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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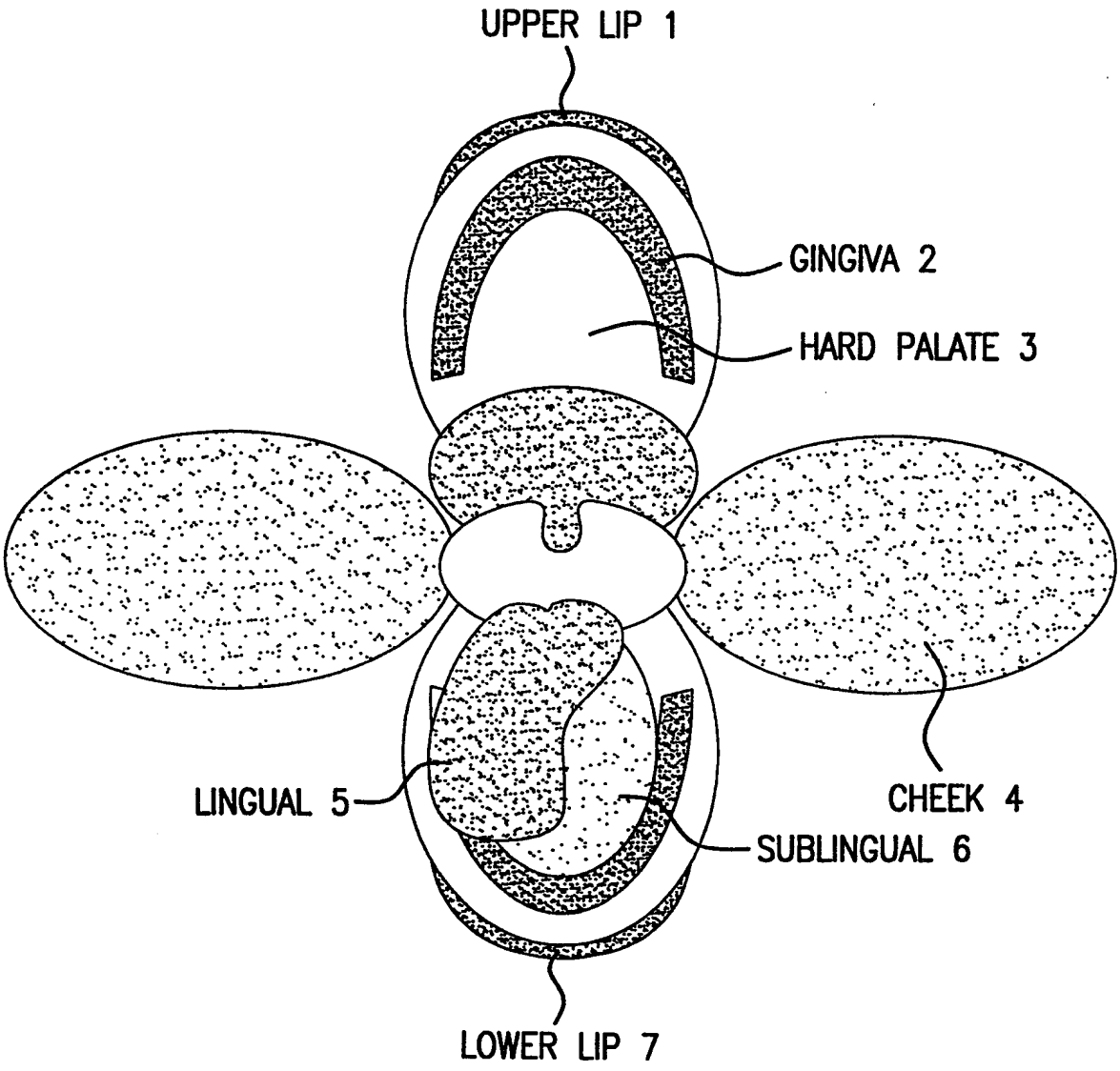
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CHEEK 4
LINGUAL 5
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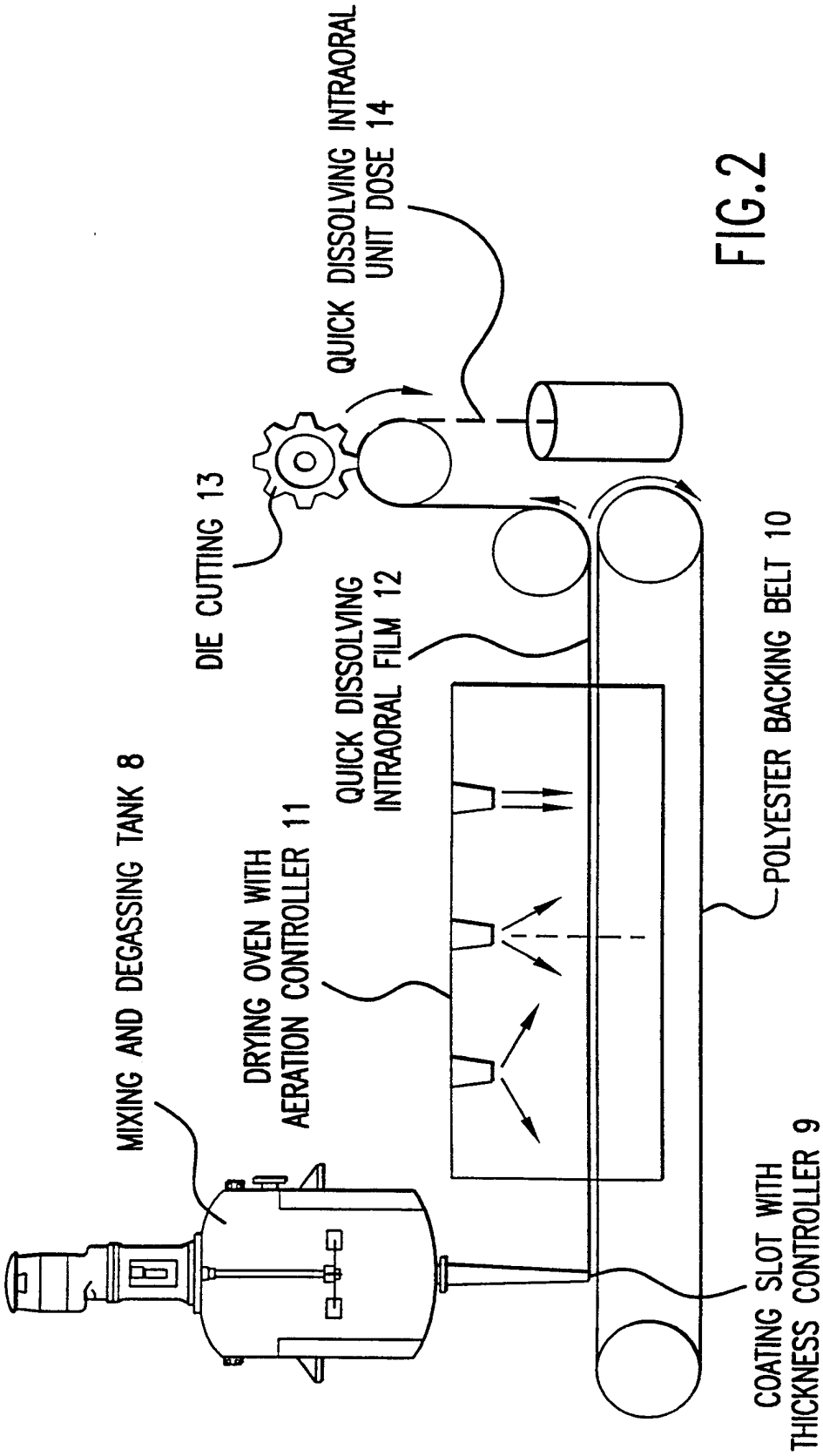
LOWER LIP 7

FIG.1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DIE CUTTING 13
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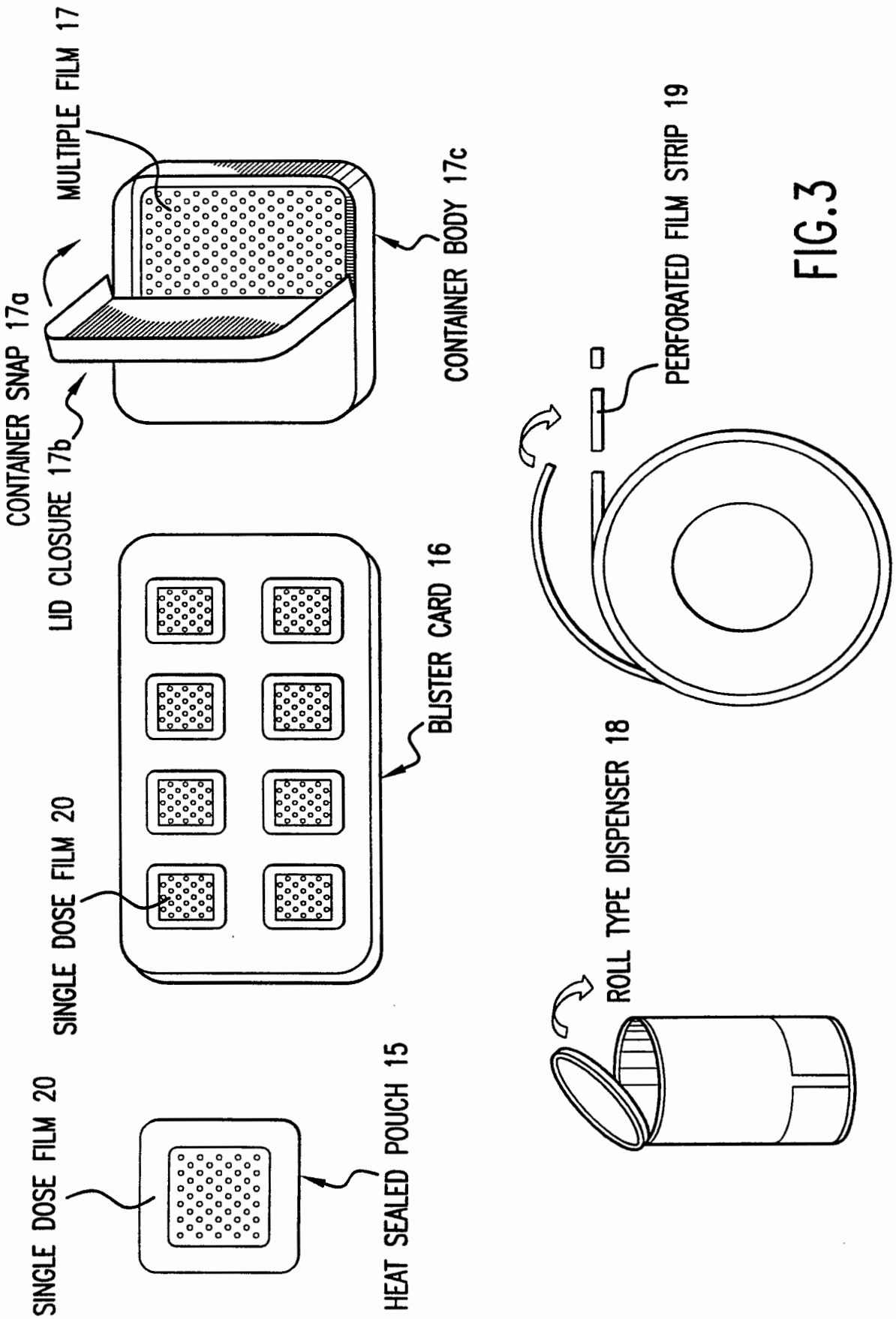
DRYING OVEN WITH AERATION CONTROLLER 11
MIXING AND DEGASSING TANK 8
POLYESTER BACKING BELT 10
COATING SLOT WITH THICKNESS CONTROLLER 9

FIG.2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CONTAINER SNAP 17a
LID CLOSURE 17b
CONTAINER BODY 17c
BLISTER CARD 16
SINGLE DOSE FILM 20
HEAT SEALED POUCH 15
SINGLE DOSE FILM 20
PERFORATED FILM STRIP 19
ROLL TYPE DISPENSER 18

