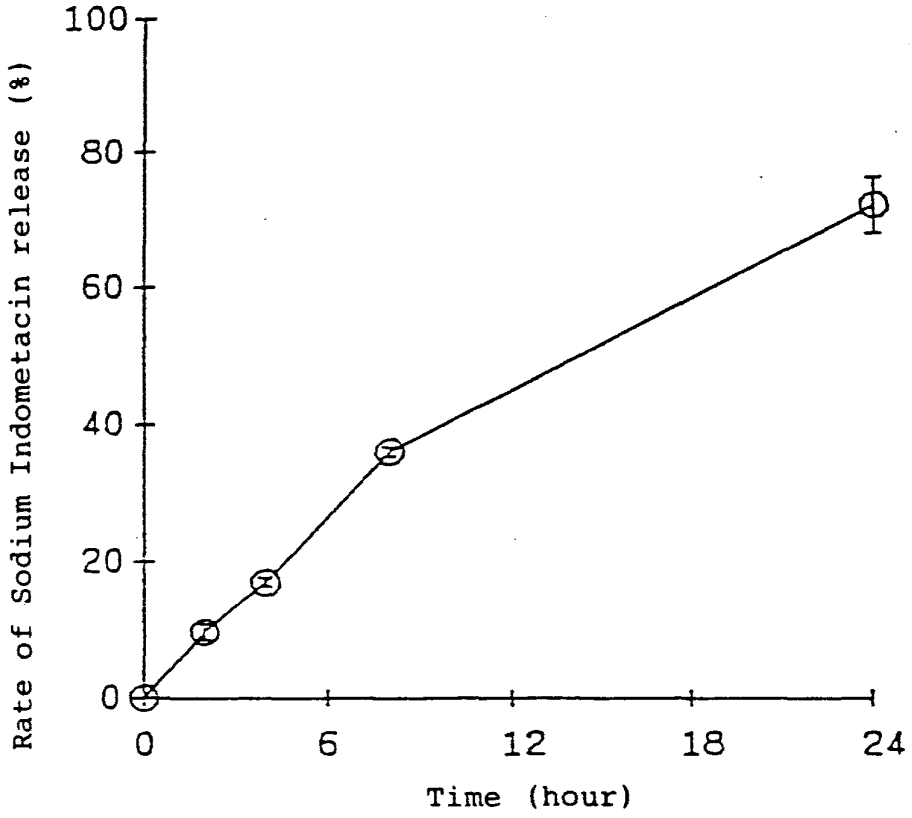
Figure 2


Rate of Sodium Indometacin release (%)
100
80
60
40
20
0
0
6
12
18
24
Time (hour)

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(54) **Sustained release with high and low viscosity HPMC.**

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WO-A-87/00044
FR-A- 2 555 901
US-A- 4 259 314
US-A- 4 389 393
US-A- 4 871 548

CHEMICAL ABSTRACTS, vol. 111, no. 16, 16th october 1989, page 393, abstract no.140370f, Columbus, Ohio, US; G. GEISSLINGER et al.: "Therapeutically relevant differences in the pharmacokinetic and pharmaceutical behavior of ibuprofen lysinate as compared to ibuprofen acid", & INT. J.CLIN. PHARMACOL., THER. TOXICOL 1989, 27(7), 324-8

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EP 0 440 462 B1

Description

BACKGROUND OF THE INVENTION

Sustained release formulations containing a pharmacologically active agent and exhibiting a zero order release rate are particularly useful.

Ibuprofen is a well-known analgesic which has been used to treat chronic pain such as that associated with arthritic and rheumatic conditions. In such cases the analgesic is best administered so as to sustain its action over a period of time and to have a uniform level of analgesic action over this extended time period. This objective can partly be achieved by the repeated administration of a rapid release dosage. However, this procedure clearly has patient acceptability problems as well as a repeated raising and lowering of the blood levels of analgesic.

Generally, the release profiles in controlled release formulations follow a classical square root of time relationship, i.e., the release rate decreases with time. In a zero order composition a plot of the rate of release of drug vs. time shows a straight horizontal line, i.e., the release rate is independent of time. Zero order sustained release compositions provide a more uniform delivery of the therapeutic agent over long periods of time.

Sustained release formulations for ibuprofen have been disclosed in EP publication 255,404, however the formulations disclosed do not provide for a zero order release rate. In WO 87/00044 a sustained release formulation, exhibiting a bimodal controlled release, is disclosed. The carrier base is composed of a bimodal hydroxypropylmethylcellulose (HPMC) and the medicament selected from an antiflammatory group such as flurbiprofen. The publication is silent on the formulation of zero order release compositions. The Boots Company PLC, EP 234,670 has disclosed a sustained release composition containing xanthan gum wherein the medicament may be ibuprofen. The Boots formulation does not solve the problem of a zero order release rate.

In FR-A-25555901 a controlled long acting dry pharmaceutical formulation comprised of at least three components selected from (a) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose; (b) 0.25 - 4.5% by weight of hydroxy components selected from (1) 5.5 - 98.5% by weight of hydroxypropyl methylcellulose or (2) 0.25 - 4.5% by weight of hydroxypropyl cellulose; and (c) 1-90% by weight of a carboxyvinyl polymer.

This reference discloses that it is the combination of these 3 elements which is critical to the disclosed invention and it does not disclose that varying the ratio of the high density HPMC to the low density HPMC will affect the delivery characteristics of the system but rather suggests that varying the relative amount of the hydroxypropyl methyl cellulose and hydroxypropyl cellulose and carboxyvinyl polymer elements will affect the delivery rate. Nowhere does this reference disclose a mixture comprising a HPMC having a molecular weight of 60,000 or greater together with a HPMC having a molecular weight of 50,000 or less. US-A-4389393 discloses a sustained release rate formulation wherein the ratio between high molecular weight HPMC and low molecular weight HPMC is 45.5:19.5 or 1:0.4. Furthermore, the formulation of this reference shows a significant % drop of released medicant after only 8 hours. US-A-4259314 discloses a method of producing a controlled long acting pharmaceutical composition wherein hydroxypropyl cellulose is considered an essential ingredient. In fact, the reference specifically discloses that the inadequacy of hydroxypropyl methylcellulose for use in long lasting troches is known. WO-A-8700044 discloses non-zero order formulations which can be achieved only by using the disclosed highly unusual biomodal HPMCs (B-HPMCs). US-A-4871548 discloses particular combinations comprising a "low number average molecular weight hydroxypropy methyl cellulose ether" having an average molecular weight of from about 9,000 to 30,000 and viscosities ranging from 3-106 and a "high number average molecular weight hydroxypropyl methyl cellulose" having an average molecular weight of 30,000 to 350,000 and viscosities ranging from 1,500 to 220,000. The ratio of the high and low molecular weight MPCs disclosed in the formulations of this reference is 1:1. Furthermore, these formulations employ an additional ingredient - lactose.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a carrier base material for therapeutically active medicaments in a solid dosage formulation wherein

the carrier base comprises:

a) a high viscosity HPMC; and

b) a low viscosity HPMC wherein the high and low viscosity HPMC are in a ratio yielding a zero order release profile for the medicament.

In the present invention it has unexpectedly been found that a zero-order release profile can be obtained by controlling the ratio of high to low viscosity HPMC in a carrier base formulation.

