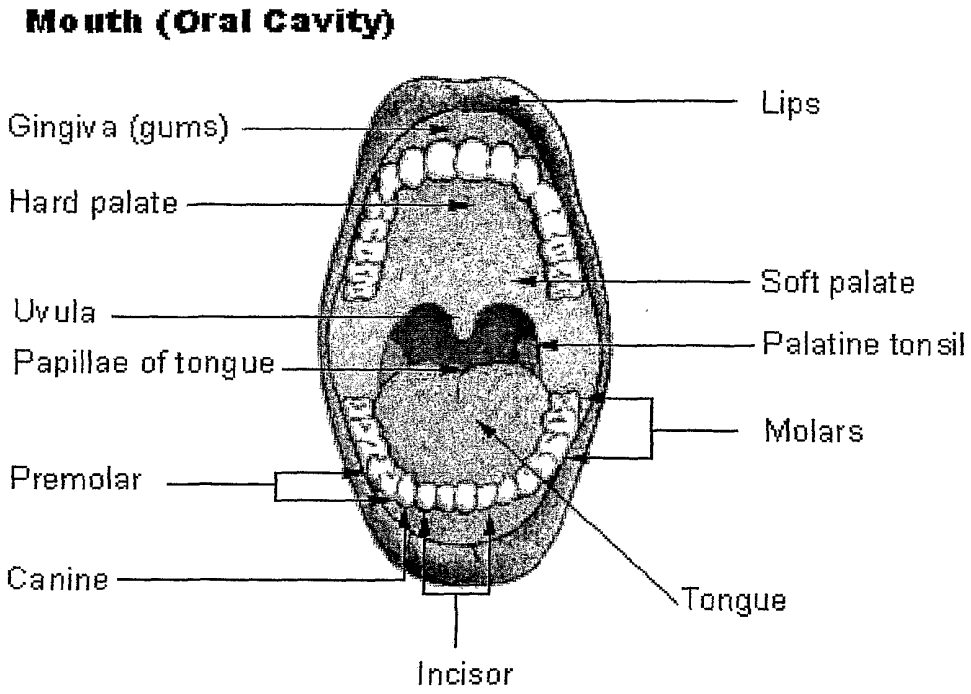
Mouth (Oral Cavity)
Lips
Gingiva (gums)
Hard palate
Soft palate
Uvula
Palatine tonsil
Papillae of tongue
Molars
Premolar
Canine
Tongue
Incisor

Fig. 11

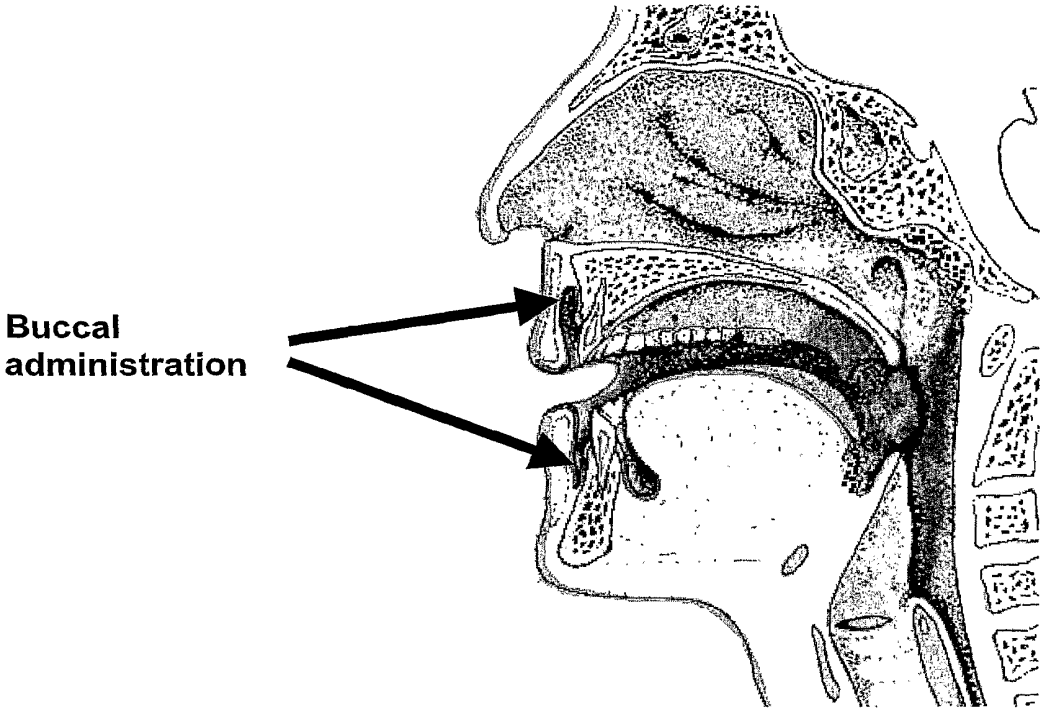

Fig. 12

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(54) **Extrudable compositions for topical or transdermal drug delivery.**

(57) An effective and convenient medicament delivery system comprising novel extrudable compositions. The preferred compositions of the invention contain a thermoplastic water-soluble polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide ; a water-soluble polymer derived from acrylic acid ; medicament ; and plasticizer. The compositions provide an effective medicament delivery system and are especially suitable for use with adhesive bandages.

EP 0 598 606 A1

BACKGROUND OF THE INVENTION

This invention relates to novel extrudable compositions for the topical application of medicaments to human or animal skin and, more particularly, to bandages containing such compositions. Adhesive bandages, wound dressings, and the like containing the novel compositions of the invention provide a superior wound care system.

Creams, ointments, solutions and powders are known to be useful for the topical application of various drugs to skin. However, the application of these materials typically is non-quantitative and it is difficult for the user to control the amount of drug delivered to the area to be treated. When such materials are used in conjunction with adhesive bandages or wound dressings, they frequently detackify (that is, result in a loss of adhesion) the adhesive portion of the bandage, thereby increasing the risk of contamination. In addition, such materials are messy and inconvenient to use, frequently soiling clothing and the like.

Various wound dressings and bandages for the topical application of medicaments are also known. For example, U.S Patent No. 4,616,644, issued October 14, 1986 in the name of Saferstein et al., describes an adhesive bandage wherein a thin coating of a high molecular weight polyethylene oxide is applied to the surface of the wound release cover of the bandage to stop bleeding faster.

U.S. Patent No. 4,880,416, issued November 14, 1989 in the name of Horiuchi et al. describes a dermal bandage comprised of a film-like adhesive material that comprises vinyl acetate polymer and a polycarboxylic acid or anhydride.

In EPO Application 0297828, Charkoudian et al. describes a bandage which is coated or impregnated with a soft, waxy, low melting composition containing a medicament. In example 1 a solution of polyethylene glycol and benzocaine is coated onto a nonwoven fabric of the type used in bandages. In example 2 Charkoudian et al. further describes impregnating a non-woven fabric with a methanol solution of polyvinyl pyrrolidone (PVP), polyethylene glycol and benzocaine, and letting the methanol evaporate. The resulting composition is extremely tacky and dissolves very slowly upon contact with wound exudate. Moreover, since the compositions have melting points below 40 °C, they cannot be subject to conventional ethylene oxide sterilization techniques.

In U.S. Patent No. 4,713,243, issued December 15, 1987, Schiraldi et al. describes a bioadhesive extruded film that is useful in intra-oral drug delivery. The thin film is comprised of a bioadhesive layer consisting essentially of 40-95 % by weight hydroxypropyl cellulose, 5-60 % of a homopolymer of ethylene oxide, 0-10 % of a water insoluble polymer, and 2-10 % of a plasticizer.

From the foregoing discussion, it will be seen that various compositions and devices useful for topically applying medicaments to the skin are known. However, such compositions have not been found to be entirely suitable when used by themselves or in connection with conventional adhesive bandages. For example, many compositions interfere with a bandage's functions to absorb wound exudate and adhere to the skin. Another problem is that upon dissolution many of these materials form a thin, free-flowing fluid having little structural integrity. As a result, the medicament is dispersed too quickly and readily spreads away from the area to be treated. Yet another problem is that many compositions of the prior art are not stable at higher temperatures and humidities. This property is crucial because the compositions may be stored for lengthy periods under less than ideal warehouse conditions. In addition, they must be able to withstand rigorous sterilization procedures.

Accordingly, it is an object of the present invention to provide a method for topically or transdermally delivering a medicament which comprises applying to the skin a novel, extrudable composition which, upon contact with body fluid, releases a controlled amount of medicament to the area to be treated.

It is another object of the invention to provide an extrudable composition for delivering a medicament to the skin which can be used alone or in conjunction with sterilized and/or adhesive bandages.

It is yet another object of the invention to provide a composition which does not readily dissolve to a free-flowing fluid upon contact with body fluids.

It is a further object of the invention to provide an extruded film that is an effective and convenient medicament delivery system.

SUMMARY OF THE INVENTION

The inventors have found that various extrudable compositions comprising:

(a) at least one thermoplastic water-soluble polymer;

(b) at least one water-soluble polymer derived from carboxylic acid;

(c) plasticizer; and

(d) at least one medicament,

can achieve the above objects and advantages.