FIG.3

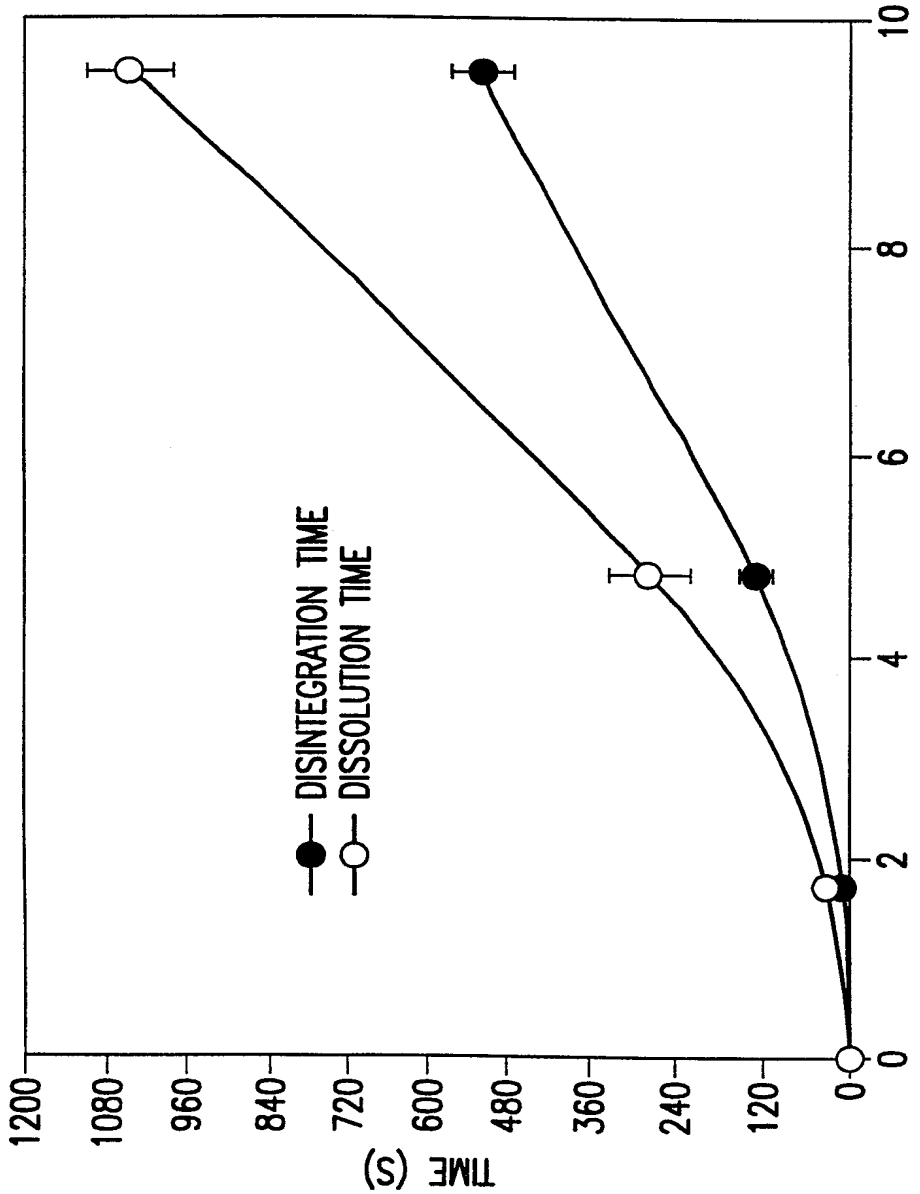
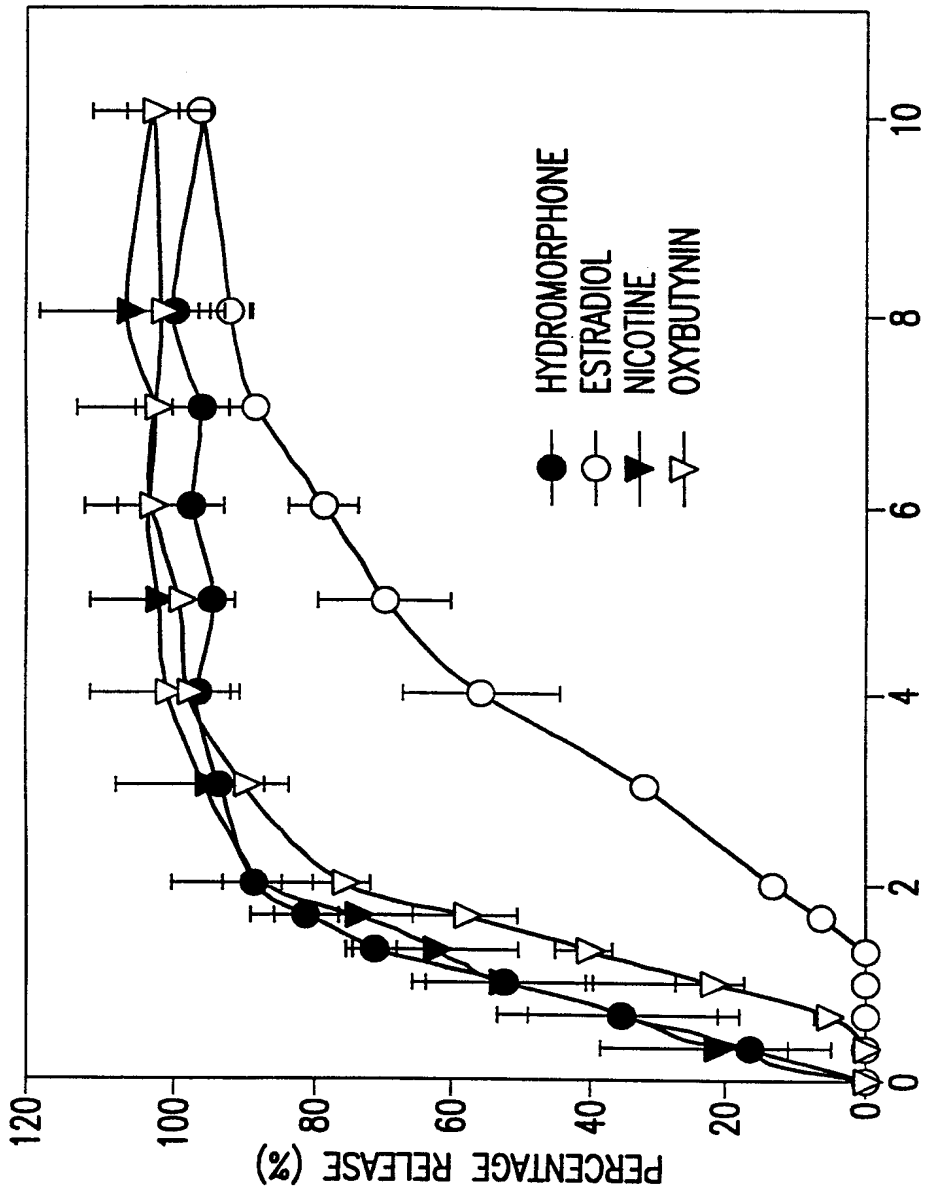

TIME (S)
1200
1080
960
840
720
600
480
360
240
120
0
0
2
4
6
8
10
THICKNESS (mil)
DISINTEGRATION TIME
DISSOLUTION TIME

FIG.4

5/6


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

FIG.5

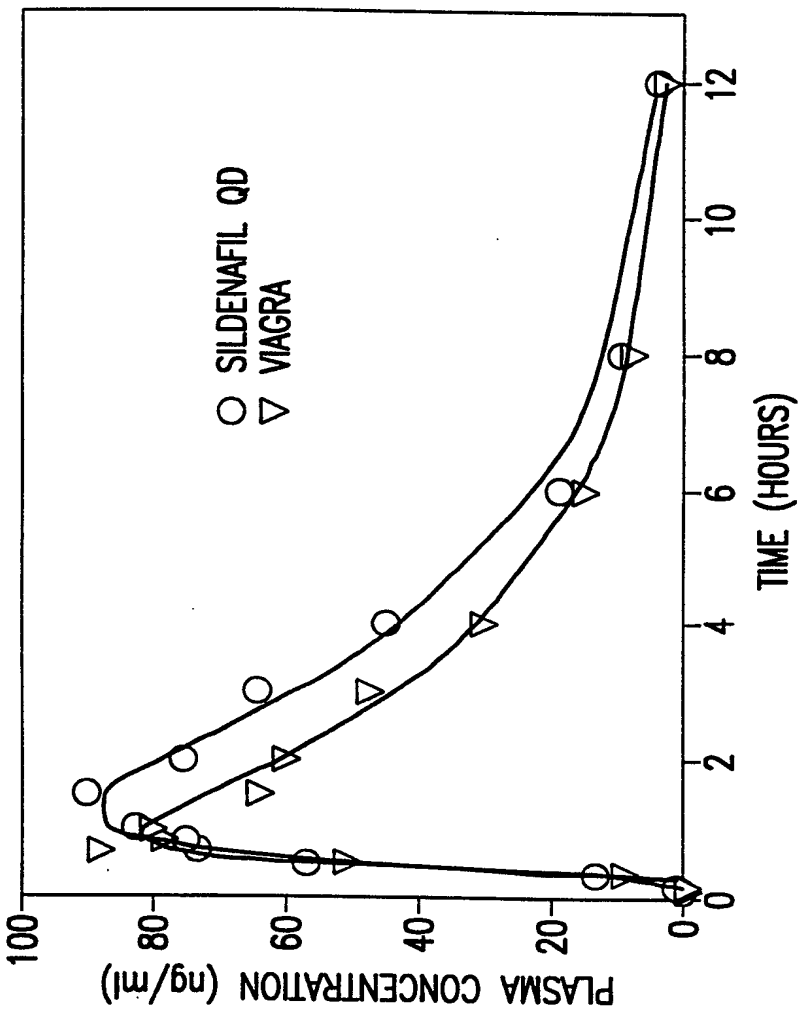
SILDENAFIL QD
VIAGRA
PLASMA CONCENTRATION (ng/ml)
TIME (HOURS)
0
20
40
60
80
100
2
4
6
8
10
12

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						

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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

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PCT/US 01/02192

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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IPC 7 A61K

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)
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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"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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INTERNATIONAL SEARCH REPORT

Information on patent family members

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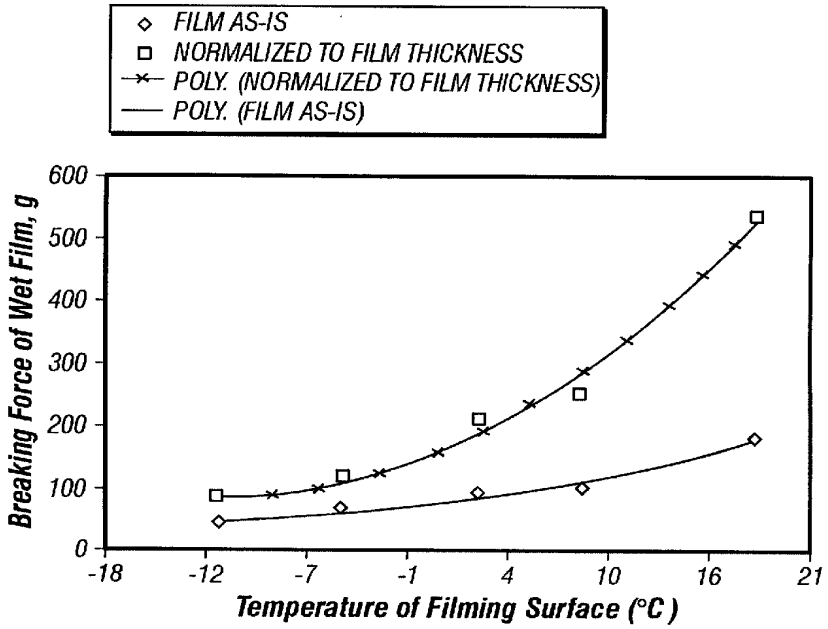

(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which 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.