A high viscosity HPMC is defined as one having a molecular weight of 60,000 or greater. A low viscosity HPMC is defined as one having a molecular weight of 50,000 or less.

The preferred low viscosity HPMCs available as Dow Methocel cellulose ethers, are: E5, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4-6 cP; E15LV, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 12-18 cP; E50LV, 28-30% methoxy, 7-12% hydroxylpropyl, viscosity = 40-60; and K100LV, 19-24% methoxy 7-12% hydroxypropyl, viscosity = 100 cP. The preferred high viscosity HPMCs, available as Dow Methocel cellulose ethers are: E4M-CR, 28-30% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; E10M-CR, 28-30% methoxy, 7-12% hydroxypropyl viscosity = 10,000 cP; K4M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 4000 cP; K15M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 15,000 cP; and K100M, 19-24% methoxy, 7-12% hydroxypropyl, viscosity = 100,000 cP.

The medicament in the present invention may be selected from ibuprofen, or salts of ibuprofen. Most preferably the medicament is ibuprofen lysine which should be taken to mean all stereoisomeric configurations including racemic ibuprofen lysine and (S)-ibuprofen-(S)-lysine;i.e. the salt formed from (S)-ibuprofen and (S)-lysine.

It should be appreciated that a zero order release profile is obtained only with a certain relative range of high to low viscosity HPMC. This may be illustrated by the combination of 1 part high viscosity E10M CR and a varying amount of any of the preferred low viscosity HPMC wherein a zero order release was found, for example:

(i) 1 part E10M CR: 3 parts E5;
(ii) 1 part E10M CR: 2 to 4 parts E15LV;
(iii) 1 part E10M CR: 3 to 9 parts E5OLV;
(iv) 1 part E10M CR: 3 to 9 parts K100LV.

These ranges are not limited to combinations where the high viscosity HPMC is E10M CR but are to be expected with any of the other preferred high viscosity HPMC.

The medicament, preferably ibuprofen lysine is mixed with Povidone USP (PVP) which functions as a binding agent. Typically the ratio of drug to PVP is 20:1.

The percent of drug/PVP granules in the pharmaceutical composition is 33.3 to 83%.

The range of ibuprofen in this invention is preferably 100 to 600 mg per tablet.

Where the medicament is ibuprofen lysine the weight range is 100 to 600 mg measured in mg ibuprofen.

The percent range of HPMC carrier base is 17-66%.

An example of the composition and processing of the controlled release dosage form is provided below:

Composition:

Ibuprofen Lysine	61.8%
PVP	3.0%
Carrier Base	34.1%
Magnesium Stearate	1.0%
	Total 99.9%

Fillers such as Avicel, lactose, manitol, dicalcium phosphate, starch or pregelatin starch 1500 may be added to the composition. Binders such as corn starch, pregelatin starch 1500, Klucel LF, methocel E3, E5, gelatin or acacia may be added as necessary by those skilled in the art. Besides magnesium stearate, other lubricants such as stearic acid, sodium stearate fumerate or calcium stearate may be employed.

Processing

A batch of ibuprofen lysine granules containing PVP was prepared. An appropriate amount of granules, typically 3.21 grams was removed and mixed in a V-blender for 10 minutes with a carrier base, usually 1.71 grams, chosen from the preferred high viscosity and low viscosity HPMC. The resultant mixture was then mixed in a V-blender for three minutes with magnesium stearate, which had previously been sieved through a #60 mesh screen. Tablets of about 980 mg were compressed on an F-press.

Tables I-V provide release profiles for controlled release tablets prepared following the processing described above and containing 600 mg Ibuprofen Lysine and 330 mg carrier base. Dissolution determinations were conducted using an automated dissolution testing unit such as a Beckman Spectrophotometer, model DU65, connected with a Vanderkamp 600 six-spindle dissolution tester. Samples were taken every hour for at least 12 to 24 hours and absorbance was read spectrophotometrically at 260 nm.

All the HPMC polymers described are available from the Dow Chemical Company. Racemic ibuprofen lysine may be prepared following the description in U.S. Patent 4,279,926. (S)-ibuprofen-(S)-lysine is prepared as described in copending application S.N. 422,466 filed October 18, 1989.

TABLE I

Release Profiles of Ibuprofen Lysine Using 25% E4MCR and 75% of a Low Viscosity HPMC			
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE	75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000
1	0.1125	0.1160	0.0820
2	0.1885	0.1935	0.1400
3	0.2570	0.2615	0.1940
4	0.3180	0.3230	0.2440
5	0.3735	0.4080	0.2920
6	0.4265	0.5290	0.3375
7	0.4945	0.6265	0.3860
8	0.5975	0.6820	0.4445
9	0.6855	0.7190	0.5045
10	0.7280	0.7405	0.5750
11	0.7520	0.7555	0.6350
12	0.7540	0.7620	0.6845
13	0.7500	0.7675	0.7225
14	0.7445	0.7680	0.7515
15	0.7405	0.7670	0.7695
16			0.7785
17			0.7825
18			0.7835
19			
20			
21			
22			
23			
24			

TABLE II

Release Profiles of Ibuprofen Lysine Using Various Ratios of E10MCR and a Low Viscosity HPMC

Time [hr]	25% E10MCR: 75% E5 MEAN ABSORBANCE	33.3% E10MCR: 66.7% E15LV MEAN ABSORBANCE	20% E10MCR: 80% E15LV MEAN ABSORBANCE
0	0.0000	0.0010	0.0010
1	0.0985	0.1140	0.1615
2	0.1670	0.1720	0.2420
3	0.2335	0.2210	0.3130
4	0.3055	0.2630	0.3760
5	0.3960	0.3050	0.4345
6	0.4800	0.3450	0.5265
7	0.5630	0.3840	0.5975
8	0.6505	0.4220	0.6525
9	0.6875	0.4600	0.7095
10	0.7165	0.4970	0.7475
11	0.7235	0.5345	0.7565
12	0.7255	0.5835	0.7590
13	0.7260	0.6410	0.7600
14	0.7245	0.6915	0.7575
15	0.7240	0.7230	0.7530
16	0.7240	0.7395	0.7525
17	0.7240	0.7425	0.7520
18	0.7245	0.7435	0.7520
19	0.7255	0.7455	
20	0.7265	0.7440	
21	0.7275	0.7420	
22	0.7290	0.7420	
23	0.7290	0.7410	
24	0.7310	0.7395	

TABLE II Cont'd

Time [hr]	25% E10MCR 75% E50 MEAN ABSORBANCE	10% E10MCR 90% E50LV MEAN ABSORBANCE	25% E10MCR 75% K100LV MEAN ABSORBANCE	10% E10MCR 90% K100LV MEAN ABSORBANCE
0	0.0000	0.0005	0.0000	0.0005
1	0.1095	0.1250	0.0790	0.1120
2	0.1855	0.1960	0.1360	0.1775
3	0.2570	0.2540	0.1845	0.2325
4	0.3220	0.3065	0.2300	0.2845
5	0.3870	0.3580	0.2715	0.3325
6	0.4505	0.4110	0.3125	0.3825
7	0.5140	0.4810	0.3525	0.4360
8	0.5780	0.5475	0.3905	0.4900
9	0.6220	0.5990	0.4305	0.5595
10	0.6645	0.6525	0.4730	0.6235
11	0.7020	0.6885	0.5210	0.6785
12	0.7255	0.7080	0.5685	0.7170
13	0.7395	0.7200	0.6045	0.7365
14	0.7510	0.7275	0.6415	0.7390
15	0.7560	0.7310	0.6715	0.7370
16	0.7600	0.7290	0.6905	0.7360
17	0.7630	0.7260	0.7080	0.7340
18	0.7650	0.7260	0.7225	0.7360
19	0.7670		0.7345	
20	0.7680		0.7395	
21	0.7700		0.7440	
22	0.7725		0.7450	
23	0.7740			
24	0.7755			