The inventors have further found that extrudable compositions comprising, about 5-70 % by weight of (a); about 1-10 % of (b); about 10-80 % of (c); and about 0.01-10 % of (d), are particularly advantageous. In one preferred group of compositions, (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide, (b) comprises at least one polymer derived from acrylic acid and (c) comprises at least one plasticizer selected from the group consisting of glycerine, propylene glycol and polyethylene glycol. The medicament comprises at least one, and preferably more, pharmaceutically acceptable therapeutic agents.

The compositions of this invention have the consistency of a non-flowing "ointment", as defined in The United States Pharmacopeia, The National Formulary (USP XXII, NF XVII), U. S. Pharmacopeial Convention, Inc., Rockville, MD, p. 1692 (1990), which is hereby incorporated by reference. After contact with body fluids, the composition dissolves into a matrix and releases the medicament, but it still possess good structural integrity.

The compositions of the invention can be placed directly on the skin as a free, extruded, single or multi-layered thin film. Alternatively, the films may be used in conjunction with a substrate like a bandage, wound dressing or blemish patch. For example, the absorbent pad material of a conventional bandage can be coated or at least partially impregnated with the composition, thereby providing a superior wound care product that rapidly delivers moisture-sensitive active ingredients to the area to be treated. Since the composition is extrudable, it can be formed into free films or coated on a substrate without the use of organic solvents.

In another preferred embodiment of the invention the novel extrudable compositions of the invention comprise:

(a) about 20-30% (by weight) of hydroxypropyl cellulose and about 0-10% of polyethylene oxide;

(b) about 1-10% by weight of a copolymer of acrylic acid and allyl sucrose;

(c) about 60-70% by weight of at least one plasticizer selected from the group consisting of glycerin and polyethylene glycol; and

(d) about 0.01-10% by weight of medicament.

The novel extrudable compositions of the present invention alleviate many of the above problems. For example, when used in connection with an adhesive bandage, they do not interfere with the bandage's absorption and adhesion functions. In addition, they may be stored for at least one week at 40 °C and 80% relative humidity without experiencing a significant weight loss (i.e., more than 10% by weight). Moreover, the compositions and their properties are not impaired by ethylene oxide sterilization at 170 °F, or E-beam or cobalt sterilization techniques. In addition, they are also sufficiently flexible so that they are comfortable to wear.

In another preferred embodiment of the invention, the extrudable compositions are used in conjunction with blemish patches to provide anti-acne medicament thereto.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a graph showing the relationship between viscosity and temperature for a typical composition of the present invention and a comparative composition.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed toward water-soluble films which rapidly dissolve in body fluids such as blood, perspiration, or wound exudate, and deliver active ingredients to a treatment site in a controlled manner.

In accordance with one embodiment of the present invention, the absorbent component of a bandage or wound dressing of known construction is coated or at least partially impregnated with the extrudable composition of the invention. Upon application to the injured area, the exudate from the wound or moisture from the skin dissolves the film, thereby converting it to a matrix having an ointment-like consistency and making the active ingredient available to treat the injury. Because of these ointment-like properties, the film is tacky and adheres to the skin.

As previously mentioned, the bandages or wound dressings which can be used in conjunction with the present invention comprise conventional adhesive or non-adhesive bandages or wound dressings of the medical or surgical type. Generally such bandages include a plastic film backing having attached thereto an absorbent pad portion. The absorbent pad material may be any of the woven or non-woven fabrics of natural or synthetic fibers heretofore employed as dressings, including for example, cotton, nylon or polyester. Suitable substrates further include woven or standard papers, and plastics. Preferred substrates include absorbent pad materials comprised of a rayon and polypropylene (10:90 weight ratio) spun bonded web, a knitted polyester fabric such as that used for DERMICEL taffeta tape manufactured by Johnson &Johnson Consumer Products,

Inc., Skillman, N.J., and a composite nonwoven fabric made of thin, breathable polyester/polyurethane laminate known as FABRELLE which is manufactured by Fabrite Industries, Woodbridge, N.J..

Suitable plastic film backings include highly plasticized polyvinyl chloride, polyurethane, polyolefins, ethylene vinyl acetate and block copolymers films such as HYTREL® copolyester ether elastomers available from E. I. DuPont, Wilmington, Delaware. These plastic films may or may not contain an adhesive, which may or may not be pressure sensitive.

Adhesive bandages further include one or more release tabs. Release tabs (such as silicone-coated release paper or other alternate materials which can be readily removed at the time of use), are applied so as to cover, in an overlaying manner, the entire adhesive side of an adhesive bandage.

In addition, each bandage can be packaged and sealed in an individual wrapper (which typically is made of glassine-paper or a similar bacterial barrier material). Each bandage is packaged before it undergoes ethylene oxide or irradiation sterilization so as to maintain sterility until the bandage is ready for use.

In another preferred embodiment of the invention, the extrudable compositions may be used in conjunction with blemish patches to treat acne. Generally such blemish patches resemble the conventional adhesive bandages described above, i.e., they comprise a plastic film or fabric backing, an absorbent pad, an adhesive, and one or more release tabs, with the extrudable composition laminated to the absorbent pad.

As an alternate configuration, the blemish patch may simply contain a layer of the extrudable composition laminated to the aforementioned absorbent pad material. The extrudable composition serves as the media for holding the anti-acne medicament as well as an adhesive for adhering the patch to the skin site. Preferably, the pad stock will have some flexibility so that it conforms to facial contours. The patch may also contain a plastic film on the side of the pad opposite to the layer of extrudable composition to control moisture vapor transmission through the patch. A thin polyurethane film will allow for high moisture vapor transmission, whereas a thin polyolefin film will result in low moisture vapor transmission through the patch. This configuration may also be used with other medicaments.

The thermoplastic, water-soluble polymers that are useful in this invention are selected from pharmaceutical grade materials, or those that are considered "generally regarded as safe" (GRAS) as food additives. They include, hydroxypropyl cellulose, and polyethylene oxide homopolymers and copolymers. The term "thermoplastic" as used herein indicates that the polymers are adequately rigid at normal temperatures and under normal conditions of stress, but are capable of deformation under heat and pressure. The term "water-soluble" as used herein indicates that the thermoplastic polymers are soluble or swellable in aqueous or aqueous-based solutions. Hydroxypropyl cellulose has an added advantage; namely, it is also soluble in non-aqueous solvents like methanol.

The compositions of the invention comprise about 5-70% of thermoplastic, water-soluble polymer, preferably about 10-40%, more preferably about 10-30%, even more preferably about 20-30% and most preferably about 23-30%.

Preferably, the thermoplastic, water-soluble polymers of the invention consist essentially of hydroxypropyl cellulose and/or polyethylene oxide. Thus, the hydroxypropyl cellulose and polyethylene oxide polymers useful for this invention can be used singly or a mixture. If a mixture of hydroxypropyl cellulose and polyethylene oxide is used, preferably they are used in a ratio of between about 1:9 to about 9:1, by weight, more preferably between about 4:6 to about 4:0, even more preferably at ratio of about 4:1.

The hydroxypropyl cellulose ("HPC") useful for purposes of the present invention is commercially available from Aqualon, Inc. (Wilmington, DE) under the trade name KLUCEL®. Preferred grades include KLUCEL EF, with an average molecular weight of about 60,000 and having a viscosity of about 300-700 cps (Brookfield) in a 10 percent water solution, or KLUCEL LF, with a molecular weight of about 100,000 and having a viscosity of about 75-150 cps in a 5 percent water solution. In general, any HPC having a number average molecular weight above about 60,000 is useful for purposes of this invention.

The homopolymer of ethylene oxide useful for purposes of this invention has a number average molecular weight of between about 100,000 to 3,000,0000 or even higher. Although polyethylene oxide ("PEO") polymers having an average molecular weight of above 600,000 are useful for several embodiments of the invention, PEO having a number average molecular weight of less than about 600,000 is preferred, less than about 400,000 is more preferred, and between about 100,000 and 400,000 is even more preferred. Such polymers are commercially available from the Union Carbide Corporation under the trade name POLYOX. Preferred grades include POLYOX WSR-N-10, which has an average molecular weight of about 100,000 and POLYOX WSR-N8, which has an average molecular weight of about 200,000.

Small amounts of other (non-thermoplastic or thermoplastic) water-soluble polymers may be used as well, replacing a small portion of the water-soluble, thermoplastic polymers. Other polymers which are useful for the present invention include, for example, homopolymers and copolymers of carboxymethyl cellulose, hydroxyethyl cellulose, polyacrylamide, polyacrylic acid and its homologs, polyvinyl alcohol, polyvinyl pyrrolidone,

polyethylene amines, polymethacrylic acid, polyvinylamine, polymethacrylamide, polyvinylmethylether, and the like. Natural gums such as polysaccharides, alginates, carrageenan, guar gum, gum agar, gum arabic, gum ghatti, gum karaya, gum tragacanth, locust bean gum, pectins, starch and its derivatives, tamarind gum, and xanthan are also useful. The gums are used to adjust the hydrophilic/hydrophobic balance of the composition, which in turn affects the solubility of the medicament in the composition.

Small amounts of polymers derived from carboxylic acids (or from pharmaceutically acceptable salts thereof) provide increased flexibility and stability to the extrudable compositions of the invention. The carboxylic acid polymers useful for the invention include any such polymer having a number average molecular weight of above about 450,000. Preferably, the compositions of the invention comprise at least one such polymer in amounts of between about 1-10% (by weight), preferably between about 3-8%, and most preferably between about 5-7%.