1/2

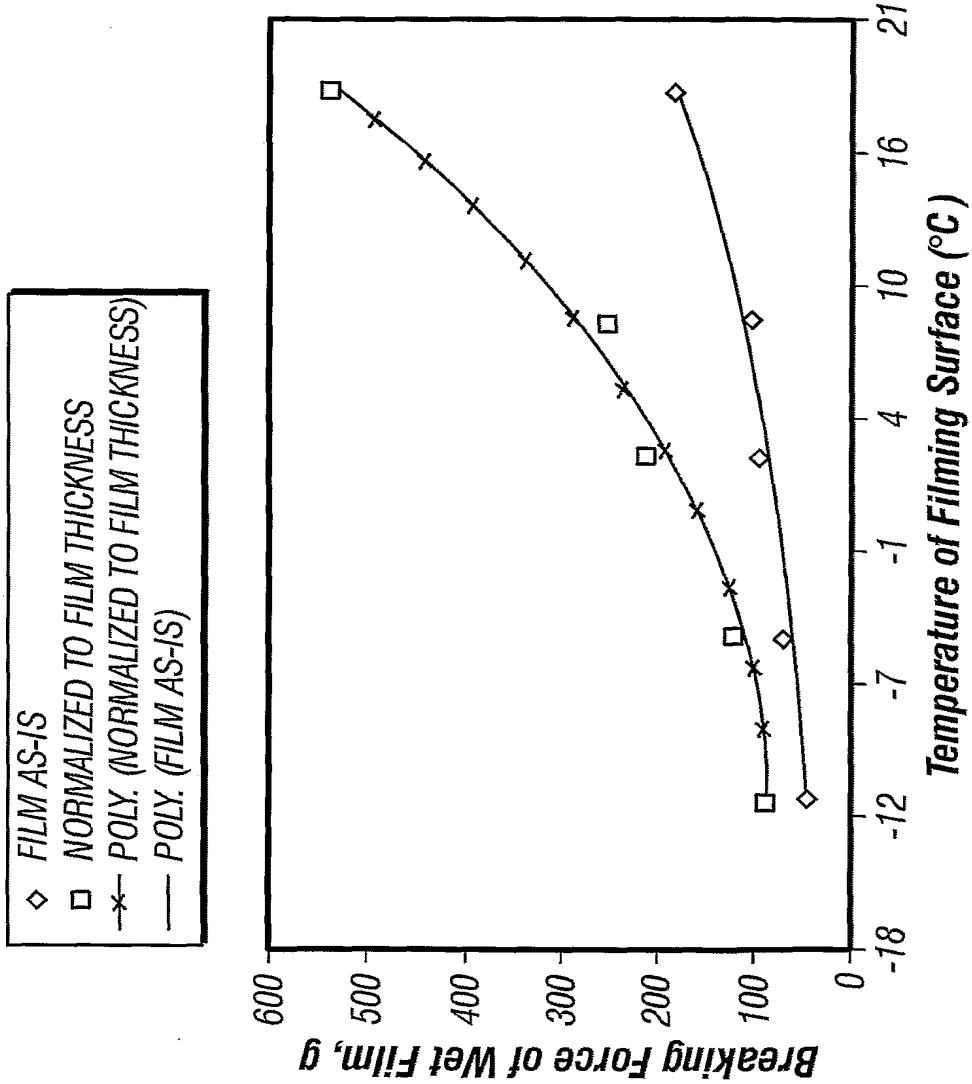
◇ FILM AS-IS
□ NORMALIZED TO FILM THICKNESS
—×— POLY. (NORMALIZED TO FILM THICKNESS)
— POLY. (FILM AS-IS)
Breaking Force of Wet Film, g
600
500
400
300
200
100
0
-18
-12
-7
-1
4
10
16
21
Temperature of Filming Surface (°C)

FIG. 1

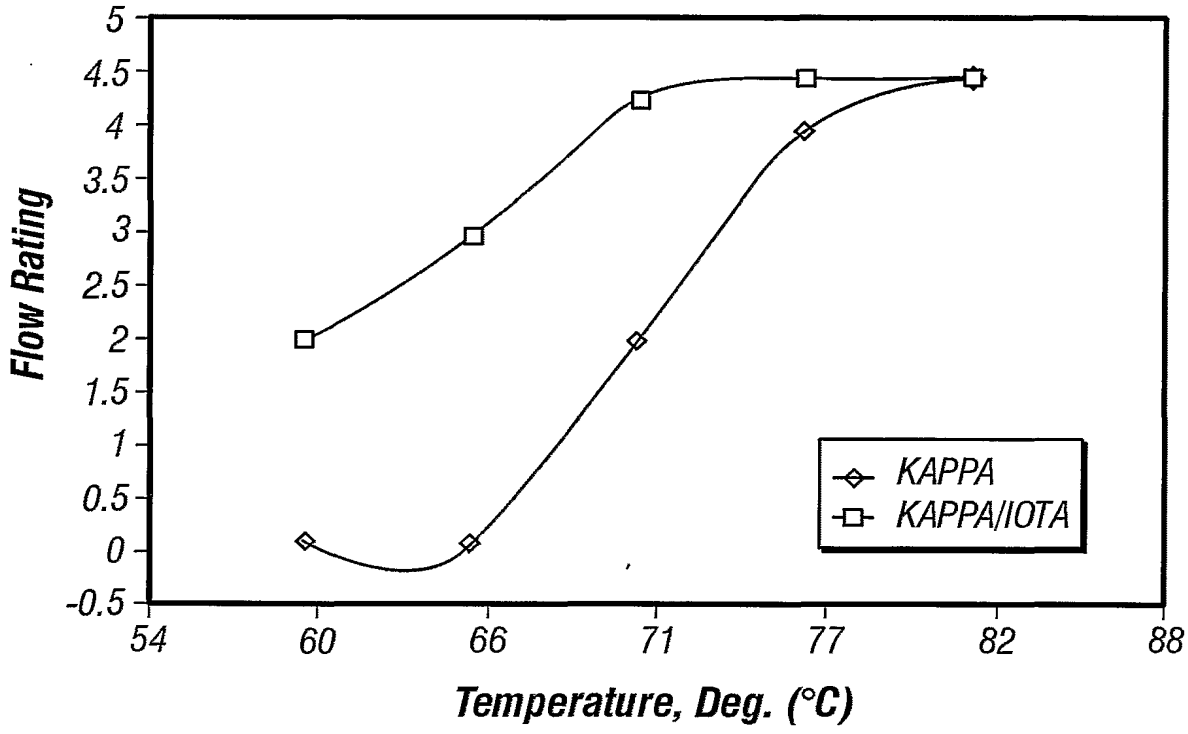
Flow Rating
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
-0.5
54
60
66
71
77
82
88
KAPPA
KAPPA/IOTA
Temperature, Deg. (°C)

FIG. 2

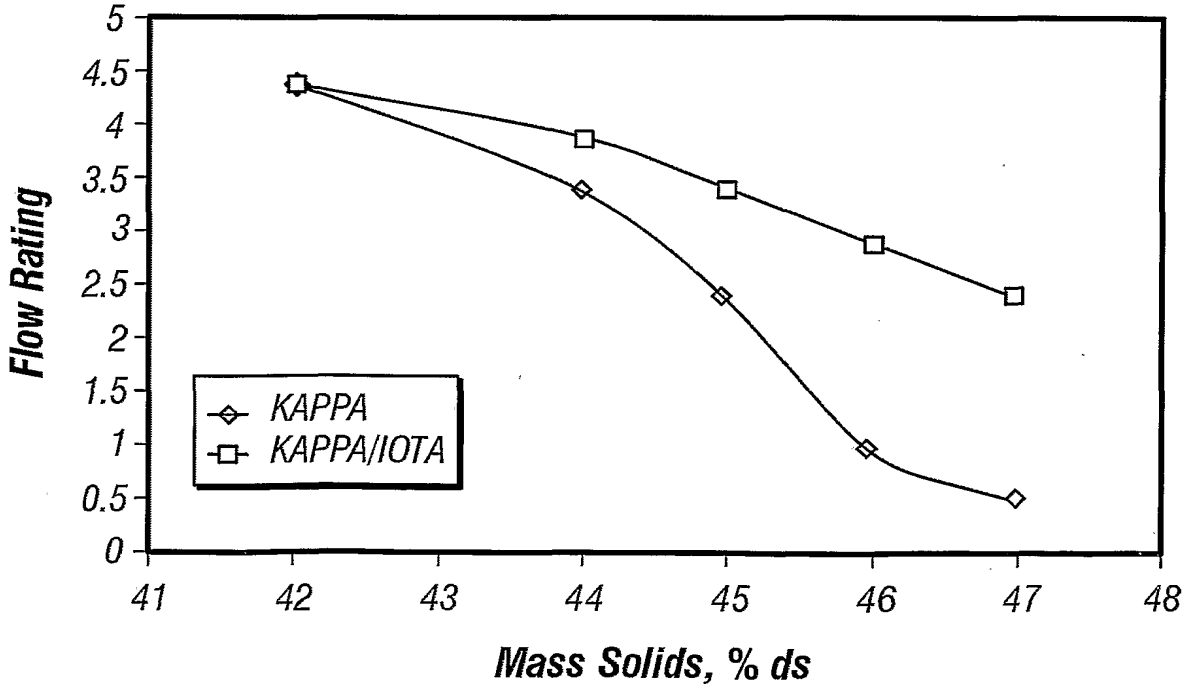
Flow Rating
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
0
41
42
43
44
45
46
47
48
KAPPA
KAPPA/IOTA
Mass Solids, % ds

FIG. 3

PCT WELTORGANISATION FÜR GEISTIGES EIGENTUM
Internationales Büro
INTERNATIONALE ANMELDUNG VERÖFFENTLICHT NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT)

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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.

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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

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* 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
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
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
		BE-A-	1000488	27-12-88
		CH-A-	676082	14-12-90
		CH-A-	672250	15-11-89
		DE-A-	3701122	23-07-87
		DE-A-	3701123	23-07-87
		FR-A-	2593063	24-07-87
		FR-A-	2593064	24-07-87
		GB-A,B	2185399	22-07-87
		JP-A-	62223109	01-10-87
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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 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	

EPO FORM P0479

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

"L" Veröffentlichung, die geeignet ist, einen Prioritätsanspruch zweifelhaft erscheinen zu lassen, oder durch die das Veröffentlichungsdatum einer anderen im Recherchenbericht genannten Veröffentlichung belegt werden soll oder die aus einem anderen besonderen Grund angegeben ist (wie ausgeführt)

"O" Veröffentlichung, die sich auf eine mündliche Offenbarung, eine Benutzung, eine Ausstellung oder andere Maßnahmen bezieht

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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
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		CH-A-	676082	14-12-90
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		DE-A-	3701122	23-07-87
		DE-A-	3701123	23-07-87
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		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:					
Information:					
5	Foreign Reference	EP00200508B1.pdf	1585276 60e3e1b4f14ed765e1d3b31fd86530fdc19c7410	no	26
Warnings:					
Information:					
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:					
Information:					
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:					
Information:					
13	Foreign Reference	EP01110546A1.pdf	258701 89be4f073ba87b8a60de50db9104a365e798d797	no	15
Warnings:					
Information:					
14	Foreign Reference	WO00018365A2.pdf	2000559 72d873af5261f8f270862205113d9ac4294850c2	no	54
Warnings:					
Information:					
15	Foreign Reference	WO00042992A2.pdf	1666727 67e6cf45106e3a2c260d0898da2b4e044be5371e	no	44
Warnings:					
Information:					
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		

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/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

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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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(54) Title: COMPOSITIONS AND METHODS FOR TOPICAL ADMINISTRATION OF PHARMACEUTICALLY ACTIVE AGENTS

(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)	1 to 50	5 to 40	10 to 30
(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

17ß-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 Applicat... 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

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° Special categories of cited documents : [10]

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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/US 92/01730

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.

Device Having a Water-Soluble Pressure-Sensitive Adhesive for Emplacement in a Mucosa-Lined Body Cavity

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.