TABLE III

Release Profiles of Ibuprofen Lysine Using Various Ratios of K4M and a Low Viscosity HPMC				
Time [hr]	50% K4M 50% E5 MEAN ABSORBANCE	25% K4M 75% E15LV MEAN ABSORBANCE	25% K4M 75% E5 MEAN ABSORBANCE	25% K4M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1155	0.1010	0.0995	0.0815
2	0.1795	0.1700	0.1565	0.1390
3	0.2315	0.2335	0.2110	0.1895
4	0.2815	0.2905	0.2630	0.2365
5	0.3655	0.3490	0.3130	0.2815
6	0.4095	0.4360	0.4395	0.3260
7	0.4465	0.5510	0.5270	0.3705
8	0.4925	0.6430	0.5815	0.4225
9	0.5695	0.6990	0.6305	0.4850
10	0.6550	0.7405	0.6580	0.5435
11	0.7045	0.7560	0.6775	0.6000
12	0.7235	0.7565	0.6950	0.6500
13	0.7360	0.7515	0.7060	0.6740
14	0.7400	0.7445	0.7175	0.6920
15	0.7460	0.7415	0.7245	0.7040
16	0.7535	0.7450	0.7260	0.7220
17	0.7525	0.7435	0.7275	0.7315
18	0.7555	0.7415	0.7270	0.7380
19	0.7605	0.7405	0.7305	
20	0.7605	0.7400	0.7305	
21	0.7650	0.7425	0.7320	
22	0.7635		0.7310	
23	0.7660			
24				

TABLE IV

Release Profiles of Ibuprofen Lysine Using Various Ratios of K15M and a Low Viscosity HPMC				
Time [hr]	25% K15M 75% E5 MEAN ABSORBANCE	25% K15M 75% E15LV MEAN ABSORBANCE	25% K15M 75% E50 MEAN ABSORBANCE	25% K15M 75% K100LV MEAN ABSORBANCE
0	0.0000	0.0000	0.0000	0.0000
1	0.1280	0.0935	0.0855	0.0950
2	0.2110	0.1540	0.1425	0.1640
3	0.2830	0.2085	0.1915	0.2225
4	0.3640	0.2590	0.2390	0.2740
5	0.4350	0.3070	0.2810	0.3215
6	0.5060	0.3530	0.3265	0.3665
7	0.6475	0.3980	0.3970	0.4120
8	0.7215	0.4470	0.4890	0.4575
9	0.7360	0.5505	0.5535	0.5040
10	0.7415	0.6200	0.5945	0.5485
11	0.7410	0.6655	0.6125	0.5910
12	0.7395	0.6815	0.6400	0.6245
13	0.7435	0.6850	0.6590	0.6490
14	0.7475	0.7040	0.6910	0.6650
15	0.7490	0.7250	0.7085	0.6845
16	0.7520	0.7365	0.7295	0.7035
17	0.7505	0.7395	0.7395	0.7160
18	0.7515	0.7390	0.7400	0.7235
19	0.7485	0.7405	0.7330	0.7305
20	0.7525	0.7405	0.7355	0.7345
21	0.7500	0.7360	0.7255	0.7385
22				0.7415

TABLE V

Release Profiles of Ibuprofen Lysine Using 25% K100M and 75% of a Low Viscosity HPMC		
Time [hr]	75% E15LV MEAN ABSORBANCE	75% E50 MEAN ABSORBANCE
0	0.0000	0.0000
1	0.0820	0.1005
2	0.1330	0.1615
3	0.1800	0.2180
4	0.2225	0.2680
5	0.2630	0.3150
6	0.3025	0.3630
7	0.3405	0.4230
8	0.3805	0.4950
9	0.4240	0.5465
10	0.4880	0.5940
11	0.5510	0.6350
12	0.5945	0.6715
13	0.6335	0.7000
14	0.6650	0.7215
15	0.6950	0.7370
16	0.7195	0.7485
17	0.7395	0.7575
18	0.7530	0.7655
19	0.7680	0.7710
20	0.7740	0.7755
21	0.7795	0.7770
22	0.7825	0.7785
23		0.7800
24		0.7820

Claims

1. A carrier base material combined with ibuprofen or a salt thereof and shaped and compressed to a solid sustained release pharmaceutical dosage form having a zero order release profile upon administration in which the carrier base material consists essentially of (a) HPMC having a molecular weight of 60,000 or greater, and (b) HPMC having a molecular weight of 50,000 or less; and wherein the ratio of (a) to (b) is from 1:2 to 1:9.

2. A zero order release pharmaceutical formulation according to Claim 1 in which the high viscosity HPMC is selected from a methocel cellulose ether wherein:
   a) % methoxy = 19-24. % hydroxypropyl = 7-12, viscosity = 4000 cps;
   b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 10,000;
   c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4,000;
   d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 15,000;
   e) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100,000;
   and the low viscosity HPMC is selected from a methocel cellulose ether wherein:
   a) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 4-6;
   b) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 12-18;
   c) % methoxy = 28-30, % hydroxypropyl = 7-12, viscosity = 40-60;
   d) % methoxy = 19-24, % hydroxypropyl = 7-12, viscosity = 100.

3. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part methocel cellulose ether wherein % methoxy = 28-30, % hydroxypropyl = 7-12 and viscosity = 10,000 and wherein the low viscosity HPMC is selected from:
   a) 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;

b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60; or
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

4. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
c) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

5. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4,000 and wherein the low viscosity HPMC is selected from:
a) 1 part wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 2 to 4 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 3 to 9 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

6. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is one part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 15,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 4-6;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
c) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60;
d) 3 to 9 parts wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100.

7. A zero order release pharmaceutical formulation according to Claim 2 wherein the high viscosity HPMC is 1 part wherein % methoxy = 19-24, % hydroxypropyl = 7-12, and viscosity = 100,000 and wherein the low viscosity HPMC is selected from:
a) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 12-18;
b) 1 to 3 parts wherein % methoxy = 28-30, % hydroxypropyl = 7-12, and viscosity = 40-60.

8. A zero order release pharmaceutical formulation according to Claim 2 wherein the medicament is selected from:
a) ibuprofen; or
b) salts of ibuprofen.

9. A formulation according to Claim 8 wherein the medicament is ibuprofen lysine.

10. A formulation according to Claim 9 wherein the medicament is (S)-ibuprofen-(S)-lysine.

11. A formulation according to Claim 10 wherein the amount of medicament as ibuprofen is 100 to 600 mg.

Patentansprüche

1. Trägergrundmaterial, kombiniert mit Ibuprofen oder einem Salz davon und geformt und komprimiert zu einer festen pharmazeutischen Dosierungsform mit langanhaltender Freisetzung mit einem Freisetzungsprofil nullter Ordnung bei der Verabreichung, worin das Trägergrundmaterial im wesentlichen besteht aus (a) HPMC eines Molekulargewichts von 60 000 oder mehr und (b) HPMC eines Molekulargewichts von 50 000 oder weniger und worin das Verhältnis von (a) zu (b) 1:2 bis 1:9 beträgt.

2. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 1, worin die hochviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:
a) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 4 000 cps,
b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 10 000,
c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4 000,
d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 15 000,

e) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100 000,

und worin das niederviskose HPMC ausgewählt ist aus einem Methocel-Celluloseether, worin:

a) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 4-6,

b) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 12-18,

c) % Methoxy = 28-30, % Hydroxypropyl = 7-12, Viskosität = 40-60,

d) % Methoxy = 19-24, % Hydroxypropyl = 7-12, Viskosität = 100.

3. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC zu einem Teil Methocel-Celluloseether ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 10 000 und worin das niederviskose HPMC ausgewählt ist aus:

a) 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60 oder

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

4. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

b) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

c) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

5. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 Teil, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 2 bis 4 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 3 bis 9 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

6. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 15 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 4-6,

b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

c) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60,

d) 3 bis 9 Teilen, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100.

7. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin die hochviskose HPMC 1 Teil ist, worin % Methoxy = 19-24, % Hydroxypropyl = 7-12 und Viskosität = 100 000 und worin die niederviskose HPMC ausgewählt ist aus:

a) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 12-18,

b) 1 bis 3 Teilen, worin % Methoxy = 28-30, % Hydroxypropyl = 7-12 und Viskosität = 40-60.

8. Pharmazeutische Formulierung mit einer Freisetzung nullter Ordnung nach Anspruch 2, worin das Medikament ausgewählt ist aus:

a) Ibuprofen oder

b) Salzen von Ibuprofen.

9. Formulierung nach Anspruch 8, worin das Medikament Ibuprofen-Lysin ist.

10. Formulierung nach Anspruch 9, worin das Medikament (S)-Ibuprofen-(S)-Lysin ist

11. Formulierung nach Anspruch 9, worin die Menge des Medikaments als Ibuprofen 100 bis 600 mg beträgt.

Revendications

1. Matériau de base de véhicule associé à de l'ibuprofène ou un sel de celui-ci et façonné et comprimé en une forme pharmaceutique solide à libération prolongée, ayant un profil de courbe de libération d'ordre zéro après administration, caractérisé en ce que le matériau de base de véhicule consiste essentiellement en (a) une HPMC ayant une masse moléculaire de 60 000 ou plus et (b) une HPMC ayant une masse moléculaire de 50 000 ou moins; et en ce que le rapport de (a) à (b) va de 1:2 à 1:9.

2. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 1, dans laquelle la HPMC à haute viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 centipoises (cP);
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 10 000 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4 000 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 15 000 cP;
   e) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 000 cP;

   et la HPMC à faible viscosité est choisie parmi un éther de cellulose de type Methocel dans lequel:
   a) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 4-6 cP;
   b) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 12-18 cP;
   c) le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 40-60 cP;
   d) le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12, viscosité = 100 cP.

3. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'éther de cellulose de type Methocel dans lequel le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 10 000 cP, et dans lequel la HPMC à faible viscosité est choisie parmi:
   a) 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
   b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
   d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

4. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
   a) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
   b) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP;
   c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

5. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:

a) 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 2 à 4 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

6. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 15 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 4-6 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
c) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP; et
d) 3 à 9 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 cP.

7. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle la HPMC à haute viscosité consiste en 1 partie d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 19-24, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 100 000 cP, et dans laquelle la HPMC à faible viscosité est choisie parmi:
a) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 12-18 cP;
b) 1 à 3 parties d'une HPMC dans laquelle le pourcentage de groupes méthoxy = 28-30, le pourcentage de groupes hydroxypropyle = 7-12 et la viscosité = 40-60 cP.

8. Composition pharmaceutique à vitesse de libération d'ordre zéro selon la revendication 2, dans laquelle le médicament est choisi parmi:
a) l'ibuprofène et
b) des sels d'ibuprofène.

9. Composition selon la revendication 8, dans laquelle le médicament est l'ibuprofène lysine.

10. Composition selon la revendication 9, dans laquelle le médicament est le (S)-ibuprofène-(S)-lysine.

11. Composition selon la revendication 10, dans laquelle la quantité de médicament, en tant qu'ibuprofène, va de 100 à 600 mg.

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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.