Homopolymers and copolymers derived from acrylic acid are preferred. Copolymers comprised mainly of acrylic acid and allylsucrose, such as those commercially available from B.F. Goodrich under the trade name CARBOPOL, are even more preferred. For example, CARBOPOL 934P, having a molecular weight of about 3,000,000 is especially preferred. Other polymers that are useful for the invention include homopolymers and copolymers derived from methyl acrylate, methacrylic acid, methyl methacrylate or hydroxyethyl methacrylate, or their amide derivatives.

Suitable pharmaceutically acceptable salts of the carboxylic acid polymers include alkali metal salts such as sodium or potassium salts and ammonium salts. The degree of neutralization of salts is not limited. The pharmaceutically acceptable salts may have any molecular weight.

Any pharmaceutically acceptable medicament or pharmaceutical agent may be delivered by the drug delivery system of the present invention. Usable medicaments include those which are capable of withstanding the heats and pressures generated in the extrusion process involved in making the films of the present invention.

Preferred medicaments include:

anesthetics and/or analgesics such as benzocaine, lidocaine, dyclonine HCl, phenol, menthol, aspirin, phenacetin, acetaminophen, ibuprofen, potassium nitrate, and the like;

anti-inflammatories such as hydrocortisone acetate, triamcinolone acetonide, glycyrrhizinate, and the like;

antihistamines such as chlorpheniramine maleate, ephedrine HCl, diphenhydramine HCl, and the like;

antibiotics such as tetracycline, doxycycline hyclate, meclocyline, minocycline, bacitracin zinc, polymyxin B sulfate, neomycin sulfate, and the like;

fungistats such as nystatin, miconazole, ketoconazole, and the like;

anti-acne agents like salicylic acid; and

antiseptics such as benzylalkonium chloride; iodine, silver solfidiazine, chlorohexidine and salts thereof, cetylpyridinium chloride, and the like.

Medicaments that are not capable of withstanding the heats and pressure generated in the extrusion process are also of use in the present invention. Such medicaments can be applied to the extruded compositions using techniques that are well-known to those skilled in the art. For example, such medicaments may be dissolved in a solvent and coated onto the extruded compositions or films. As the solvent evaporates, it leaves behind the medicament. Anti-acne medicaments like retinoic acid and benzoyl peroxide can be utilized in the present invention in this manner.

The medicament should be added in a pharmaceutically effective amount, i.e., an amount sufficient to prevent, cure or treat a disease to which the pharmaceutical preparation of this invention is to be applied. The compositions of the invention typically comprise at least one medicament, and preferably more than one, in amounts ranging from between about 0.01 to 10%, by weight.

Plasticizers useful for purposes of the present invention include block copolymers of polyethyleneoxide and polypropyleneoxide such as PLURONIC® F 127 and TETRONIC® 1302; glycols such as propylene glycol and polyethylene glycol; polyhydric alcohols such as glycerin and sorbitol; glycerol esters such as glycerol triacetate; fatty acid triglycerides such as NEOBEE® M-5 and MYVEROL®; mineral oils; vegetable oils such as castor oil, and the like. These plasticizers may be used singly or in any combination.

The purpose of the plasticizer is several fold; namely, to improve polymer melt processing by reducing polymer viscosity, to increase adhesion to the skin, to increase the dissolution rate in body fluids, and/or to impart flexibility to the final product. In addition, the plasticizer can impart "ointment-like" characteristics to the final product as defined by U.S.P. "Hydrophilic Ointments or Gels."

Compositions of the invention comprise between about 10-80% (by weight) of plasticizer, preferably between about 30-80%, more preferably between about 30-70%, and most preferably between about 60-70%.

Preferred plasticizers include propylene glycol or polyethylene glycol (PEG) polymers having a number

average molecular weight of from about 200 to 20,000. Although PEG polymers having higher average molecular weights are useful in the present invention, such polymers having an average molecular weight between 200 to 3500 are preferred. More preferred are PEG polymers having an average molecular weight of between 200 and 1500, such as CARBOWAX 600 (available from Union Carbide Corporation), which has an average molecular weight of about 600. Glycerin (especially Grade 916 USP, available from Emory), is also preferred plasticizer.

In one preferred embodiment of the invention, the extrudable compositions comprise, and preferably consist essentially of:

a. thermoplastic water-soluble polymer;

b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof;

c. plasticizer; and

d. medicament.

The inventors have found that the advantages attained by the novel compositions are due to the unique formulations described herein.

Preferably the compositions of this embodiment comprise about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight. More preferably, they comprise about 10-40% of (a), about 1-10 % of (b), about 30-80% of (c), and about 0.01-10% of (d). Even more preferably, they comprise about 20-30% of (a), about 3-8% of (b), about 30-70% of (c), and about 0.01-10% of (d). Most preferably, the compositions comprise about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d).

In accordance with the teachings above and in another preferred embodiment, the extrudable compositions of the invention comprise about 10-30% of (a), about 1-10% (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

In yet another embodiment, the compositions of the invention comprise about 20-30% hydroxypropyl cellulose and about 0-10% polyethylene oxide, about 1-10% of a copolymer derived from acrylic acid and allyl sucrose, about 0.01-10% of said medicament, and about 60-70% of glycerin; by weight. Even more preferably, they comprise about 22-29% hydroxypropyl cellulose and about 4-7% polyethylene oxide, about 5-7% of said copolymer, about 0.01-10% of said medicament, and about 60-70% glycerin; by weight.

In yet another embodiment which has been found to be particularly suitable for blemish patches, the extrudable compositions of the invention comprise about 22-27% hydroxypropyl cellulose, about 5-7% of said acrylic acidallyl sucrose copolymer, about 0.01-10% medicament, and about 60-70% glycerin; by weight. Alternatively, such a composition may comprise about 10-15% hydroxypropyl cellulose and 15-20% polyethylene oxide, about 5-7% of said acrylic acid-allyl sucrose copolymer, about 0.01-10% medicament, and about 30-40% of glycerin and 30-40% polyethylene glycol; by weight.

The inventors have further found that for certain applications that are especially suitable for use with adhesive bandages, the carboxylic acid polymer may be left out of the extrudable composition altogether. In practicing this embodiment of the invention the extrudable composition comprises polyethylene oxide, plasticizer and medicament.

Preferably, the extrudable compositions of this embodiment comprise about 15-80% of polyethylene oxide and about 20-85% of plasticizer, by weight. More preferably they comprise about 25-70% of polyethylene oxide and about 30-75% of plasticizer, by weight. Even more preferably they comprise about 35-60% of polyethylene oxide and about 40-65% of plasticizer, by weight. Of course, about 0-10% (preferably 0.01-10%), by weight, of a medicament can replace the equivalent amount of any of the above ingredients. The preferred plasticizer for use in this composition is polyethylene glycol.

The extrudable compositions of the invention may be prepared by mixing the above ingredients in a variety of ways well-known to those skilled in the art. For example, the preweighed ingredients can be added to an intensive mixer such as a Brabender Prep Center or a Baker Perkins Blender and mixed at 80-95 °C, with or without solvent. Thus, the compositions can be prepared as hot melts. Alternatively, aqueous solvents or alcohols (like methanol) can be used.

The resultant blend can be cast at elevated temperatures, at say, about 50 to 140°C. Alternatively, the blend can be extruded using a single or twin extruder, or pelletized. If extruded, film thicknesses may vary from "thin" films of about 1.0 mil to "thick" films of about 20 mils or greater, the thickness depending on the intended use of the product. The film can also be extrusion coated onto a variety of substrates as discussed above and then subjected to heat and pressure to form a laminate. Temperatures on the order of 21°-130°C and contact pressures of up to 40 pounds per linear inch are suitable for forming the laminate. Additional films or insoluble ingredients, such as a water-insoluble medicaments, may be coated or laminated onto the resultant product.

When used in connection with an absorbent pad, the compositions of the invention may be at least partially impregnated into the absorbent pad using any technique well-known to those skilled in the art. Alternatively,

the film or composition can be applied adjacent to the body facing surface of the absorbent pad by the use of elevated temperatures and pressures. In the latter embodiment, the film or composition is distinct or discernable from the underlying absorbent pad.

Moisture sensitive or water-insoluble active ingredients also can be blended into the compositions of the invention without degradation or separation from the solid components, since the remaining components of the extrudable composition are frequently soluble in aqueous and non-aqueous solvents and are also useable as hot melts.

In addition to the polymers and plasticizers, minor amounts of other non-essential but customary ingredients will often be used if desired, e.g., antioxidants, foamers, neutralizing agents, stabilizing agents, fillers, preservatives, flavors, and colorants. For example, the extrudable composition can be modified to impart more or less tack contain a color, or to produce a scent to heighten the sensory cue to the user that the product is working. Another modification includes adding fumed silica to improve absorption and stability of the compositions. The fumed silica is generally added in an amount ranging from about 0.01 to about 5% by weight of the total composition. As another example, sodium bicarbonate and/or citric acid can be added to the compositions to enable them to foam upon contact with moisture. The pH of the extrudable composition is also generally controlled within the range of about 3 to 8.

This invention will now be illustrated in greater detail by reference to the following examples, but it should be understood that they are not intended to limit the present invention. In these examples, all the parts, percents and ratios are by weight unless otherwise indicated.

EXAMPLE 1

An ointment film was formed by adding 100 gms of polyethylene oxide (POLYOX N-10) to 200 gms of polyethylene glycol (CARBOWAX 600) in a Brabender heated at 80 °C. The components were blended for five minutes to fully plasticize the polyethylene oxide. Then, 26 gms of copolymer of acrylic acid and allyl sucrose (CARBOPOL 934P), was slowly added to the blend and mixed for an additional 30 minutes. The resultant ointment was extrusion coated onto unitized pad stock to form a flexible, aesthetically pleasing film.