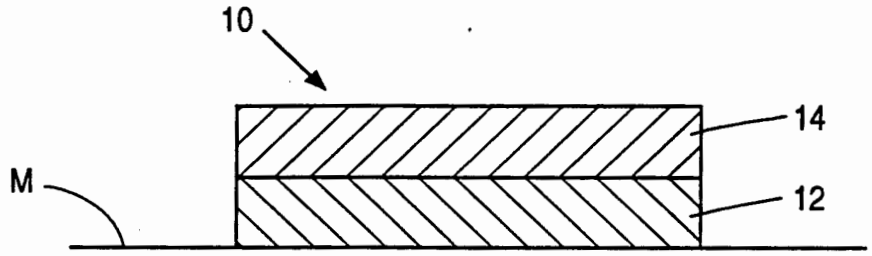


FIG. 1

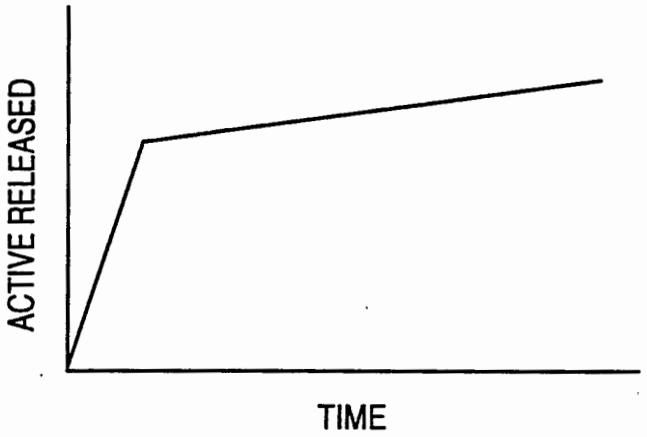


FIG. 5

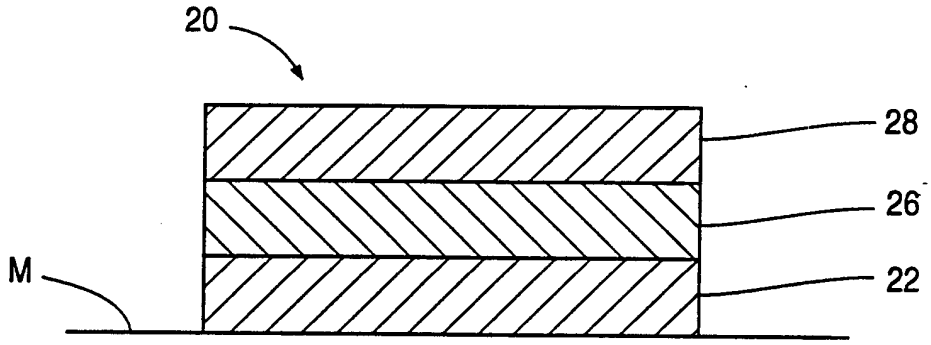


FIG. 2

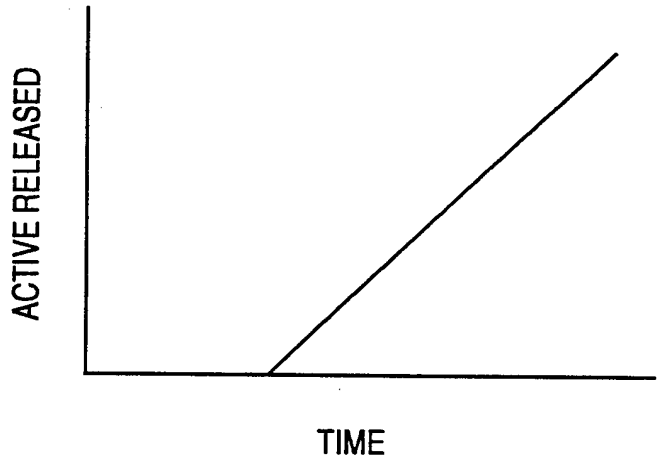


FIG. 6

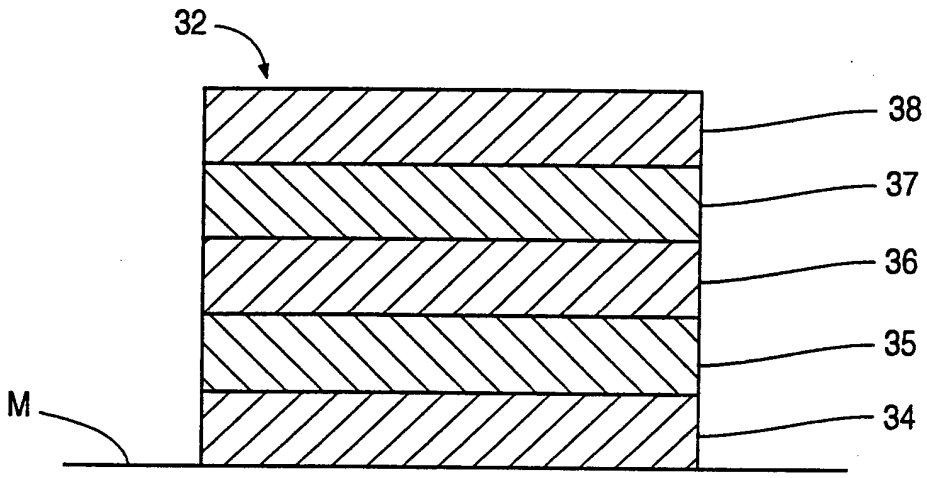


FIG. 3

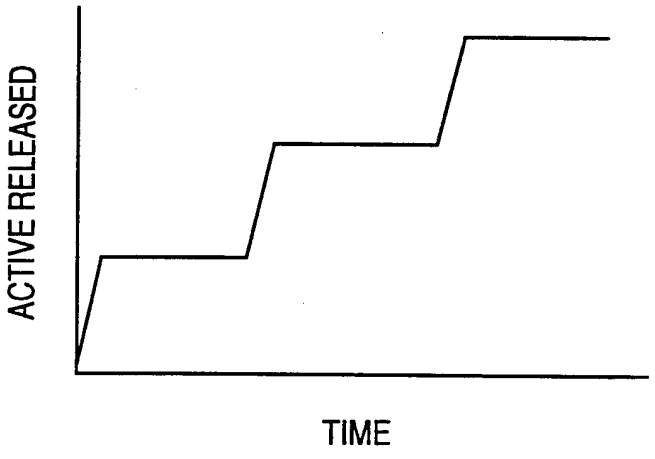


FIG. 7

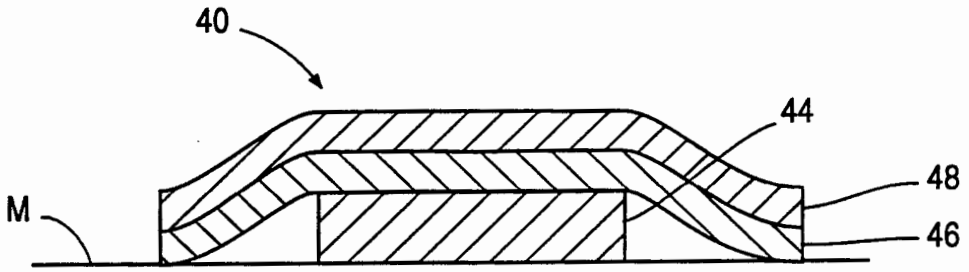


FIG. 4

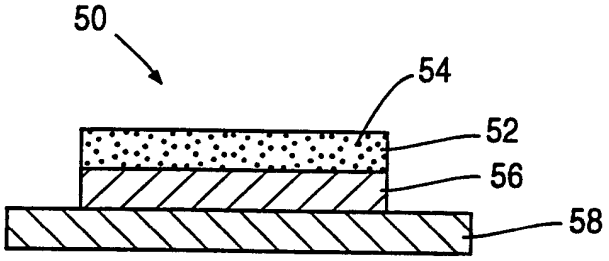


FIG. 8

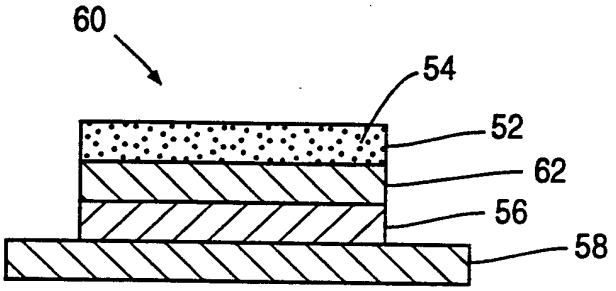
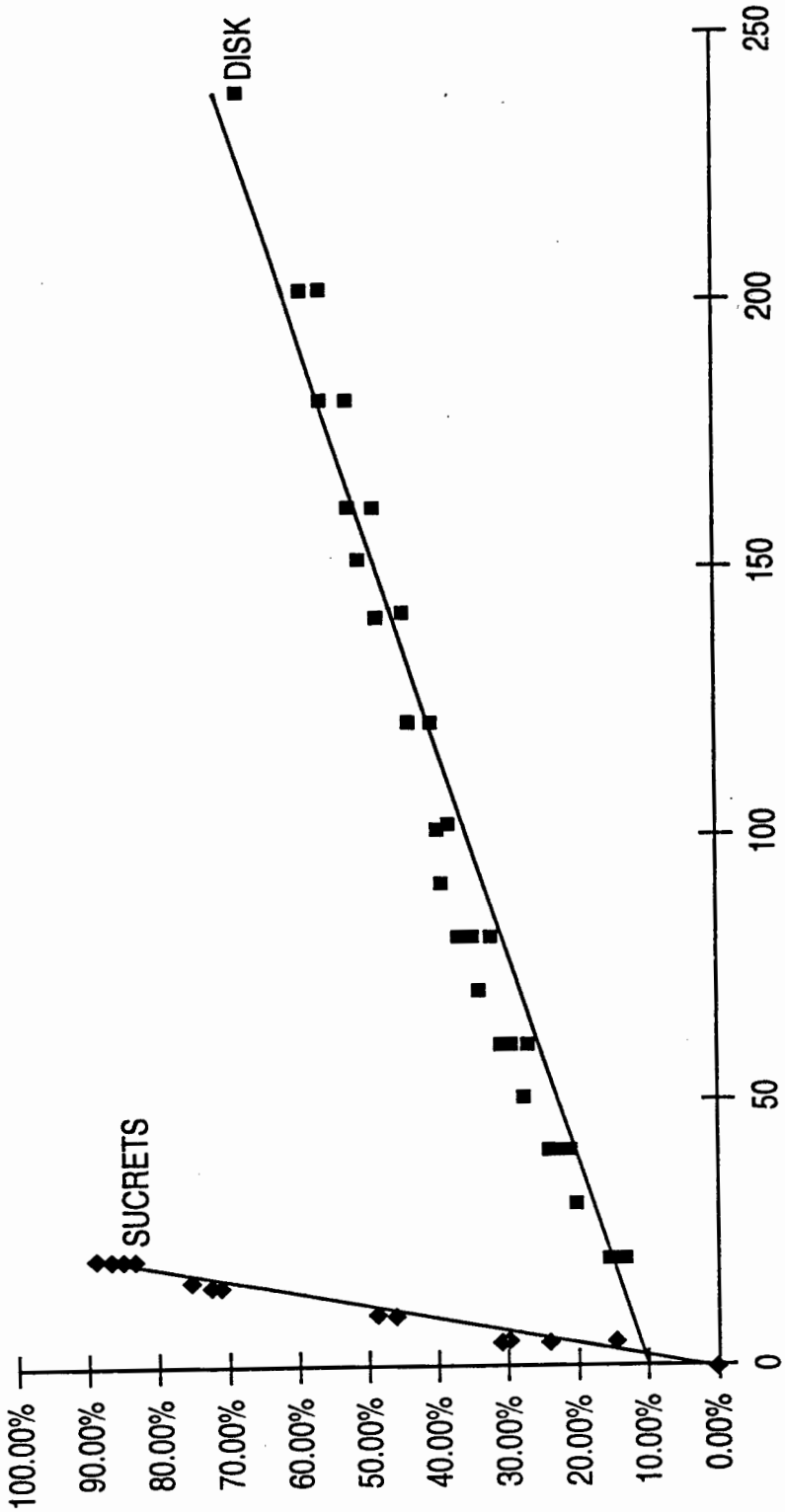