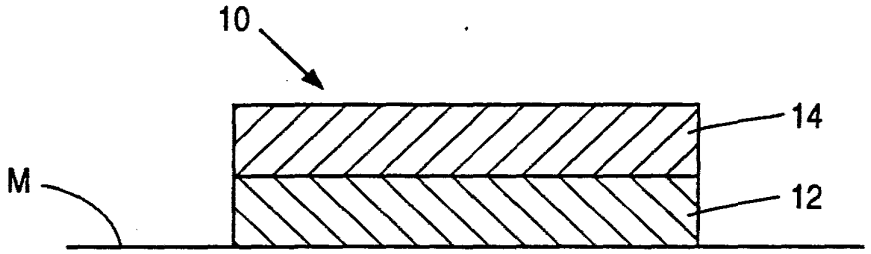

FIG. 1

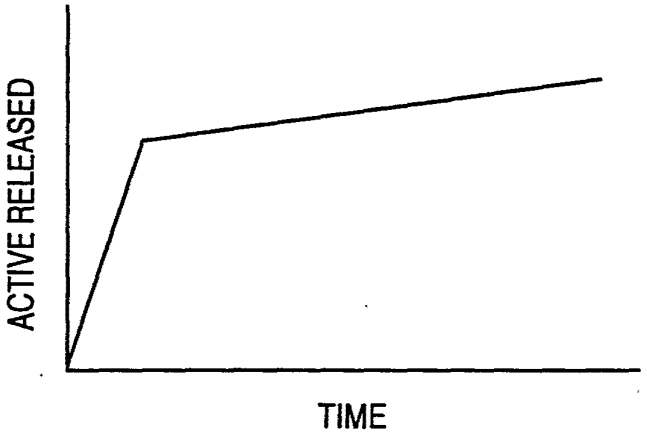

FIG. 5

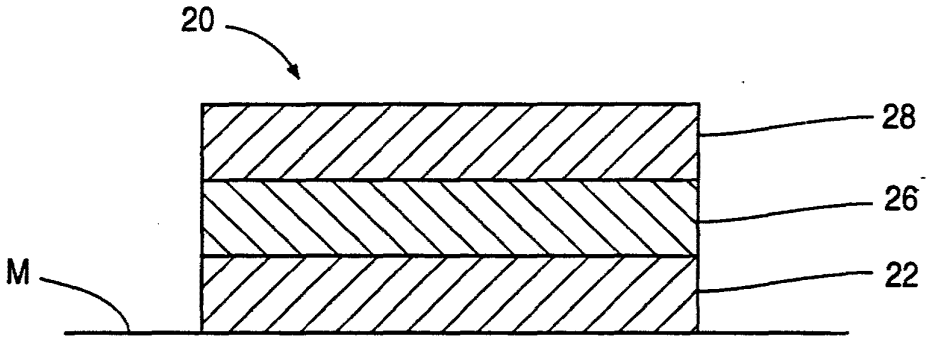

FIG. 2

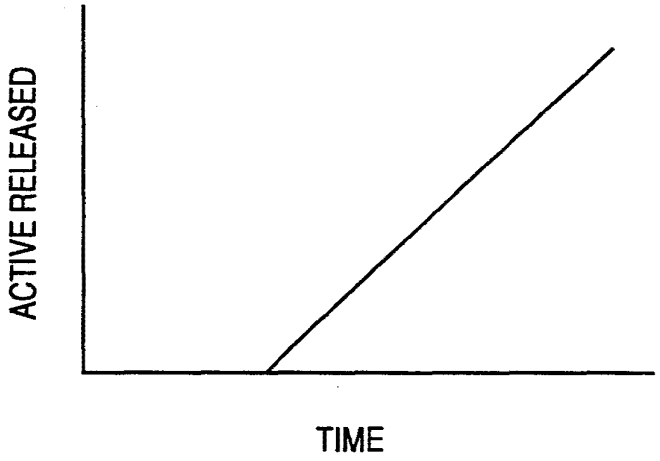

FIG. 6

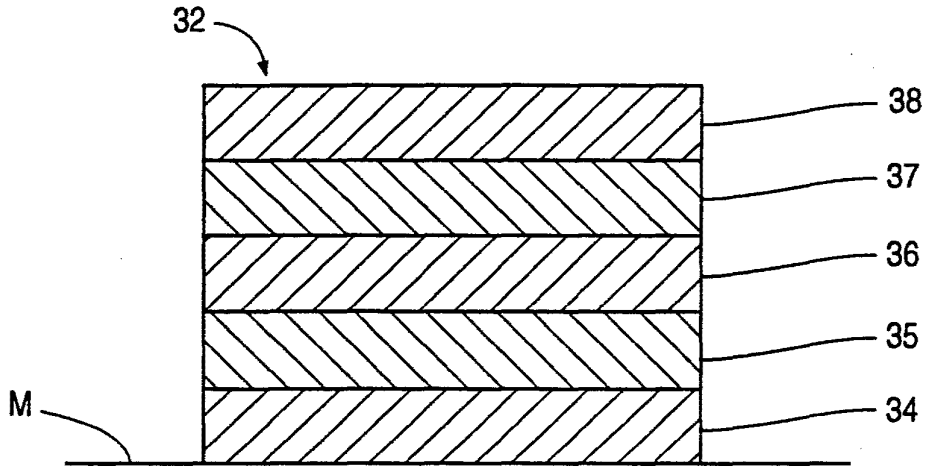

FIG. 3

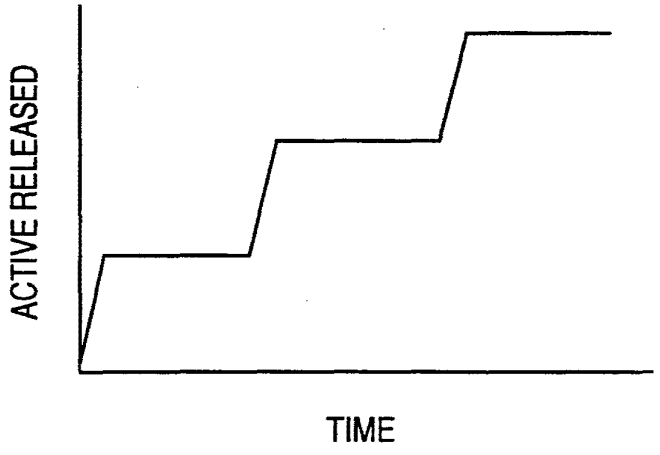

FIG. 7

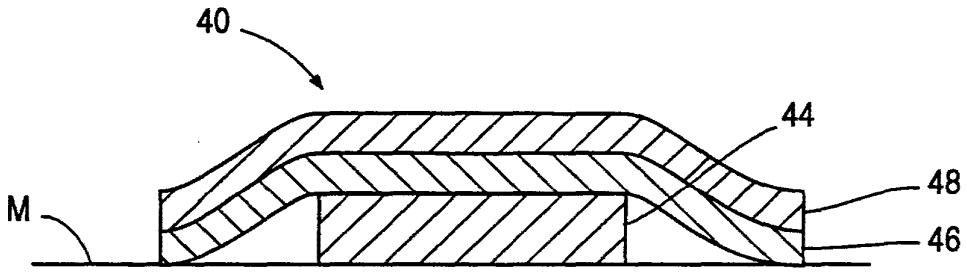

FIG. 4

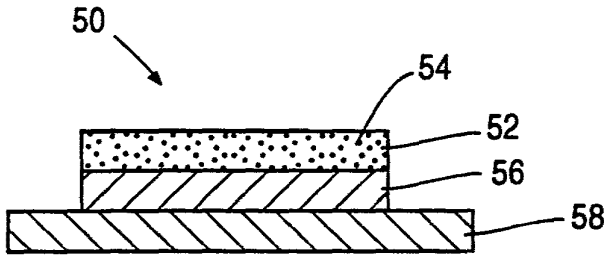

FIG. 8

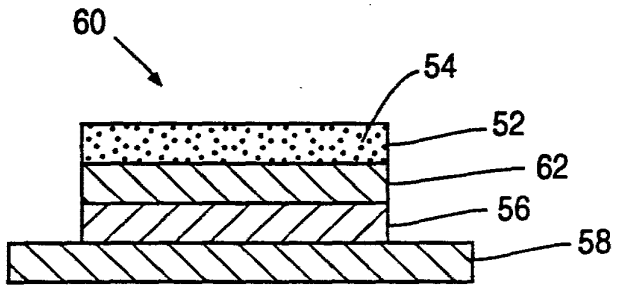

FIG. 9

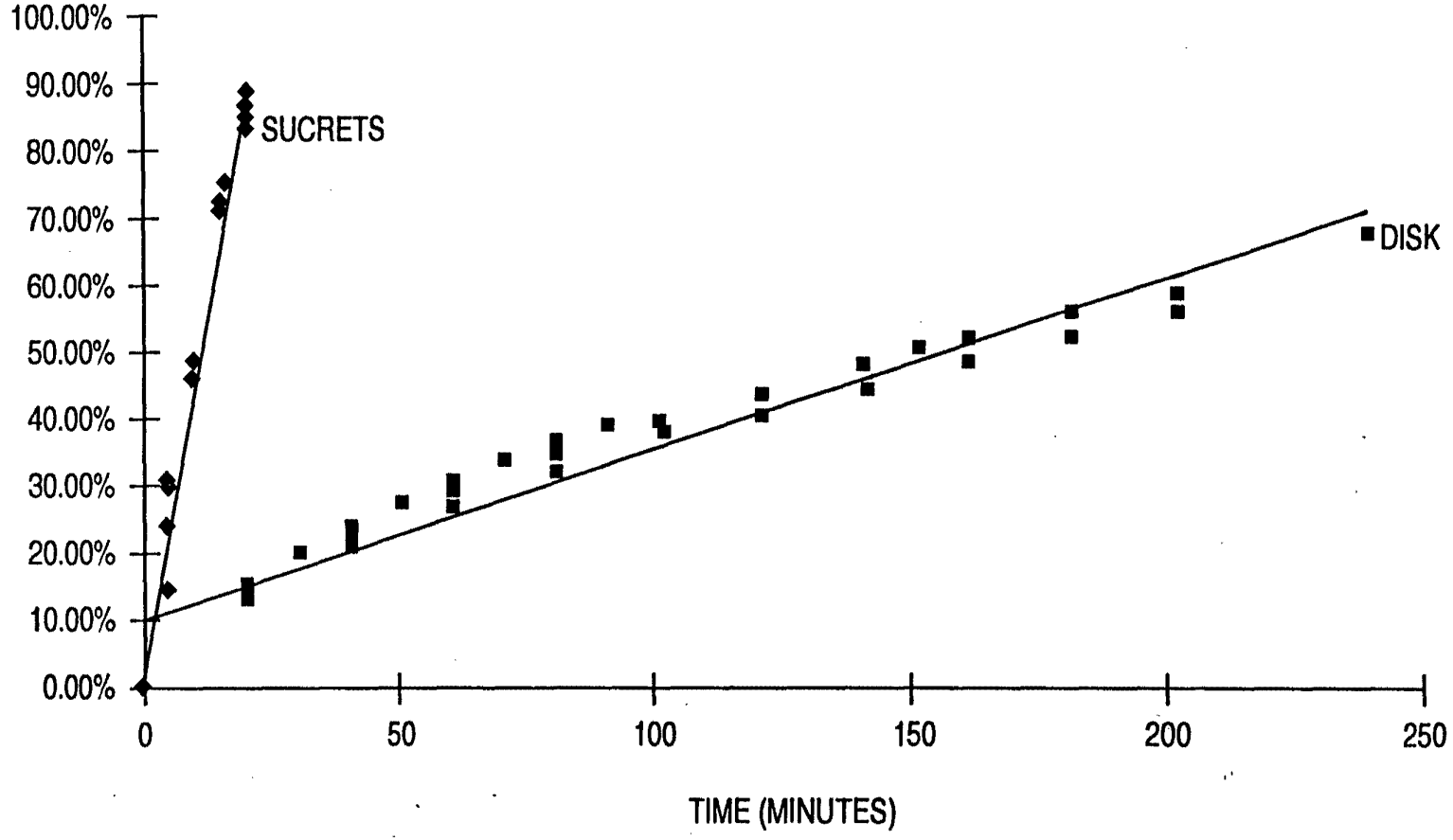

FIG. 10

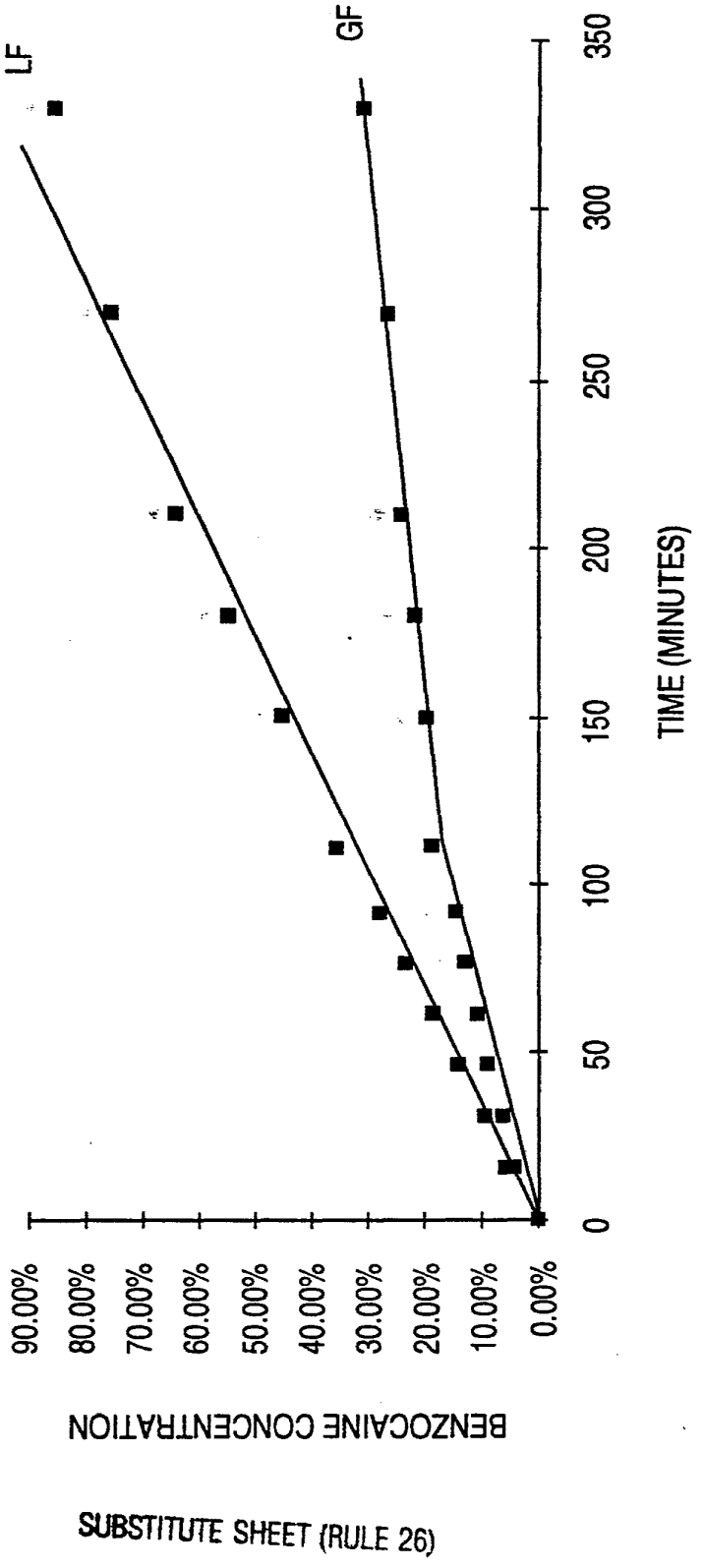

FIG. 11

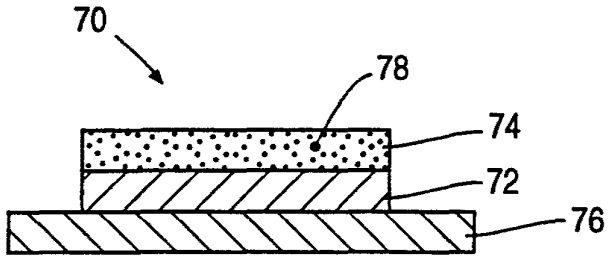

FIG. 12

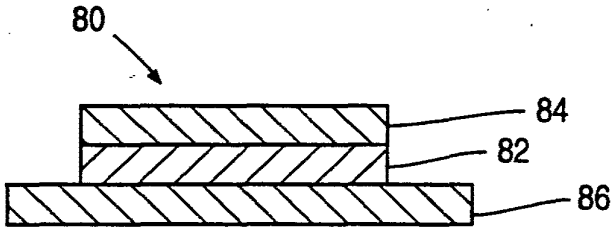

FIG. 13

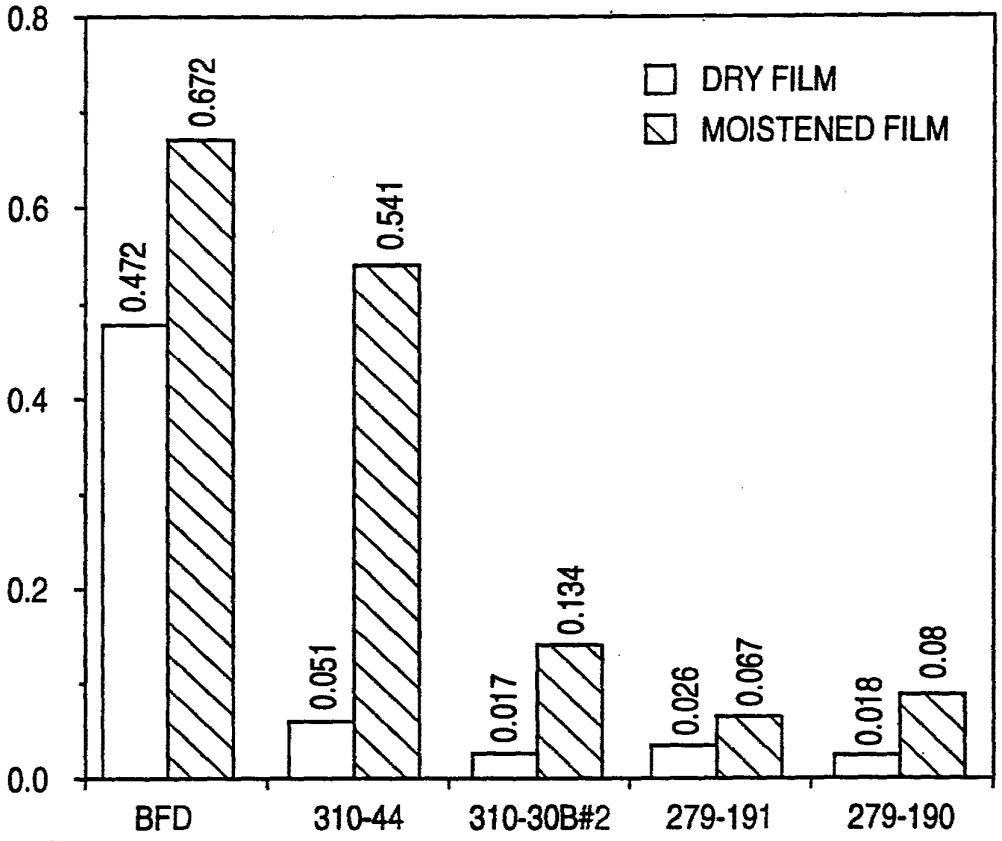

FIG. 14

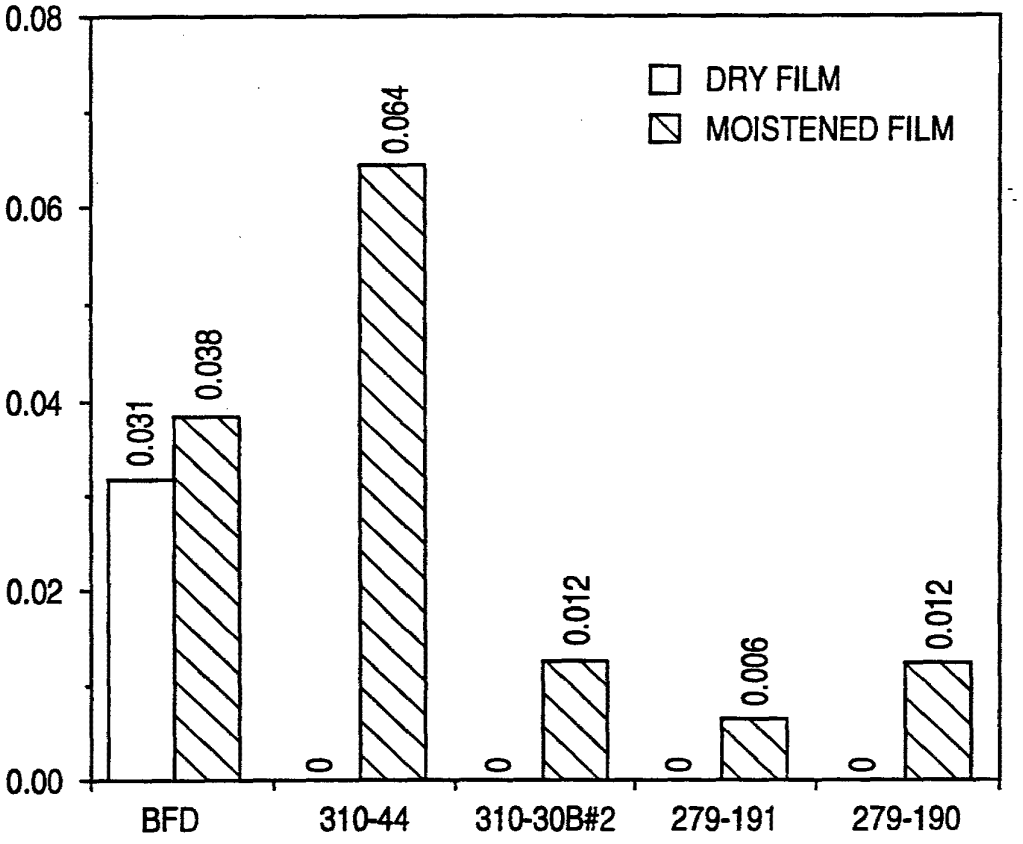

FIG. 15

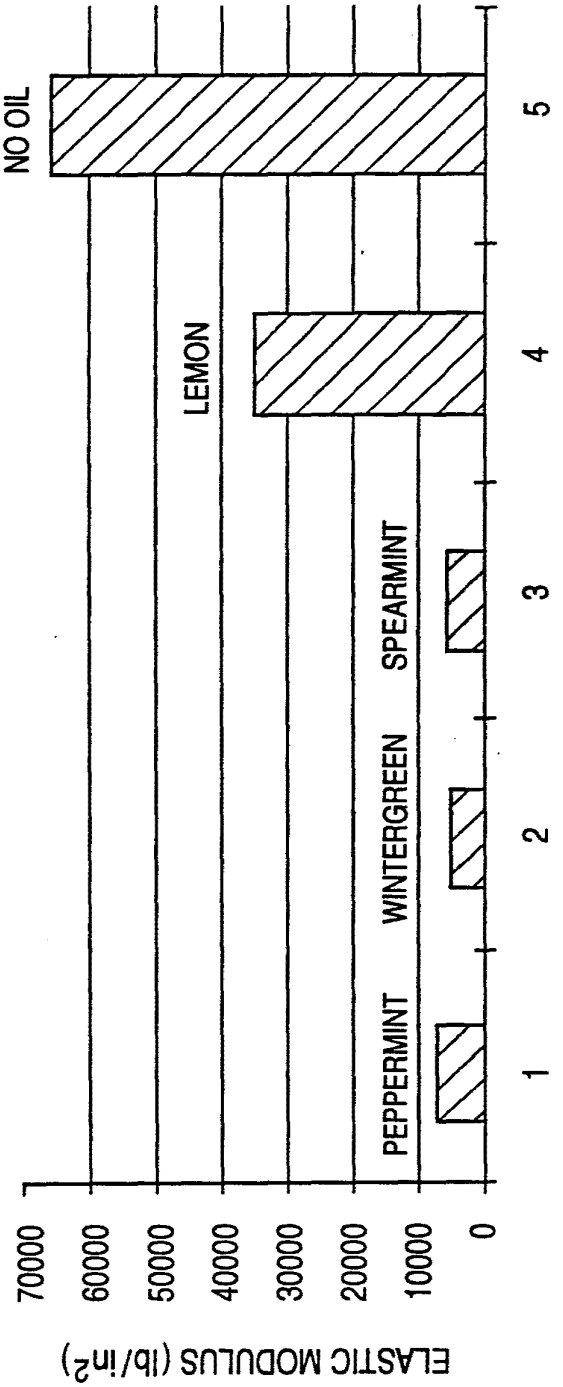

FIG. 16

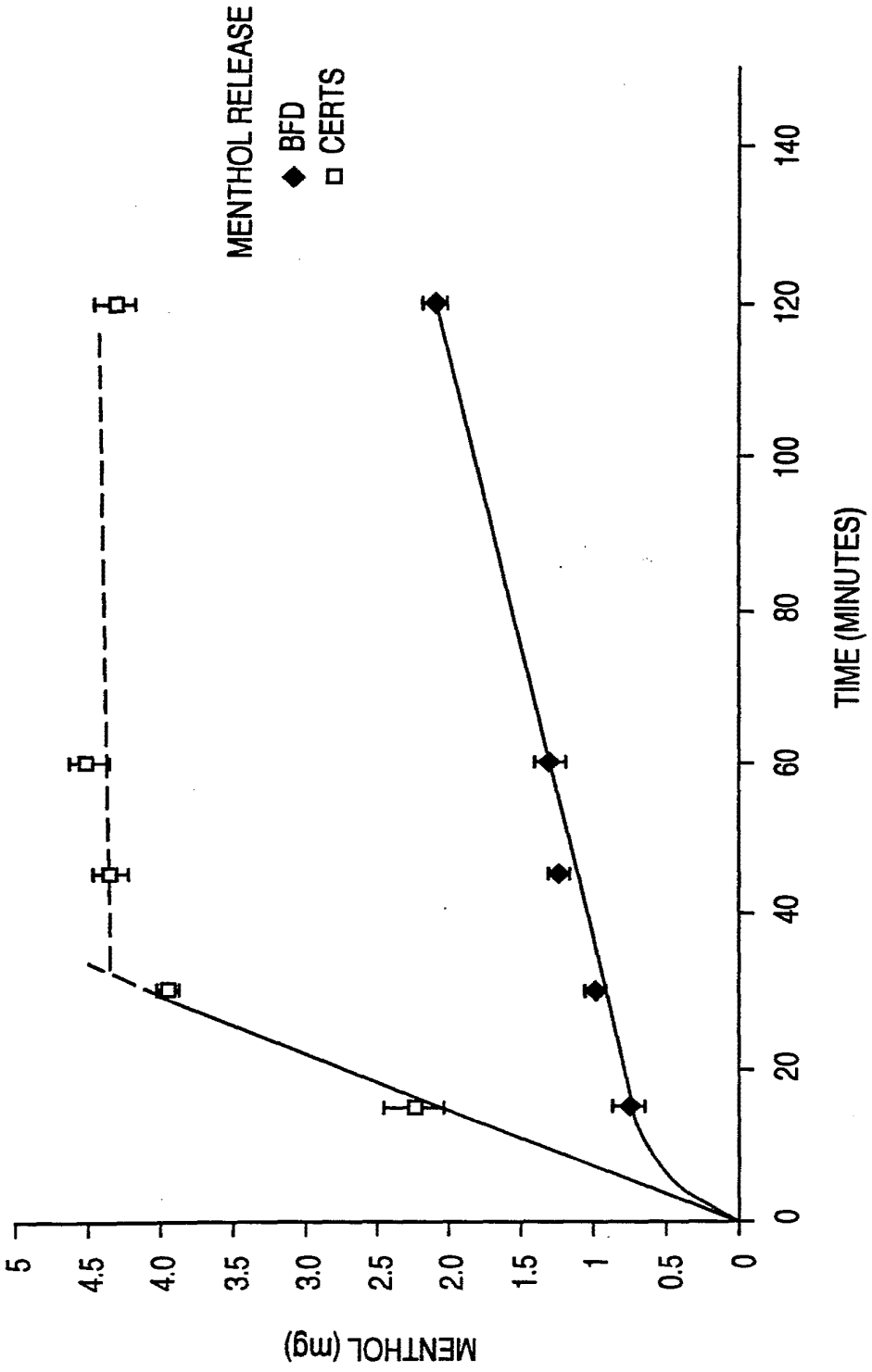

FIG. 17

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C08L 1/26, C08K 5/10, 5/11, 15/00
A61K 6/00, A61F 13/00

A3

(11) International Publication Number: **WO 95/05416**