EXAMPLE 2

Various antibiotics and antiseptics were added to the composition of Example 1 at the concentrations shown below. The resulting compositions were then coated onto pad stock to form a film layer.

Sample	Antibiotic/Antiseptic	Concentration
A	Bacitracin Zinc[1]	500 units/gm
	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/gm
B	Neomycin Sulfate[2]	3.5 mg/mg
	Polymyxin B Sulfate[3]	10,000 units/gm
C	Benzalkonium Chloride	0.13 (% w/w)

[1]Activity = 71000 U/gm
[2]Activity = 0.7 gm/gm
[3]Activity = 7700 U/gm

Samples A, B and C were not sterilized.
Additional samples were prepared as follows:
Sample D = Sample A ethylene oxide sterilized at 165°F (with moisture).

Sample E = The film sample of Example 1 without antibiotics/antiseptics or sterilization.

Sample F = NEOSPORIN Maximum Strength Ointment (Burroughs-Welcome Co.) coated onto filter paper.

Sample G = Untreated filter paper.

Sample A-G were then tested to determine their antimicrobial activity using the zone of inhibition method. Agar base layers were poured into petri dishes and allowed to solidify. The base layers were then covered with a seeded (inoculated) agar layer. The seeded agar layer contained three test microorganisms Staphylococcus epidermidis, Micrococcus luteus and Bordetella bronchiseptica (evaluated separately) as recommended in the USP Pharmacopeia XXII for testing neomycin, bacitracin and polymyxin, respectively.

Pieces of each of the Samples (8 sq. mm) were placed active side down on each seeded agar plate (6 squares were evaluated per test organism). The samples were incubated at 35°C for 18 hours. The clear zones of inhibition were measured and are reported below as the average of the six zones:

Clear Zone in Millimeters			
Sample	M. luteus	S. epidermidis	B. bronchiseptica
A	11.7	11.0	11.7
B	0.0	11.2	11.7
C	17.2	16.0	4.0
D	5.8	10.5	10.7
E	0.0	0.0	0.0
F	10.5	14.2	7.5
G	0.0	0.0	0.0

The above results demonstrate that the compositions of the present invention (Samples A-D) exhibit good antimicrobial activity.

EXAMPLE 3

Approximately 0.5% (by weight) of fumed silica (CABOSIL M-5) was added to the composition of Example 1. The fumed silica is added to moisture-sensitive active-containing films to absorb moisture and improve the stability of the films.

EXAMPLE 4

Approximately 100 gms of sodium bicarbonate and 50 gms of citric acid were added to the ointment blend of Example 1 (after the addition of the copolymer of acrylic acid and ally sucrose) and the blend was mixed for an additional 10 minutes. The resulting film foamed effervescently upon contact with water.

EXAMPLE 5

Blemish Patch

Two extrudable compositions were prepared. Both vehicles were anhydrous, hydrophilic blends made from the following raw materials:

	Low Tack Vehicle	High Tack Vehicle
Acrylic Acid - Ally Sucrose Copolymer (CARBOPOL 934P)	5.6%	6.2%
Polyethylene Glycol (CARBOWAX 600)	32.3%	0
GLYCERIN (USP 99.5%)	32.3%	67.0%
Hydroxypropyl Cellulose (KLUCEL EF)	11.1%	24.8%
Polyethylene Oxide (POLYOX N-10)	16.7%	0
Salicyclic Acid	2.0%	2.0%

Mixing was performed in a Baker-Perkins Blender at a screw speed of 30 RPM, blade speed of 36 RPM, at 80 °C for about 30 minutes. The polyethylene glycol and/or glycerin were premixed and then added to the mixing bowl of the blender. The hydroxypropyl cellulose, acrylic acid-allyl sucrose, copolymer and polyethylene oxide (low tack only) were also premixed in a "V" blender for about three and a half minutes. After approximately two-three minutes, the premixed powders were added at once to the mixing bowl. The viscosity of the blend quickly increased and began generating sheer force. The blend was masticated for about twenty-five minutes and then salicylic acid was added.

Pelletizing the Ointment

After mixing for about thirty minutes (total mixing time), the blend was extruded as a rod directly into the pelletizer. (Prior to reaching the pelletizer, a cooling stage may be added to ensure a solidified ointment.) The pellets had a diameter of approximately 1/4" or less.

Extruding the Ointment

A Killian extruder was used for extrusion. Initial settings were as follows:

ZONE 1	ZONE 2	ZONE 3	ZONE 4	DIE
150 °F	160 °F	175 °F	180 °F	200 °F

SCREW SPEED	LINE SPEED
50 RPM	21 FT/MIN

The extruded film was laminated to two substrates; clear unitized pad stock used in BAND-AID® brand adhesive bandages and flexible fabric. (The roll may require a silicone release sheet as a carrier paper.) No finishing was required.

EXAMPLE 6

Rheological Data

Figure 1 is a graph showing the relationship between viscosity and temperature of a composition of the present invention (Composition A) and a composition from EP Application No. 0297828 to Charkondian et al. (Composition B). The viscosity is reported in poises.

Composition A was prepared and then extruded into a film. Composition B was prepared in accordance with Example 2 of EP Application No. 0297828, except that benzocaine was omitted, and the viscosity was measured after the methanol solvent was removed.

Composition A (weight %)

Acrylic Acid-Allyl Sucrose Copolymer - 6.42%
(CARBOPOL 934P)
Hydroxypropyl Cellulose - 25.7%
(KLUCEL EF NF)
Glycerine - 65.78%
Potassium Hydroxide (dry) - 2.0%
Fumed Silica (CABOSIL M-5) - 0.1%
Dye - trace amount

Composition B

Polyvinylpyrrolidone - 40 gms.
Polyethylene Glycol 400 - 60 gms.
Methanol - 125 ml.

The viscosity of Compositions A and B was measured on a Rheometrics RDS-7700 parallel plate rheometer at 10 rad./sec. The resulting data is shown on Figure 1. Since the composition of the present invention is more viscous, it will be more resistant to flow than the composition of EP Appln. No. 0297828. This is an important property of the composition of the present invention, since it is not desirable to have the film and resulting medicament flow from the bandage or the traumatized area of the skin to which it is applied.

EXAMPLE 7

An additional extrudable composition suitable for use in a blemish pad was prepared using procedures similar to those described in Example 5. The composition contained (weight%) :

Glycerine - 53%
Acrylic Acid - Ally Sucrose Copolymer
(CARBOPOL 934P) - 6%
Hydroxypropyl Cellulose
(KLUCEL EF NF) - 26%
Fumed Silica (CARBOSIL M-5) - 1%
Salicylic Acid - 2%
Na-Ca Salt of Polyvinyl Menthyl Ether
Maleic Anhydride (GANTREZ MS-955) - 12%

EXAMPLE 8

A composition was prepared by blending 28% polyethylene oxide (POLYOX N-80) (having an average molecular weight of about 200,000) with 72% polyethylene glycol (CARBOWAX 600), in a Brabender mixer for one hour at 80 °C. The blend was coated onto release paper and laminated at 60 °C onto unitized pad stock. The resultant films had thicknesses of between 1 to 3 ounces/yd^2. The films did not interfere with the conventional absorption of the pad stock, and did not flake or peel.

EXAMPLE 9

Blends of polyethylene glycol (PEG) (number average molecular weight of between 200-1450) and polyethylene oxide (PEO) (number average molecular weight of approximately 100,000) having the proportions shown below were prepared and laminated onto unitized pad stock using procedures similar to those described in Example 8.

Sample	PEG	PEO (% w/w)
A	51	49
B	62.5	37.5
C	25	75
D	83.3	16.7
E	5	95
F	86	14

The films were evaluated for their flexibility, dissolution rate and stability at elevated temperatures and humidity. Samples A and B were preferred because they exhibited good flexibility and dissolution rates. Samples C and D had acceptable properties, and Samples E and F were found to have unacceptable properties.

EXAMPLE 10

When the medicament is heat or pressure sensitive, composition of the invention can be blended without medicament, and extrusion coated onto a substrate. Then, the medicament can be deposited onto the film using any technique well-known to those skilled in the art. The following is an example of this technique.

Layer 1 have the composition shown below was blended and extrusion coated onto flexible fabric using procedures similar to those described in Example 5.

Layer 1	**wt %**
Acrylic Acid - Allyl Sucrose Copolymer (CARBOPOL 934P)	6.5
Glycerin (Emory 916 USP)	54.5
Hydroxypropyl Cellulose (KLUCEL JF EF)	26.0
Fumed Silica (Cabosil M-5)	1.0
Na-Ca Salt of a Copolymer of Polyvinyl Menthyl Ether and Maleic Anhydride (GANTREZ MS-955)	12.0

A solution of benzoyl peroxide was prepared by mixing the composition shown below with an equal amount (by weight) of acetone. This solution was then coated onto Layer 1. Layer 2 was dried and the acetone was allowed to evaporate, which resulted in a tacky benzoyl peroxide-containing layer laminated to Layer 1. The resulting structure is suitable for use as a blemish patch.