FIG. 9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SUCRETS
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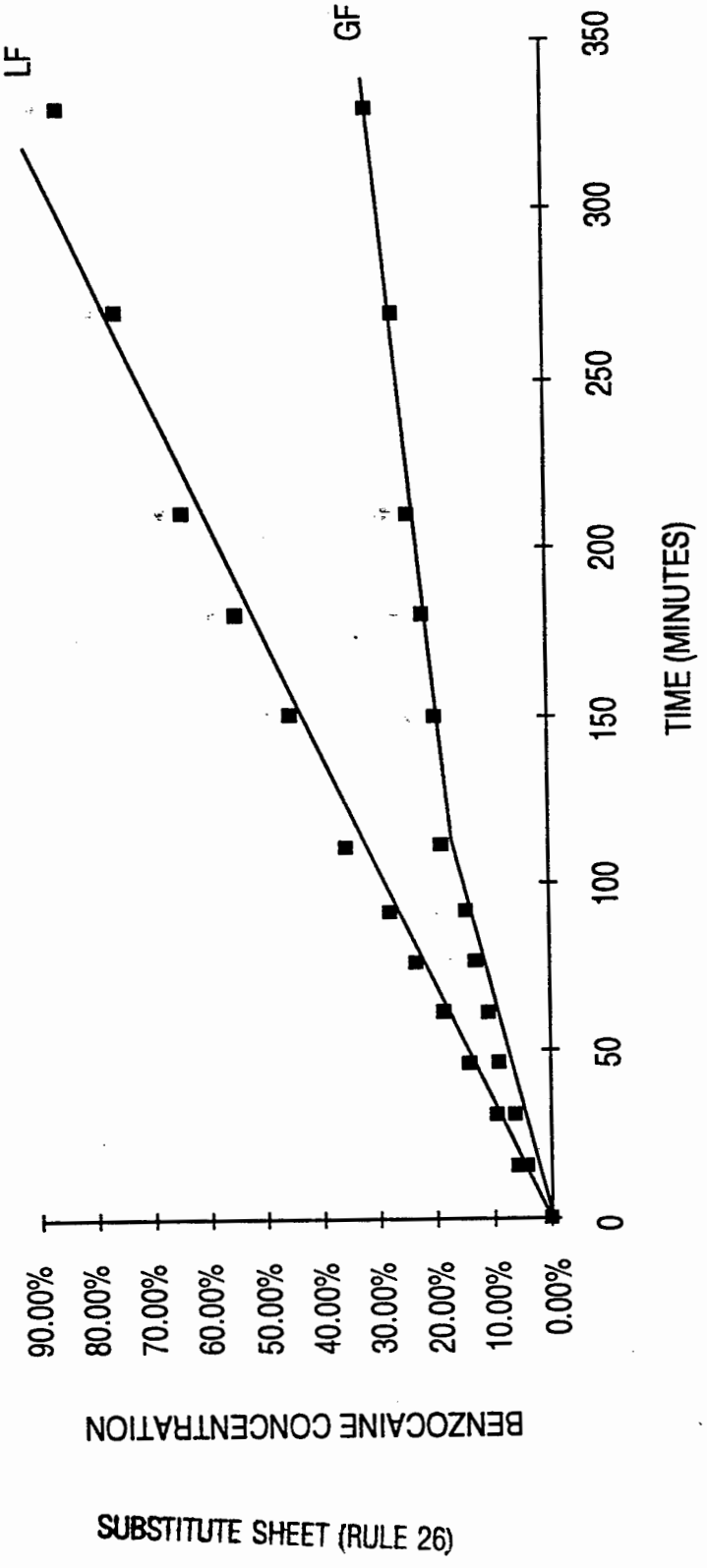
90.00%
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
0
50
100
150
200
250
TIME (MINUTES)
DYCLONINE CONCENTRATION

FIG. 10


LF
GF
0
50
100
150
200
250
300
350
TIME (MINUTES)
0.00%
10.00%
20.00%
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40.00%
50.00%
60.00%
70.00%
80.00%
90.00%
BENZOCAINE CONCENTRATION

FIG. 11

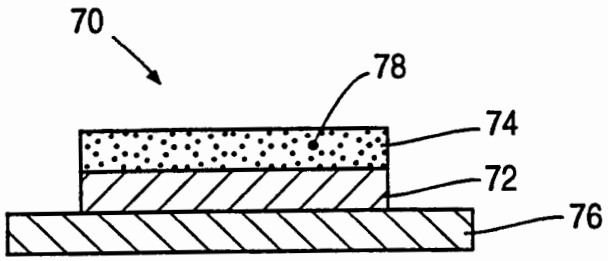

FIG. 12

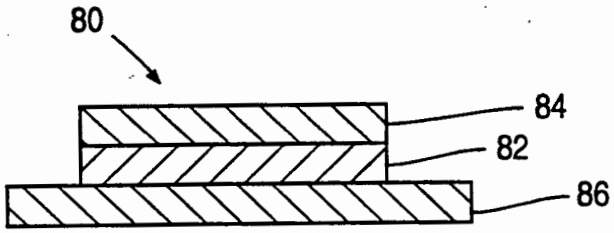

FIG. 13

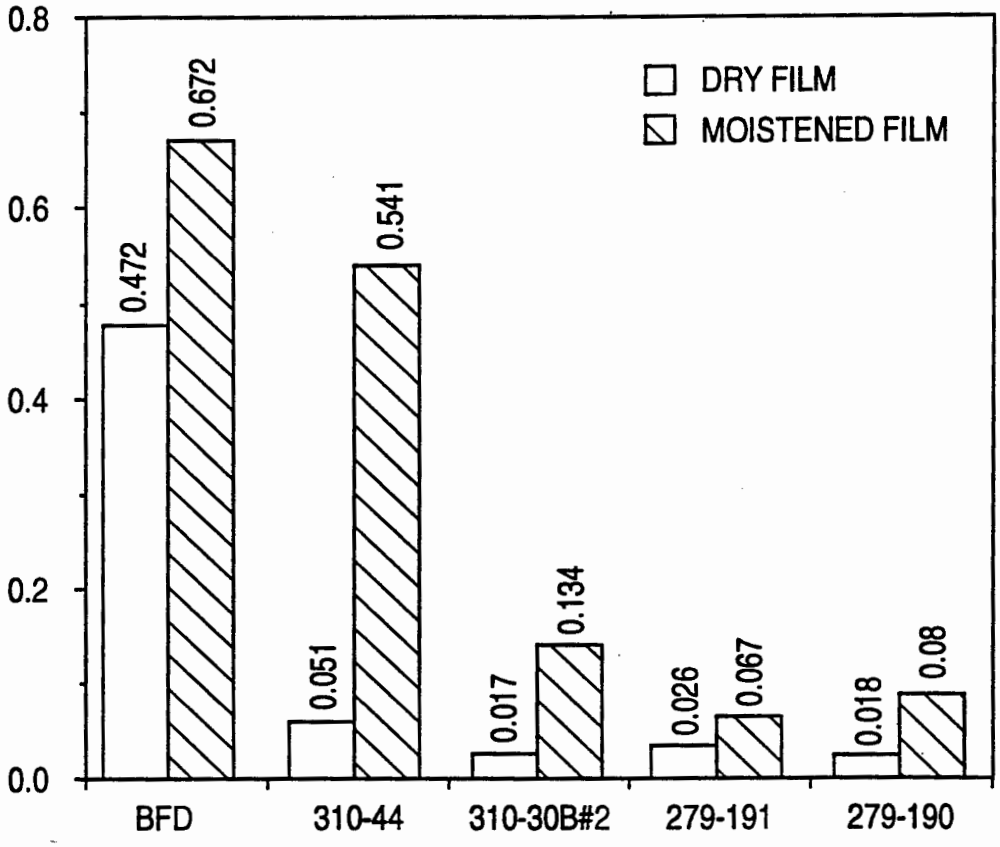
0.8
0.6
0.4
0.2
0.0
DRY FILM
MOISTENED FILM
0.472
0.672
0.051
0.541
0.017
0.134
0.026
0.067
0.018
0.08
BFD
310-44
310-30B#2
279-191
279-190

FIG. 14

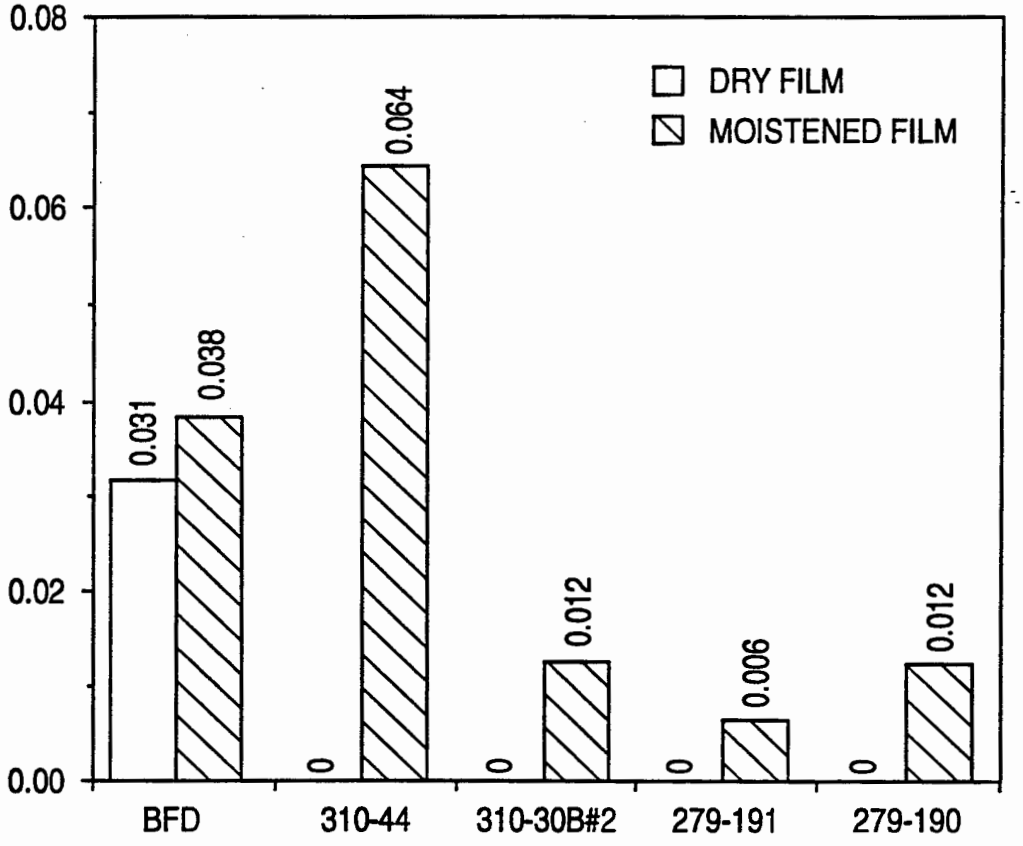
0.08
0.06
0.04
0.02
0.00
DRY FILM
MOISTENED FILM
0.031
0.038
0
0.064
0
0.012
0
0.006
0
0.012
BFD
310-44
310-30B#2
279-191
279-190

FIG. 15

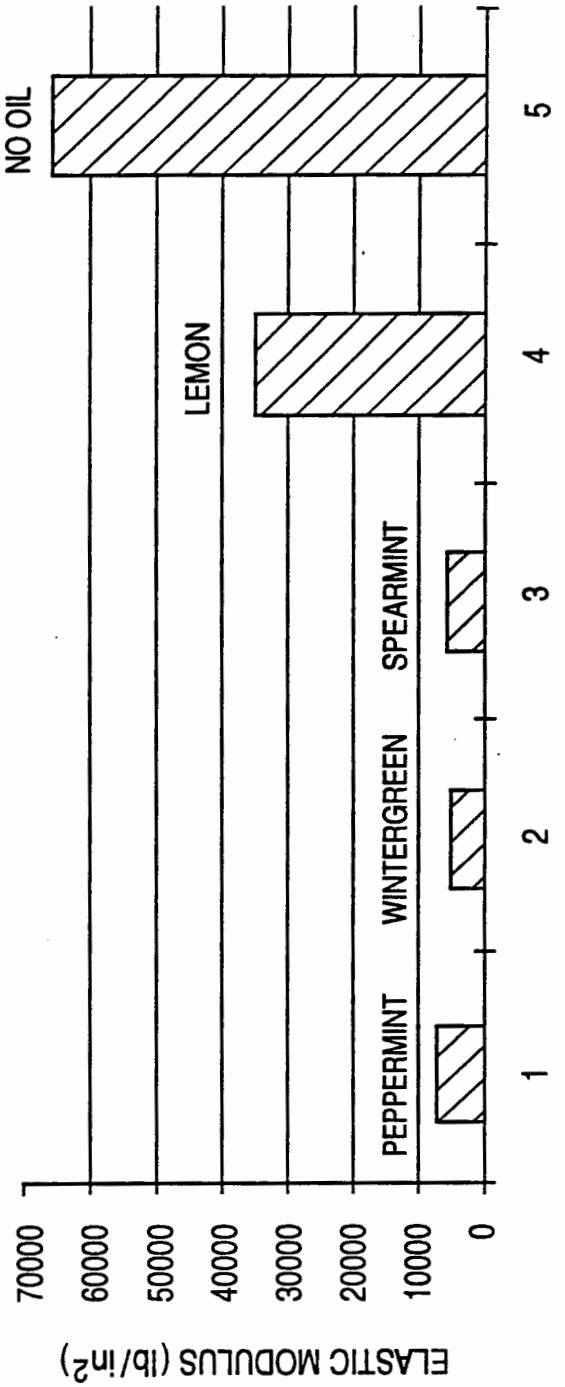
NO OIL
LEMON
PEPPERMINT
WINTERGREEN
SPEARMINT
1
2
3
4
5
70000
60000
50000
40000
30000
20000
10000
0
ELASTIC MODULUS (lb/in²)

FIG. 16

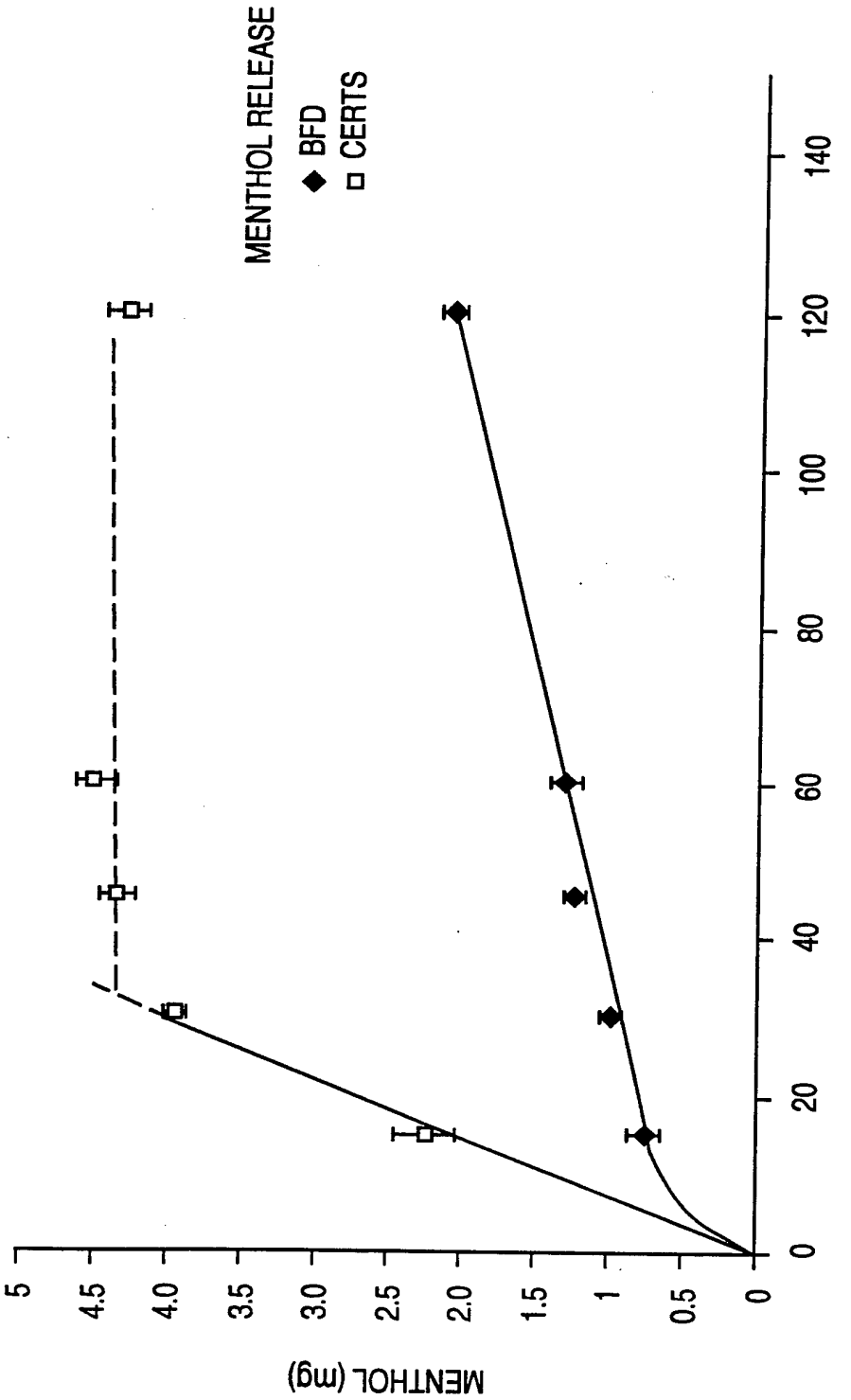
MENTHOL RELEASE
◆ BFD
□ CERTS
MENTHOL (mg)
0
0.5
1
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5
0
20
40
60
80
100
120
140
TIME (MINUTES)

FIG. 17

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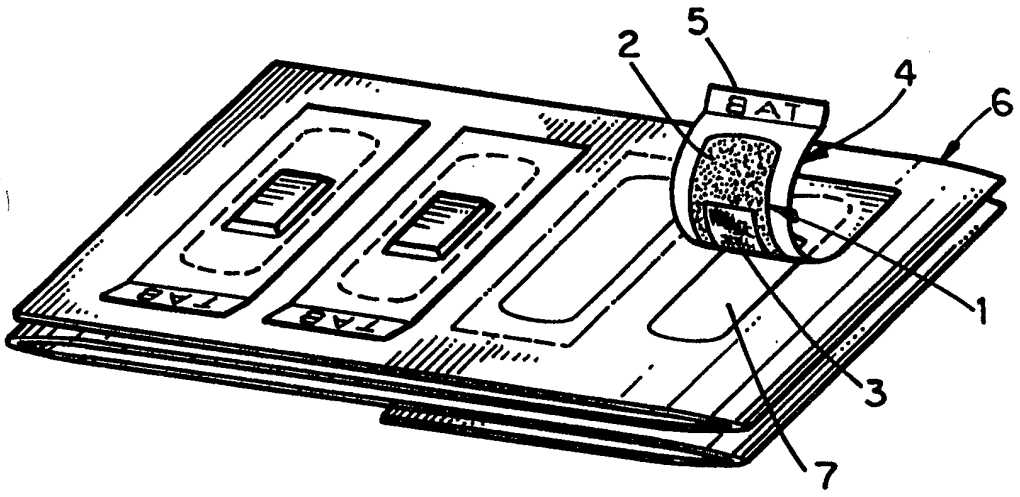

(57) Abstract

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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GA	Gabon				

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.