Layer 2	wt %
Benzoyl Peroxide	10.0
Dimethylaminoethyl Methacrylate	65.0
Triacetine	25.0

Additional solvents may be added to enhance solubility. However, any solvent used must have a low boiling point and high vapor pressure to ensure that critically high temperatures are not reached during the drying step.

EXAMPLE 11

Examples of Multilayered Films

A single-layered film containing the medicament "A" is made in accordance with the present invention, and is extruded onto a substrate. A second extruded film containing medicament "B" is then extruded onto the first layer. Thus, the "B-containing" film is in contact with the skin and "B" is the first medicament that comes in contact with the inflamed skin or wound. For example, the B-containing film may contain lidocaine for pain relief and the A-containing film may contain hydrocortisone for reducing inflammation. Additional film laminates containing many separate drug layers and different medication strategies can be constructed.

Diffusion of the "bioactive-type" drugs typically occurs at skin temperature, e.g., 33 to 35 °C. In order to minimize transfer or co-mingling of drugs between separate film layers, the compositions can be stored under cold conditions (say, for example, at approximately 4 °C) and brought to room temperature when needed.

Various modifications can be made to the above-described embodiment without departing from the spirit and scope of the present invention.

Claims

1. A composition comprising:
   a. thermoplastic water-soluble polymer;
   b. a water-soluble polymer derived from a carboxylic acid or a pharmaceutically acceptable salt thereof; and
   c. plasticizer.

2. The composition of claim 1 further comprising:
   d. medicament.

3. The composition of claim 2 comprising about 5-70% of (a), about 1-10% of (b), about 10-80% of (c), and about 0.01-10% of (d), by weight.

4. The composition of claim 2 comprising about 10-40% of (a), about 1-10% of (b), about 30-80% of (c), and about 0.01-10% of (d), by weight.

5. The composition of claim 2 comprising about 23-30% of (a), about 5-7% of (b), about 60-70% of (c), and about 0.01-10% of (d), by weight.

6. The composition of claim 2 wherein (a) comprises at least one polymer selected from the group consisting of hydroxypropyl cellulose and polyethylene oxide.

7. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of greater than about 600,000.

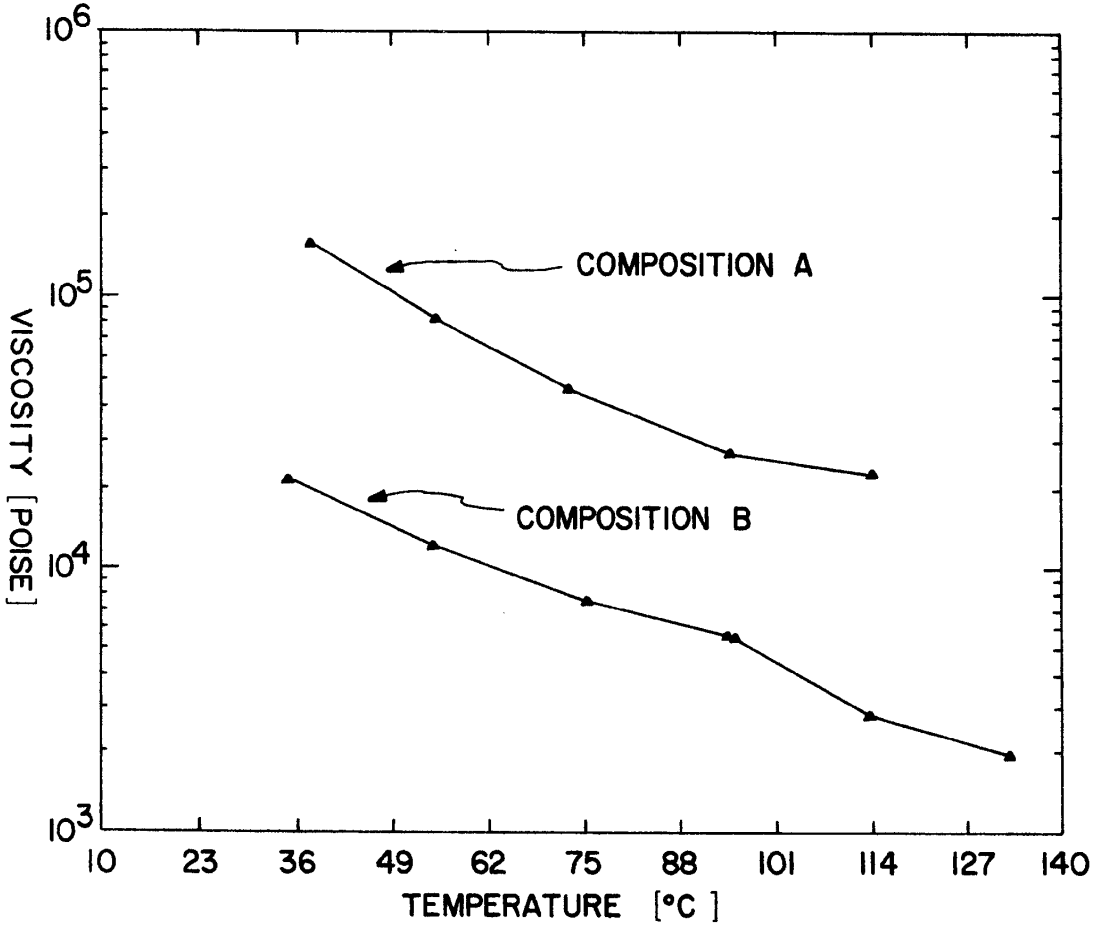
8. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of less than about 600,000.

9. The composition of claim 6 wherein said polyethylene oxide has a number average molecular weight of

between about 100,000 and 400,000.

10. The composition of claim 6 wherein said hydroxypropyl cellulose has a number average molecular weight greater than about 60,000.

FIG.1


10^6
10^5
10^4
10^3
VISCOSITY [POISE]
COMPOSITION A
COMPOSITION B
10
23
36
49
62
75
88
101
114
127
140
TEMPERATURE [°C]

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 93 30 9172

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.5)
X	WO-A-91 05574 (MEDIPRO SCIENCES LIMITED) * examples *	1	A61L25/00
D,Y	US-E-RE33093 (MICHAEL T. SCHIRALDEI ET AL.) & US-A-4 713 243 (MICHAEL T. SCHIRALDI ET AL.)	1-10	
P,Y	EP-A-0 551 626 (LEK) * claims *	1-10	
A	EP-A-0 386 960 (AMERICAN CYANAMID COMPANY) * claims *	1	
A	US-A-4 303 066 (MARK J. D'ANDREA) * abstract *	1	

TECHNICAL FIELDS SEARCHED (Int.Cl.5)

A61L

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	10 February 1994	ESPINOSA, M

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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A : technological background
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D : document cited in the application
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EPO FORM 1503 03.82 (P04C01)

PTO/SB/08a (05-07)
Approved for use through 11/30/2007. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

U.S.PATENTS						Remove
Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5234957		1993-08-10	Mantelle	
	2	5271940		1993-12-21	Cleary et al.	
	3	5272191		1993-12-21	Ibrahim et al.	
	4	5346701		1994-09-13	Heiber et al.	
	5	5393528		1995-02-28	Staab	
	6	5411945		1995-05-02	Ozaki et al.	
	7	5413792		1995-05-09	Ninomiya et al.	
	8	5433960		1995-07-18	Meyers	

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	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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	10	5462749		1995-10-31	Rencher	
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	26	4631837		1986-12-30	Magoon	
	27	6072100		2000-06-06	Mooney et al.	

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	Application Number	11775484
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	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Andrew H. Berks, Reg. No. 36,089/	Date (YYYY-MM-DD)	2008-01-29
Name/Print	Andrew H. Berks	Registration Number	36089

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7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

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EFS ID:	2782531
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Andrew Henry Berks/Barbara Thomas
Filer Authorized By:	Andrew Henry Berks
Attorney Docket Number:	1199-4B CIP
Receipt Date:	29-JAN-2008
Filing Date:	10-JUL-2007
Time Stamp:	15:14:18
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	1199-4B_CIP_IDS2.pdf	12384203 d329a9c2db12fc58858a4ea4c9edd86dbe344b81	no	9
Warnings:					
Information:					

2	Foreign Reference	WO09215289A1.pdf	2708703 81787667d640edac405d1bd440f1ec8857c7c3fd	no	62
Warnings:					
Information:					
3	Foreign Reference	WO09505416A2.pdf	3314755 7df764cb4acb162cda19b6aec69d95ce08ec89fc	no	79
Warnings:					
Information:					
4	Foreign Reference	WO09518046A1.pdf	1771914 67d6836cdb0660dff4fbbdbb9e476a5487b2a8a8	no	44
Warnings:					
Information:					
5	Foreign Reference	WO03030882A1.pdf	3468456 8f85202ab23b4d8297ed315e6b4c3ecad7deae2a	no	77
Warnings:					
Information:					
6	Foreign Reference	WO03030883A1.pdf	3495280 5baea410922b241f8f9c793740402dad01a255e8	no	66
Warnings:					
Information:					
7	Foreign Reference	WO2005102287.pdf	2171625 c45129d979c558dbc4b349e80cced3497af6a88f	no	56
Warnings:					
Information:					
8	Foreign Reference	EP00598606A1.pdf	757025 df12c2c2c1dd57028f8f24397652ea9c20e15ed7	no	15
Warnings:					
Information:					
9	NPL Documents	Article-Lazaridou_et_al.pdf	1040475 d7cf9497dd8a02956e7f42a9c57174df2aef7623	no	12
Warnings:					
Information:					
10	NPL Documents	Article-Polyethylenglykole.pdf	95950 2ca2cf9dacb941aa3594d37057afad88a897dbbd	no	2
Warnings:					
Information:					