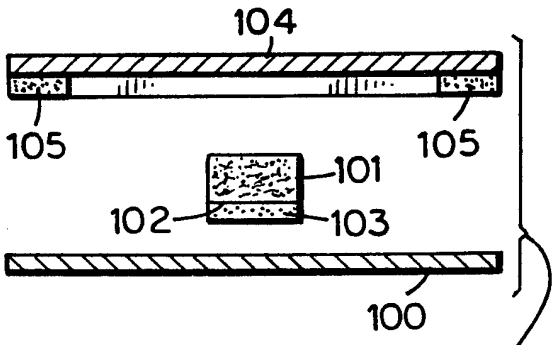


Fig. 1

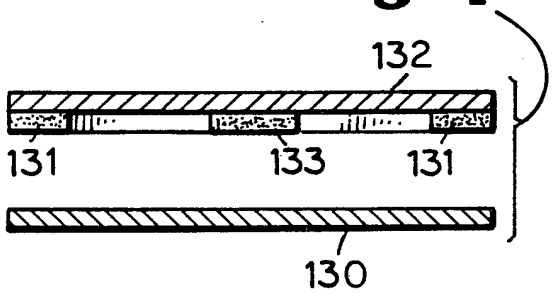


Fig. 4

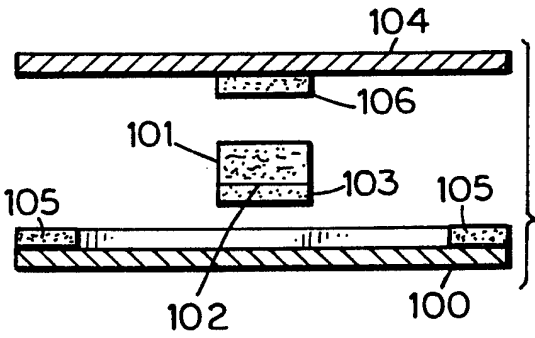


Fig. 2

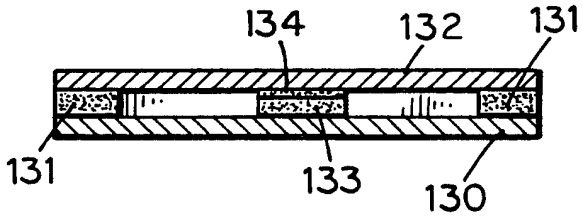


Fig. 5

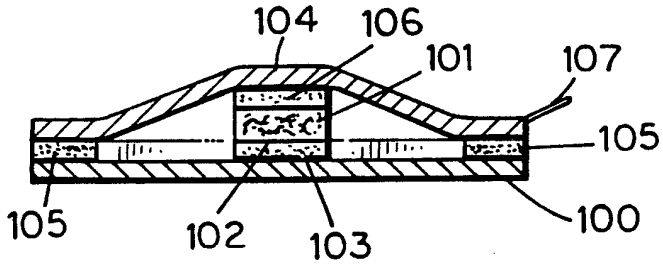


Fig. 3

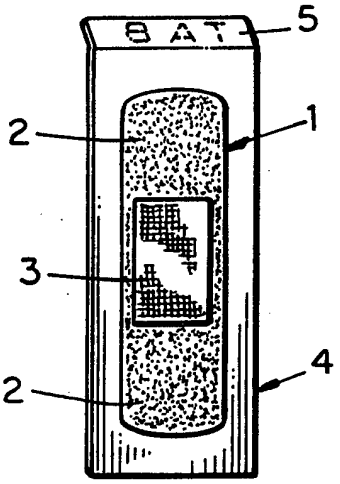


Fig. 6

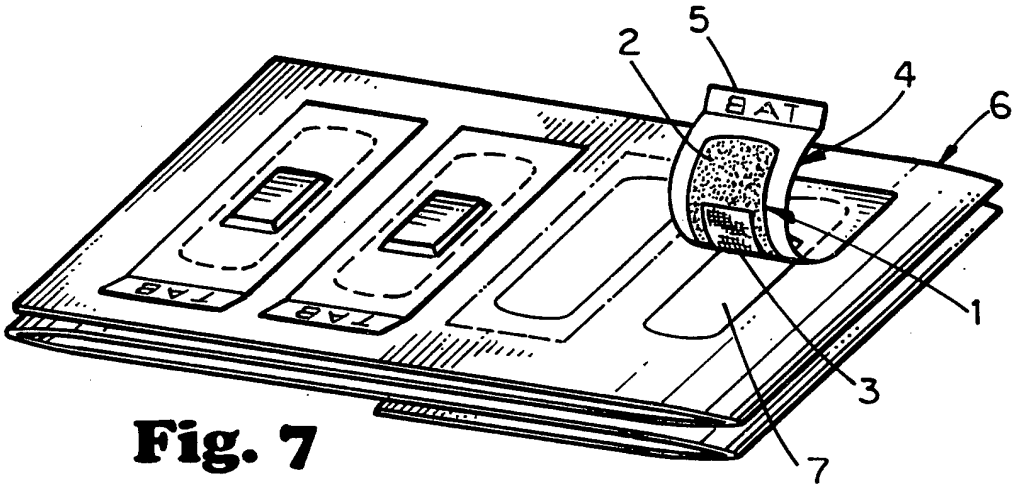


Fig. 7

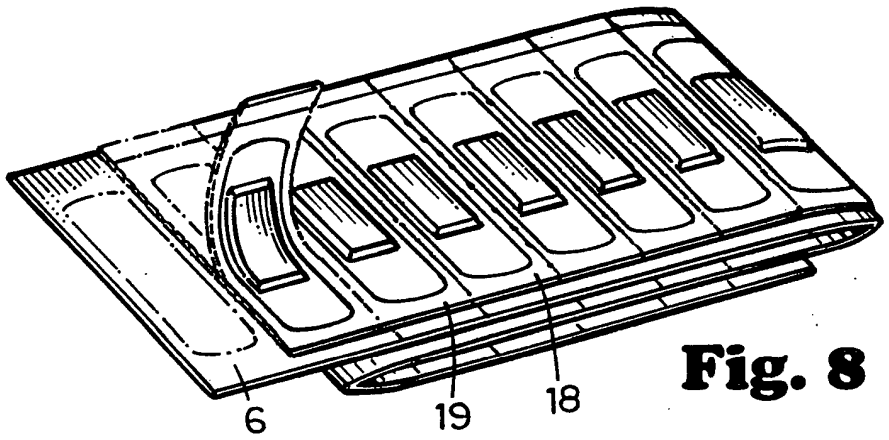


Fig. 8

Fig. 11

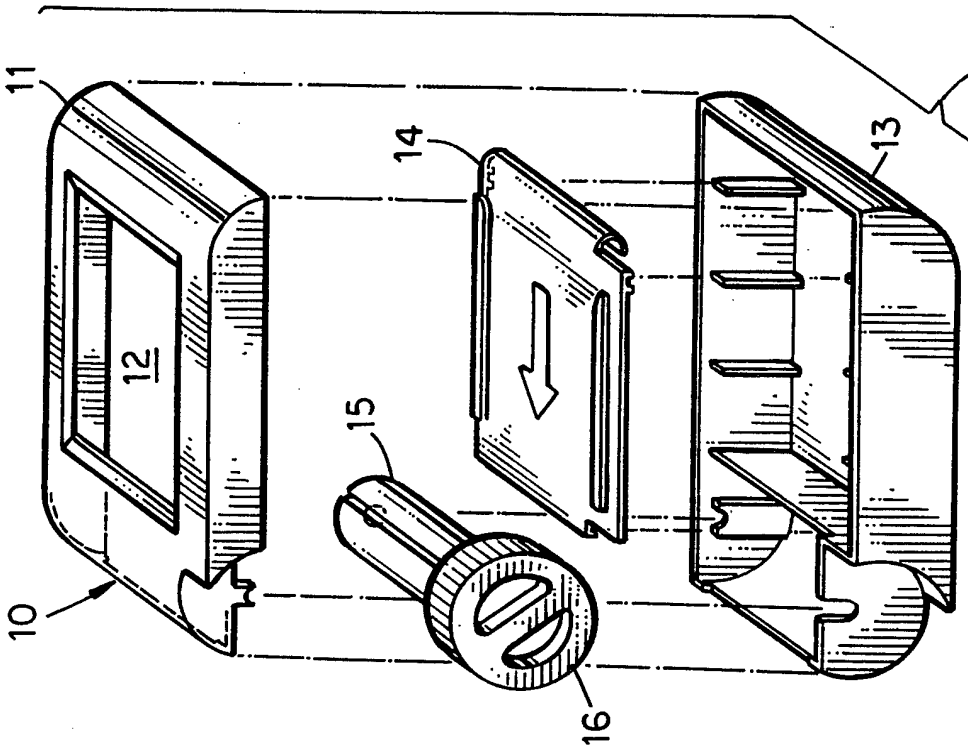


Fig. 9

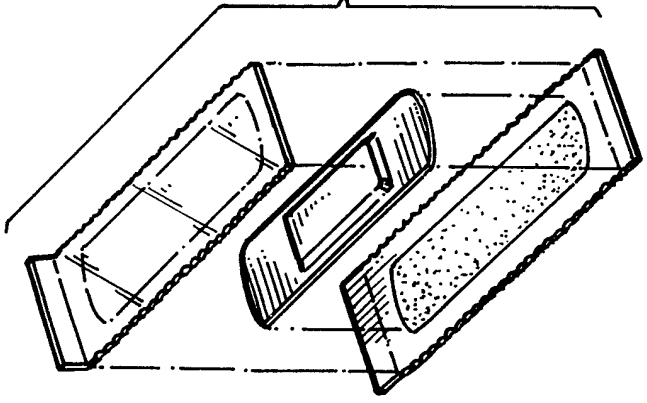
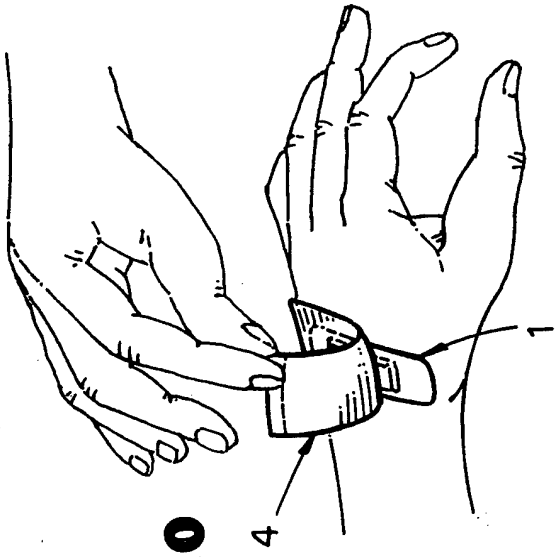


Fig. 10



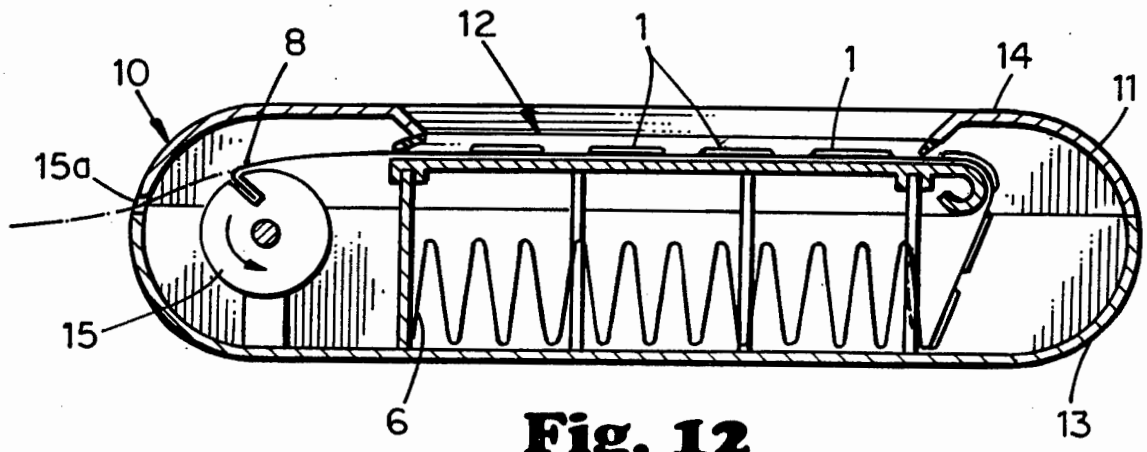


Fig. 12

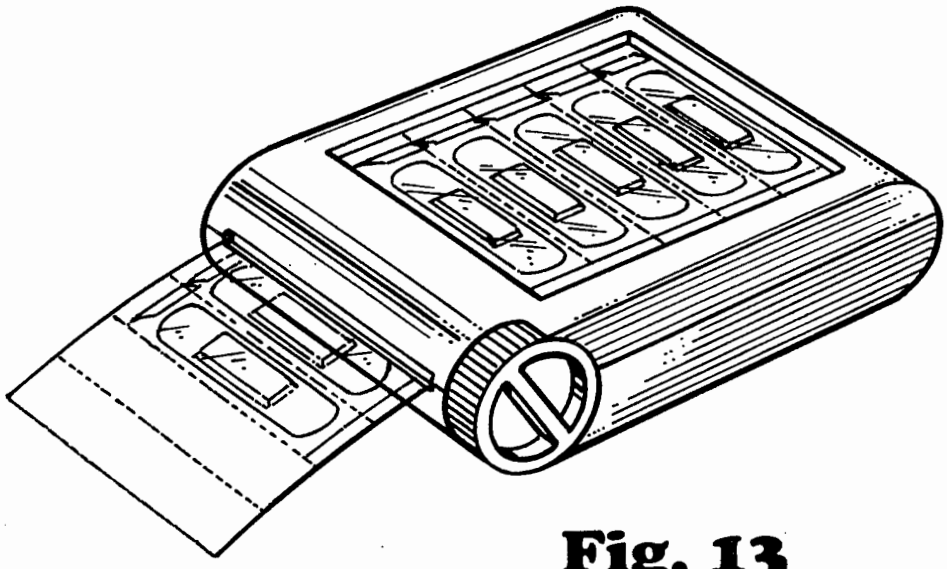


Fig. 13

Fig. 14

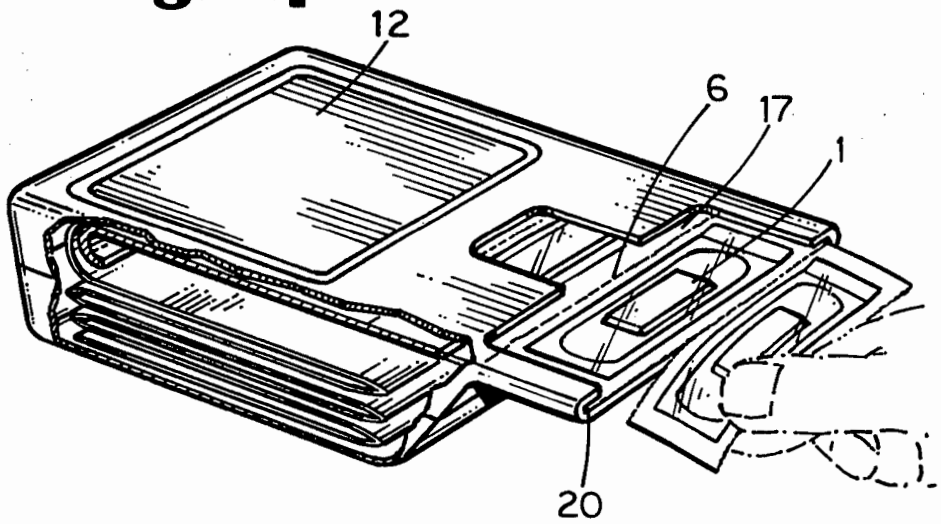


Fig. 15

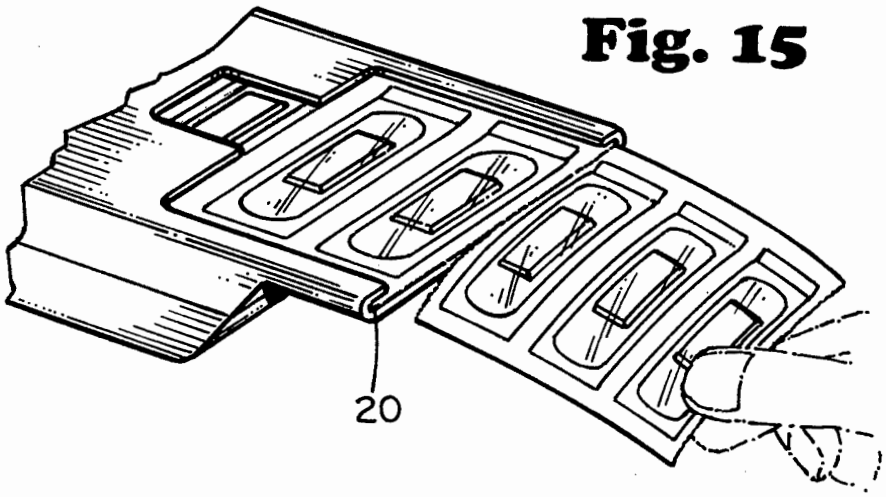
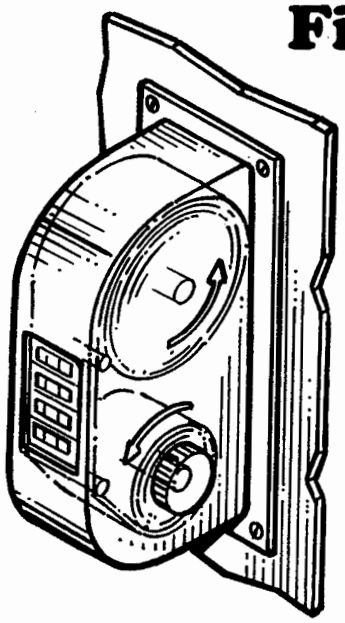


Fig. 16



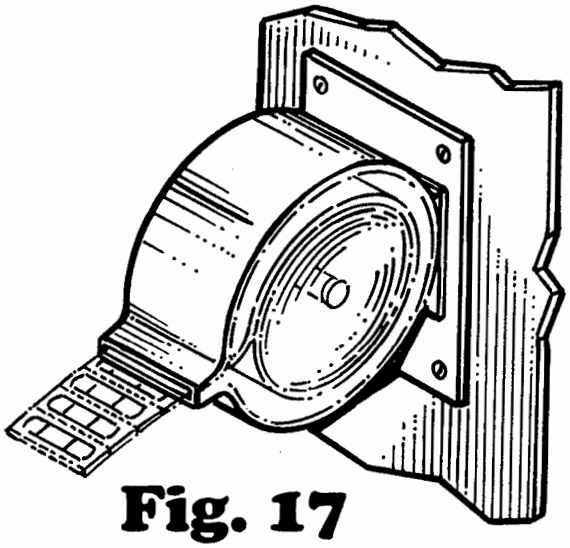


Fig. 17

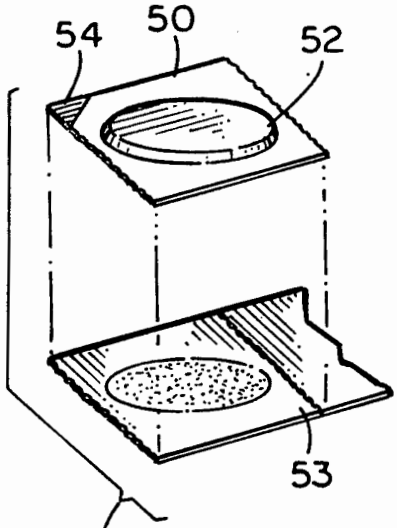


Fig. 18

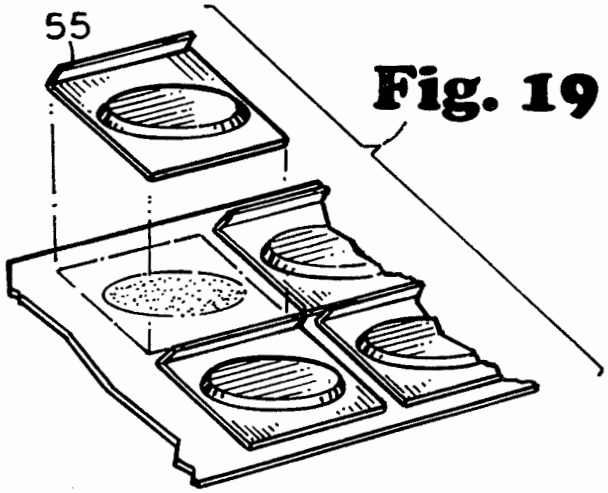


Fig. 19

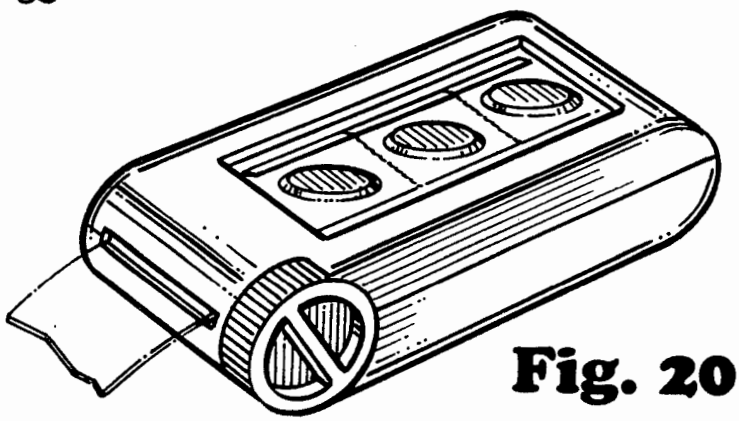
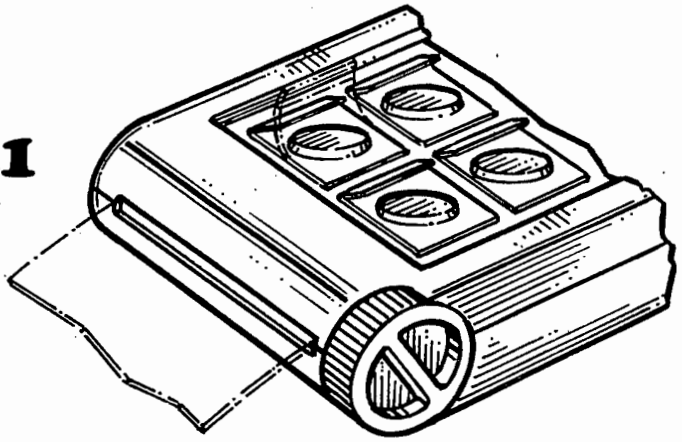


Fig. 20

Fig. 21



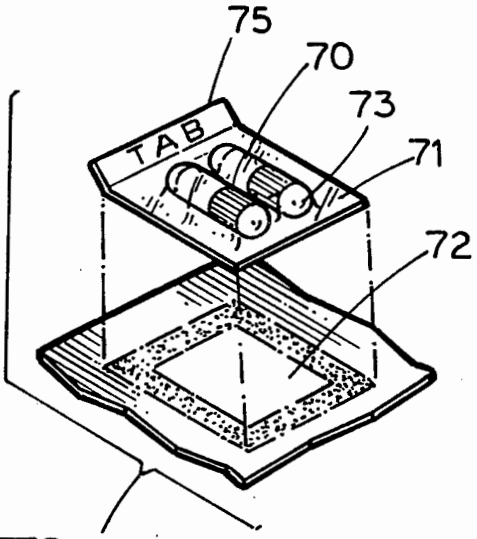


Fig. 22

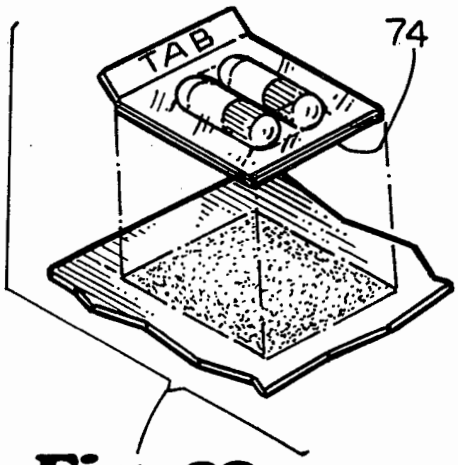


Fig. 23

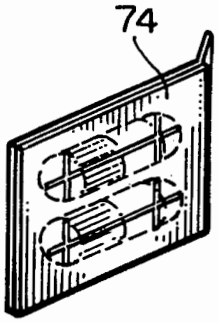


Fig. 24

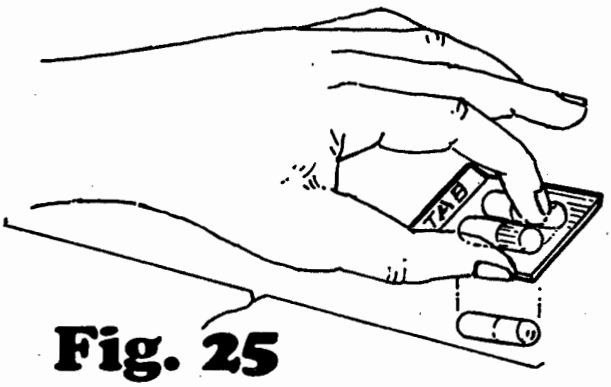


Fig. 25

Fig. 26

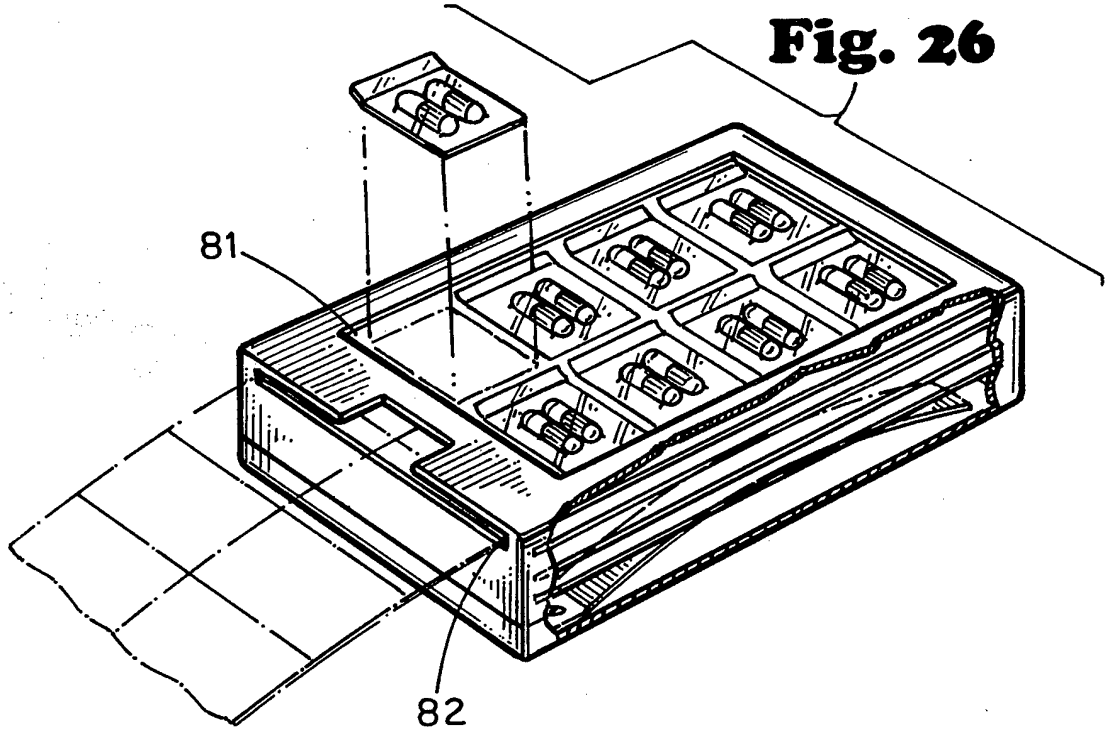
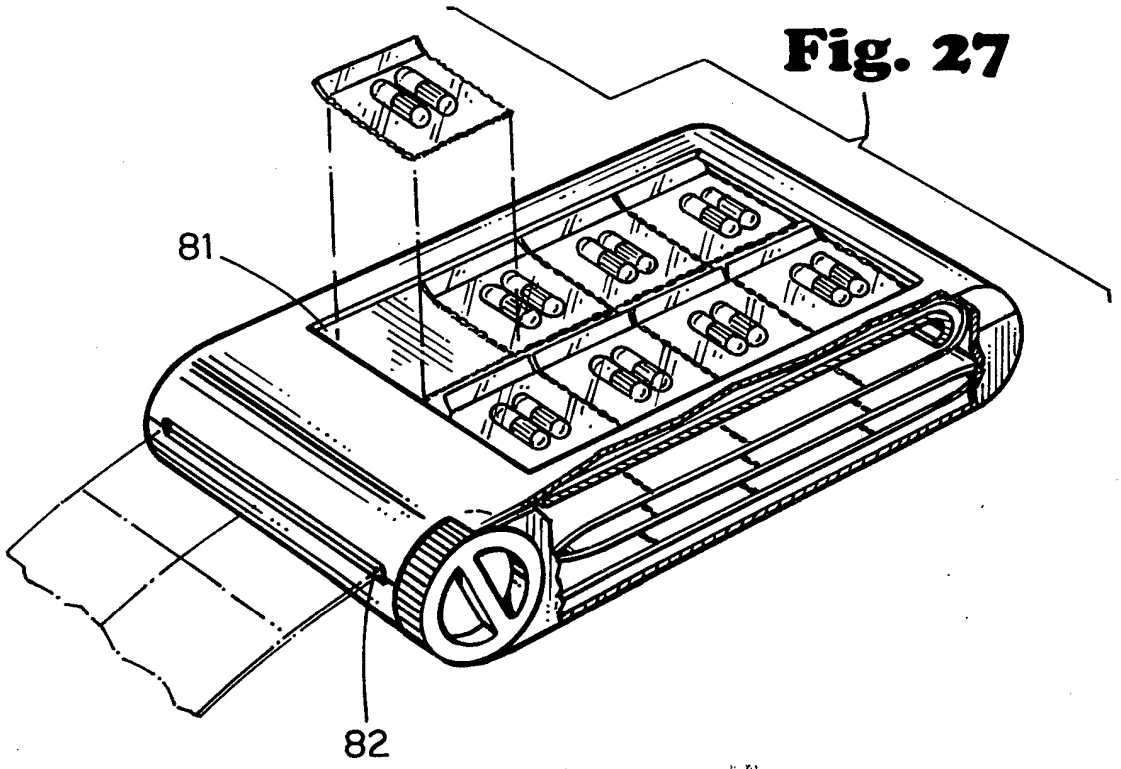


Fig. 27



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.

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"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
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer STEVE MEYERS Telephone No. (703) 308-0771 Sheila M. Veney Paralegal Specialist Group 2400

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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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B65D 1/09; A61B 19/08

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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(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.

WO 03/030882 A1

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,