11	NPL Documents	Article-Repka-Bioadhesive.pdf	821731 83f1a5cfe7cc8dbdef7937a303dee6980ac283ca	no	12
Warnings:					
Information:					
12	NPL Documents	Article-Repka-Vitamin_E.pdf	529225 cbb6e7065d42c273f2c0706006a3f51c6b64dc37	no	8
Warnings:					
Information:					
13	Information Disclosure Statement (IDS) Filed	1199-4B_CIP_IDS3.pdf	5544883 1ed253fea14b60194ccbfac5fc7521ea71e81a03	no	6
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New International Application Filed with the USPTO as a Receiving Office
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APPLICATION NUMBER	FILING OR 371(c) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP

CONFIRMATION NO. 5059

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY11791

Title: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Publication No. US-2008-0044454-A1
Publication Date: 02/21/2008

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

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Pre-Grant Publication Division, 703-605-4283

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Yang et al.	Examiner: Melissa Mercier
Application No.: 11/775,484	Group Art Unit: 1615
Filed: July 10, 2007	Docket: 1199-4B CIP
For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS	Dated: July 7, 2010

Confirmation No. 5059

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO RESTRICTION REQUIREMENT

Sir:

In response to the Restriction Requirement dated June 7, 2010, a response to which is due by July 7, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Original) A drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Original) The drug delivery composition of claim 1, wherein the uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout said matrix.

10. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 5% by weight.

11. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 2% by weight.

12. (Original) The drug delivery composition of claim 9, wherein said drug variance is less than 0.5% by weight.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking ~~and/or controlled-release~~ agent, and

wherein the active component is uniformly distributed in the film composition.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Currently Amended) The drug delivery composition of claim 18, wherein the taste-masking ~~and/or controlled-release~~ agent is a thin film coating over the particulate active component.

21. (Currently Amended) The drug delivery composition of claim 18, wherein the taste-masking ~~and/or controlled release~~ agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose;

hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (New) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-

hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Remarks

The Examiner has required restriction of the pending claims. Claims 1-34 are pending. The Examiner requires election between the following Groups pursuant 35 U.S.C § 121, as follows:

Group I:	Claims 1-17 drawn to a drug delivery composition, classified in class 424, subclass 439;
Group II:	Claims 18-24, drawn to a thin film drug delivery composition, classified in class 424, subclass 484;
Group III:	Claim 25, drawn to a drug delivery vehicle, classified in class 424, subclass 484;
Group IV:	Claims 26-28, drawn to a method of preparing a thin film drug delivery vehicle, classified in class 514, subclass 400+;
Group V:	Claims 29-33, drawn to a method of preparing a thin film vehicle having a substantially uniform distribution of components, classified in class 514, subclass 400+; and
Group VI:	Claim 34, drawn to a method of preparing a self supporting, edible film having a substantially uniform distribution of components, classified in class 514, subclass 400+.

The Examiner alleged that the various groups were unrelated for various reasons. In particular, with respect to Groups I and II (which, coincidentally are in the same class), the Examiner stated that the coating of Group II can have either a taste masking or controlled release agent. Further, the Examiner alleged that the film in Group II is not required to be flow able.

The Applicant has amended the independent claim of Group II (claim 18) to recite that the coating on the particulate active component is a taste-masking agent. It is further noted that the independent claim of Group I (claim 1) does not recite a flowable film, rather it recites a flowable film forming matrix, which is "capable of being dried without loss of uniformity in the

stationing of said particulate bioeffecting agent therein." One of ordinary skill in the art would understand that a film-forming matrix is used to form the final film composition. Claims 1 and 18 (and those dependent thereon) are directed to film compositions.

Given the present amendment to claim 18, it is respectfully requested that claims 1-17 and claims 18-24 be maintained and examined together. There is no added burden on the Examiner to search these two groups.

In view of the requirement for restriction, the Applicant elects to prosecute the claims of Group I, including claims 1-17. In light of the amendments submitted herein, the Applicant respectfully requests that the amended claims 18-24 be considered along with claims 1-17. It is further noted that the requirement for restriction has been made, at least in part, between product claims and method claims, and that the Applicant has elected claims directed to the product. Should these claims be allowable, the Applicant will seek to rejoin those method claims that recite the same limitations of the allowed product claims.

The Applicant makes this election without prejudice to seeking rejoinder of the withdrawn claims or to filing one or more divisional applications directed to any non-elected groups. The Applicant further makes the amendments herein without prejudice to filing one or more divisional applications seeking claims directed to the now-canceled language of the claims of Group II.

New claims 35-36 have been added, which are dependent upon claim 1 and further define the scope of the invention. In particular, claim 35 defines the taste masking agent of claim 1, and claim 36 further defines the bioeffective agent of claim 1. Support for these amendments may be found, for example, at paragraphs [0107] and [0132] of the application as filed. No new matter is introduced through this amendment. These claims are part of Group I, and are thus elected herein.

Fees due with two new dependent claims are due with this submission, and the

Commissioner is authorized to charge payment of these fees to Deposit Account No. 08-2461. No other fees are due. However, if any additional fee should be due, the Commissioner is hereby authorized to charge payment of any fees associated with this communication to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. § 1.136.

In view of the documents submitted herewith, Applicant respectively urges that the application is in condition for examination. Please direct any questions regarding this submission to Applicant's undersigned agent.

Respectfully submitted,

/Jon A. Chiodo/
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Attorney for Applicants

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Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Jon Anthony Chiodo/Shannon Farischon
Attorney Docket Number:	1199-4B CIP

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in excess of 20	2202	2	26	52
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
		Total in USD ($)		**52**

Electronic Acknowledgement Receipt

EFS ID:	7966875
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Shannon Farischon
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-4B CIP
Receipt Date:	07-JUL-2010
Filing Date:	10-JUL-2007
Time Stamp:	14:33:19
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$52
RAM confirmation Number	810
Deposit Account	082461
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)	
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)	
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1199_4B_CIP_Amendment_Response_Restriction_Requirement_07072010.pdf	96281 b4acfa01831c7c8490d1fbd56447f742e3e0908e	yes	12

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Response to Election / Restriction Filed	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	12

Warnings:					
Information:					
2	Fee Worksheet (PTO-875)	fee-info.pdf	30429 11b6ef83aa2cc4b3c818a4f3b3e10082b7137386	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	126710		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☒ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	07/07/2010	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 34	= 2	X $26 =	52	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	52	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/KATRINA HARLING/

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 09/09/2010
HOFFMANN & BARON, LLP
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EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
09/09/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA S. MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-36 is/are pending in the application.

4a) Of the above claim(s) 25-34 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-24,35 and 36 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 1-29-08.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, comprising claims 1-17 in the reply filed on July 7, 2010 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Additionally in view of Applicants arguments and amendment to claim 18, Group II, comprising claims 18-24 have been rejoined with Group I.

Therefore, claims 1-24 and newly presented claims 35 and 36 are under prosecution in this application. Claims 25-34 are withdrawn as reading on non elected groups.

Priority

Applicant's claim of priority date of October 12, 2001 is present in the filing of Provisional Application 60/328,868.

Information Disclosure Statement

Receipt of the three Information Disclosure Statements filed on January 29, 2008 is acknowledged. Signed copies are attached to this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 and 35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claim 1, Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other. It is the understanding of the Examiner that an intimate admixture is a mixture and not a coated particle. Therefore, Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste making agent is coated on the particulate bioeffecting agent.

Regarding claim 35, the phrase "such as" and “including” renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8-12, 14-19, 22, and 35-36 are rejected under 35 U.S.C. 102(e) as being anticipated by Bess et al. (US Patent 7,067,116).

Bess discloses fast dissolving orally consumable solid film containing a taste masking agent and a pharmaceutically active agent at weight ratio of dissolving 1:3 to 3:1 (Title). The films include a water soluble film forming polymer and a taste masked pharmaceutically active agent (abstract).

Examples of water soluble film forming polymers include pullulan, HPMC, hydroxyethyl cellulose, hydropropyl cellulose, PVP, carboxymethyl cellulose PVA, sodium alginate, PEG, xanthan gum, for example (column 5, lines 1-16).

The active agents include antimicrobial agents, NSAIDS, anti-tussives, decongestants, anti-histamines, expectorants, anti-diarrheals, PPI's, CNS depressants and stimulants (columns 2 and 3).

The taste masking agent is an ion exchange resin includes synthetic polymer of acrylic acid, methacrylic acid, sulfonated styrene, and sulfonated divinylbenzene or partially synthetic polymers of modified celluloses and dextrans (column 4, lines 1-24). Less preferred embodiments partially taste masking agents of magnesium trisilicate and polymers such as Eudragit E and/or cellulosics, such as ethylcellulose (column 4, lines 60-67).

The active agents adsorbed to the ion exchange resin is in the range from about 25-75% by weight of the pharmaceutically active agent/resin adsorption complex, thereby meeting the limitations of claims 14-15. The recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent.

The pharmaceutically active agent/resin adsorption complex can also be coated in the range from about 40 to about 70% w/w pharmaceutically active agents/resin complex. Variation in the amount of coating and/or the use of coating/uncoated complex mixtures can be employed to selectively modify the dissolution profile (column 11, lines 43-53).

The particle size of the coated and uncoated pharmaceutically active agent/resin adsorption complex is about 60-200 microns (column 11, lines 54-58).

Plasticizers, surfactants, and polyalcohol's are optional ingredients; therefore, they are not required by Bess in order for the film to perform as disclosed.

The films can additionally include polyethylene oxide compound (column 8, line 15-18).

Regarding claim 19, Bess discloses his formulations are cast on a suitable substrate and dried to form a film (column 8, lines 47-48); however, this is considered a product by process limitation. Applicant is directed to MPEP 2112 which discloses "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Since the methods of preparing the films disclosed in the reference recite numerous mixing steps of the same structural elements as recited in the instant claims,

it is the position of the Examiner that absent of showing of evidence to the contrary, the films would inherently possess the same uniformity as recited in instant claims 9-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-12, 17, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (WO 00/42992) in view of Ghana et al (US Patent 5,653,993).

Chen discloses a water soluble hydrocolloid; mucosal surface coated forming film, having an effective dose of an active agent (page 3, lines 30-33).

The hydrocolloid includes a polymer selected from the group consisting of natural, semi-natural and synthetic biopolymers (page 4, lines 1-3).

The active agents is selected from the group consisting of therapeutic agents, dietary supplements, and hygiene aids, for example sildenafil citrate, nicotine, hydromorphone, oxybutynine, or estradiol (page 4, lines 7-10). The active agent can be encapsulated in a material that is different than the hydrocolloid. Encapsulation is additionally utilized to achieve masking of taste of active agents that are bitter (page 9, lines 13-15).

The hydrocolloid is a water soluble non gelling natural polysaccharide, polypeptide or protein (page 14, lines 12-31).

The films can be cast or extruded (page 15-16).

Chen does not disclose the particle size of the encapsulated active agents.

Ghanta discloses the preparation of taste masked microcapsules. The encapsulating material is cellulose acetate phthalate and gelatin (abstract).

The average/mean microcapsule diameter ranges from about 25 to about 600 microns (column 3, lines 59-62).

The gelatin used can be of any origin so long as it is of pharmaceutical grade. The gelatin, for example, can have a number average molecular weight of about 27,000 to 70,000 (column 4, lines 43-47).

It would have been within the skill of the ordinary practitioner to have used the particle size disclosed by Ghanta in order to make the encapsulated active agents utilized by Chen since both references discloses the particles are suitable for taste masking and Ghanta discloses they do not form agglomerates (column 3, lines 33-35), thereby allowing for a more uniform distribution.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the particle size of the microcapsules in Chen since Ghanta discloses in order to make wider use of NSAIDs while substantially eliminating the bitter taste, aftertaste and adverse mouth feel and make these drugs more pleasant upon taking them orally, there has long been desired a way to insure delivery of these drugs in their desired concentrations while avoiding their extremely bitter taste, lingering aftertaste and adverse mouth feel effects referred to above connected with their ingestion orally, thereby encouraging patient compliance.

Claims 1-4, 9-13, 17-20, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Grass et al. (US Patent 3,237,596).

Schiraldi discloses a bioadhesive extruded single or multilayered thin film having a water soluble or swellable polymer matrix, bioadhesive layer consists essentially of 40-95% by weight of a hydroxypropyl cellulose, 5-60% of a homopolymer of ethylene oxide, 0-10% of a water-insoluble polymer such as ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and 2-10% of a plasticizer, said film having incorporated therein a medicament, such as anesthetics, analgesics, anticaries agents, anti-inflammatories, antihistamines, antibiotics, antibacterials, fungistats, etc (abstract).

Schiraldi does not disclose the medicament being coated with a taste masking polymer having a particle size of 200 microns or less.

Grass discloses a method of coating discrete solids. The solids have a particle size of about 5 to about 200 microns (column 1, lines 10-15). Spherical particles of acetaminophen coated with 12-hydroxystearyl alcohol are disclosed in the Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have employed the method of coating medicaments as disclosed by Grass for incorporation into the films disclosed by Schiraldi in order to achieve the taste masking, sustained dissolution, enteric properties, improved stability, delayed interaction, wettability, and improved flow properties of the active agent for incorporation into drug formulation.

Claims 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Thakur et al. (US 2004/0156901).

The teaching of Schiraldi are discussed above and applied in the same manner.

Schiraldi does not disclose the medicament being coated with a taste masking water soluble polymer

Thakur discloses particulate cores of active agents coated with a taste masking polymer, preferably cellulose acetate (paragraph 0034), which is a water soluble polymer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used coated active agents, as discussed by Thakur in

order to provide dosage forms in which pharmaceutical agents with unappealing tastes can be masked and allow for increased patient compliance.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA S. MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/Carlos A. Azpuru/
Primary Examiner, Art Unit 1617

Notice of References Cited	Application/Control No. 11/775,484	Applicant(s)/Patent Under Reexamination YANG ET AL.	
	Examiner MELISSA S. MERCIER	Art Unit 1615	Page 1 of 1

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*	A	US-7,067,116	06-2006	Bess et al.	424/78.1
*	B	US-5,653,993	08-1997	Ghanta et al.	424/440
*	C	US-4,713,243	12-1987	Schiraldi et al.	424/676
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*	E	US-2004/0156901	08-2004	Thakur et al.	424/471
	F	US-			
	G	US-			
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	I	US-			
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	K	US-			
	L	US-			
	M	US-			

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Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	Art Unit
	MELISSA S MERCIER	1615

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
East-see attached	9-6-10	MMercier
Palm inventor search	9-6-10	MMercier

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/MELISSA S MERCIER/ Examiner.Art Unit 1615	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

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	Examiner Name	Unassigned
	Attorney Docket Number	1199-4B CIP

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
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	2	XP-002298105; Polyethylenglykole; Internet: www.roempp.com; 09/20/2004	☐
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EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	96	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 10:47
L2	291	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 11:02
L3	308	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND (coat encapsulate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:23
L4	177	"4713243"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:28
L5	52	"6284264"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:46
L6	47	"5393528"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:49
L7	17	"1110546"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:52

EAST Search History (Prior Art)

L8	19068	film AND (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:53
L9	5583	film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:54
L10	89	edible WITH film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:55
L11	45	"4849246"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:02
L12	3	"0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:09
L13	0	"0514691A"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
L14	0	"EP0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
L15	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:20

EAST Search History (Prior Art)

L16	19	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size AND film	USPAT	OR	ON	2010/09/05 14:24
L17	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:29
L18	21	taste adj1 masking SAME (drugactive drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
L19	37	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
L20	159	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:35
L21	45	"5215755"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:14
L22	47	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size AND spherical	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:41

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	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	December 9, 2010

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Dated: December 9, 2010

Signature: /Marcy Mancuso/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.111

Sir:

In response to the Office Action dated September 9, 2010, a response to which is due by December 9, 2010, the Applicant responds as follows:

Amendments to the claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) A drug delivery composition comprising:

(i) a flowable water-soluble film forming matrix;

(ii) a particulate bioeffecting agent uniformly stationed therein; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 5% by weight per film unit.

11. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 2% by weight per film unit.

12. (Currently amended) The drug delivery composition of claim ~~9~~ 1, wherein said ~~drug variance~~ variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble film forming matrix comprising at least one water-soluble polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and

(b) a coated particulate active component uniformly stationed therein;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Currently amended) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch~~, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch~~; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins~~, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein~~; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics,

prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Remarks

Claims 1-8 and 10-36 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claim 9 is cancelled and claims 1, 10, 11, 12, 18, and 35 are amended. Support for the amendments to the claims may be found, for example, in the original claims, and the specification. No new matter is added.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection under 35 U.S.C. §112, Second Paragraph

The Office Action rejects claims 1-17 and 35 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner asserts that "Applicant has not particularly pointed out how the combined particulate and taste masking agents can have a particle size of 200 microns or less when they are intimately associated with each other." Moreover, the Examiner asserts that "Applicant has not pointed out if both the particulate bioeffecting agent and the taste masking agent have the claimed particle size or if the particle size is only applicable when the taste masking agent is coated on the particulate bioeffecting agent." *See* Office Action, page 3, second paragraph.

Applicants respectfully disagree with the Examiner and traverse the rejection. Claim 1 clearly recites that "the **combined particulate and taste-masking agent** have a particle size of 200 microns." Accordingly, it would be clear to one skilled in the art that, regardless of whether the combined particulate bioeffecting agent is intimately associated with the taste masking agent or whether the particulate bioeffecting is coated with the taste masking agent, it is the

combination of the particulate bioeffecting agent and the taste masking agent that has a particle size of 200 microns. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner also rejects claim 35 for containing the terms "such as" and "including." Without conceding the propriety of the rejections, claim 35 is amended to more clearly recite various novel features of the claimed invention, with particular attention to the Examiner's comments. Specifically, claim 35 is amended to delete the terms "such as" and "including," thereby obviating the rejection. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

It is well settled that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *See* MPEP §2131.

Independent claims 1 and 18 require that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Bess does not teach or suggest such a feature.

At most Bess teaches that its process involves "adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting

the uniform mixture on a suitable substrate; and drying the cast mixture to form a film." *See* column 12, lines 13-17.

The instant specification teaches that the ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique. *See* for example paragraphs [0068] and [0069]. Nowhere does Bess teach or suggest the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Moreover, claim 18 requires "the coating on the particulate active component is a taste-masking agent." Bess fails to teach or suggest such a feature.

Although Bess discloses a presence of a coating, nowhere does Bess teach or suggest a coating that is a taste-masking agent, as claimed.

The Examiner asserts that "the recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent." *See* Office Action, page 4, last paragraph. Applicants respectfully disagree. Although, Bess discloses the taste masking agent as an ion exchange resin, the ion exchange resin does not necessarily form a coating. At most, Bess teaches that "The ratio of the pharmaceutically active agent adsorbate to ion exchange resin adsorbent in the adsorption complex is about 1:3 to about 3:1, preferably about 1:2 to about 2:1, most preferably about 1:1. The only limit to using ratios in excess of 1:3 is an economic and aesthetic one." *See* column 9, lines 55-60. Nowhere does Bess teach or suggest a taste-masking coating, as required by claim 18 and Bess fails to teach or suggest "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit," as required by claims 1 and 18.

Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana"). Applicants respectfully traverse the rejection.

Chen is cited for its alleged disclosure of water soluble hydrocolloid, mucosal coating, an effective dose of agent. The Examiner acknowledges that Chen fails to teach or suggest the particle size of the encapsulated active agents. *See* Office Action, page 7, line 12. Nevertheless, the Examiner cites Ghana as allegedly curing the deficiencies of Chen.

By this Amendment, independent claim 1 is amended to recite that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit." Chen and Ghana, whether considered independently or combined, fail to teach or suggest such features.

Neither Chen nor Ghana disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so. Thus, the Examiner has not provided any rationale to modify Chen or Ghana in order to arrive at the presently claimed invention.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

There are several problems addressed by the present invention. One such problem is the delivery of bad-tasting actives in a dosage form which inherently exposes a high degree of the active to the taste buds. This is because most films are relatively thin by nature with planar surfaces and such the active is readily exposed to the taste buds as the film is dissolved. Thus, in view of the relatively large surface area of exposure, determining the proper size of the taste-masked particles was an important finding. Drug delivery films are not only relatively thin, but often dimensionally small. Thus, the smaller particles allow for a more uniform distribution to be readily achieved. Particles which are too large may self aggregate and cause a loss of uniformity of drug content per unit volume of film. Particles which are too large will also require more taste-masking material to effectively cover the active. Additionally, particles larger than 200 microns will present a gritty mouth feel and may be thicker than the film per se.

In short, the claimed invention solves the problems associated with effective delivery of a uniform amount of taste masked drug in a film dosage unit.

In particular, self aggregation or conglomeration of particles leads to **non-uniformity** of distribution of the drug in the film. The failure to achieve a high degree of accuracy with respect to the amount of active ingredient in dosage cut from the film can be harmful to the patient and may not meet the stringent governmental or agency standards relating to variation of active in dosage forms.

Self aggregation in film containing a pharmaceutical active increases the probability of perception of an unpleasant tasting film, as well as destroys the uniformity of the pharmaceutical agent in the film.

The claimed invention introduces a composition and processes as a solution that overcomes the above-mentioned problems.

Such a solution includes specific features such as particle size; maintaining the uniform distribution of active components by locking-in or substantially preventing migration of the active components within the visco-elastic film and resulting film product; and particular taste-masking agents.

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen merely mixes taste modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

Uniformity is important in oral film products, particularly products intended for delivery of pharmaceutical actives such that regulatory approval of the product may be obtained. As further explained on page 22 of the present application, the films prepared in accordance with the present invention have a "high degree of uniformity of the components of the film [which] makes them particularly well suited for incorporating pharmaceuticals". (lines 26-29). Specifically, the film products have:

> no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix.
>
> (page 38, lines 16-20).

In contrast, Chen fails to teach or suggest and has absolutely no appreciation for the need to achieve dried films that are uniform in content.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, the Supreme Court addressed the standard for obviousness in its decision of *KSR International Co. v. Teleflex Inc.*, et al., 550 U.S. 389; 127 S.Ct. 1727; 167 L.Ed.2d 705; 82 U.S.P.Q.2d 1385 (2007). In order for an examiner to establish a prima facie case of obviousness

after KSR, some degree of predictability is necessary. (82 U.S.P.Q.2d at 1395-97). *Takeda Chemical Industries Ltd. V. Alphapharm Pty. Ltd.*, 83 USPQ.2d 1169 (Fed. Cir. 2007) is a post KSR decision in which the Federal Circuit articulated standards for establishing non-obviousness which again includes predictability of success. (83 USPQ.2d at 1176-79). Further, Section 2143.02 (II) of the MPEP states that "Obviousness does not require absolute predictability, however, at least some degree of predictability is required."

Clearly, the disclosure of Chen and Ghana does not provide sufficient predictability or expectation to support a prima facie case of obviousness as it fails to disclose, teach or suggest the drug delivery composition of the present invention.

Accordingly, the Examiner has not presented a prima facie case of obviousness as the examiner fails to present, inter alia, any evidence that the drug delivery composition contains the elements and properties, as claimed, nor has the Examiner presented any rationale to modify the cited references to arrive at the claimed composition.

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1–4, 9-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Applicants wish to remind the Examiner of the "*Basic Requirements of a Prima Facie Case of Obviousness*", which can be found in M.P.E.P. §2143. According to these requirements, the following are necessary to establish a prima facie case of obviousness: (1) a reference or combination of references must provide some suggestion or motivation to modify the reference or to combine the teachings; (2) there must be a reasonable expectation of success; and (3) there must be a teaching or suggestion of all claim limitations.

Schiraldi is directed to a bioadhesive extruded film. Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final end product. As the Examiner notes, the components are merely blended together.

The Examiner has not provided any teaching to suggest that the extruded film of the present invention is uniform. Nothing in the reference suggests that simply blending components guarantees uniformity. Furthermore, a liquid plasticizer is added to the powder blend during the blending process. According to Schiraldi, the purpose of the plasticizer is to "…improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product."

Thus, the films of Schiraldi must be extruded, and Schiraldi teaches away from a casted film product. "The film of the present invention has the advantage of being an extruded film,

rather than a cast film." (Schiraldi, col. 3, ll. 64-65). Accordingly, one of skill in the art would not find that the components utilized by Schiraldi would provide a casted film.

Grass is cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content, as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Moreover, there is no rationale suggested in Schrialdi that the extruded film should be modified to be a casted film. Furthermore, there is no rationale suggested by Grass that its method can be used in a casted film product. In addition, there is no level of predictability in the teaching of Schiraldi that their components could be used in a casted film. There is also no level of predictability in the teachings of Grass that their formulations would be useful in a casted film product.

There is no rationale in Schiraldi or Grass to modify their teachings, in order to arrive at the claimed invention. Furthermore, there is no predictability in the teachings of Schiraldi or Grass to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Grass does not teach all the claim limitations.

Therefore, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Schiraldi in view of Thakur

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 9, 3rd paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content, as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
Registration No. 60,808

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Electronic Acknowledgement Receipt

EFS ID:	9002680
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	09-DEC-2010
Filing Date:	10-JUL-2007
Time Stamp:	15:52:16
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Amendment_and_Response.pdf	164555 13388a2192b087f5d60f0afeaf619d79714a0d45	yes	21

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	21
Warnings:			
Information:			
	Total Files Size (in bytes):	164555	

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New Applications Under 35 U.S.C. 111
If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371
If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office
If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PTO/SB/06 (07-06)
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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

	(Column 1)	(Column 2)	SMALL ENTITY ☒		OR	OTHER THAN SMALL ENTITY	
FOR	NUMBER FILED	NUMBER EXTRA	RATE ($)	FEE ($)		RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

		(Column 1)		(Column 2)	(Column 3)	SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
AMENDMENT	12/09/2010	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 35	Minus	** 36	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

		(Column 1)		(Column 2)	(Column 3)					
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/AMANDA FORD/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	3007848		1961-11-07	J.H. Stroop	
	2	4478658		1984-10-23	Wittwer	
	3	5044761		1991-09-03	Yuhki et al.	
	4	5605696		1997-02-25	Eury et al.	
	5	5733575		1998-03-31	Mehra et al.	
	6	5800832		1998-09-01	Tapolsky et al.	
	7	5806284		1998-09-15	Gifford	
	8	5881476		1999-03-16	Strobush et al.	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
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	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

	9	6660292	B2	2003-12-09	Zerbe et al.	
	10	6800239	B2	2004-10-05	Horstmann et al.	
	11	6824829	B2	2004-11-30	Berry et al.	
	12	7005142	B2	2006-02-28	Leon et al.	
	13	7579019	B2	2009-08-25	Tapolsky et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20050048102	A1	2005-03-03	Tapolsky et al.	
	2	20070148097	A1	2007-06-28	Finn et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

	1	1 510 999	GB		1978-05-17	Schering Aktiengesellschaft		☐
	2	WO 03/030881	WO	A1	2003-04-17	Kosmos Pharma		☐
	3	WO 2008/011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc.		☐

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NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT (Not for submission under 37 CFR 1.99)		
	Application Number	11775484
	Filing Date	2007-07-10
	First Named Inventor	Robert K. Yang
	Art Unit	1615
	Examiner Name	Mercier, Melissa S.
	Attorney Docket Number	1199-4 B CIP

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☒ Fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☐ None

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Julie Tabarovsky, Reg. No. 60,808/	Date (YYYY-MM-DD)	2010-12-15
Name/Print	Julie Tabarovsky	Registration Number	60,808

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**