(43) International Publication Date: 23 February 1995 (23.02.95)

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(30) Priority Data:

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08/109,273	19 August 1993 (19.08.93)	US

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(63) Related by Continuation
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Filed on 19 August 1993 (19.08.93)

(71) Applicant *(for all designated States except US)*: CYGNUS THERAPEUTIC SYSTEMS [US/US]; 400 Penobscot Drive, Redwood City, CA 94063 (US).

(72) Inventors; and
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(74) Agents: KENNEDY, Bill et al.; Morrison & Foerster, 755 Page Mill Road, Palo Alto, CA 94034-1018 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments

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23 March 1995 (23.03.95)

(54) Title: WATER-SOLUBLE PRESSURE-SENSITIVE MUCOADHESIVE

(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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GA	Gabon				

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09305

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C08L 1/26; C08K 5/10, 5/11, 15/00; A61K 6/00; A61F 13/00
US CL :523/111,120; 524/43,312; 424/435; 428/40, 355
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. : 523/111,120; 524/43, 312; 424/435, 449; 428/40,355

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)

APS: POLYVINYL PYROLIDONE, GLYCEROL, PRESSURE SENTITIVE ADHESIVE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,529,748 (WIENECKE) 16 July 1985, see entire document.	1,2,7-8
Y	US, A, 4,713,243 (SCHIRALDI ET AL) 15 December 1987, column 2, lines 30-60 and column 3, line 10 to column 4, line 38.	1,2,7
Y	US, A, 5,166,233 (KUROYA ET AL) 24 November 1992, see entire document.	1,2,7
Y	US, A, 4,373,036 (CHANG ET AL) 08 February 1983, see entire document.	1,2,7
Y	US, A, 5,158,825 (ALTWIRTH) 27 October 1992,column 1, lines 45-68 and column 2, lines 19-55.	1,2,7

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"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
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 OCTOBER 1994	Date of mailing of the international search report 13 FEB 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 PAUL MICHL Telephone No. (703) 308-2351

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/09305

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 4,910,247 (HALDAR) 20 March 1990, column 3, line 20 to column 4, line 29.	1-4
A	US, A, 5,064,717 (SUZUKI ET AL) 12 November 1991, column 3, lines 33-54 and column 10, lines 21-33.	1-8
X	US, A, 4,292,299 (SUZUKI) 29 September 1981, columns 2-5.	9-18,24-49
Y		19-23
Y	JP, A, 62-59513 (KYUKYU YAKUHIN KOGYO) 28 February 1990, pages 2-12.	19-23

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : **B65D 1/09, A61B 19/08**

A1

(11) International Publication Number: **WO 95/18046**

(43) International Publication Date: 6 July 1995 (06.07.95)

(21) International Application Number: PCT/US94/14885

(22) International Filing Date: 28 December 1994 (28.12.94)

(30) Priority Data:

08/173,978	28 December 1993 (28.12.93)	US
08/327,989	24 October 1994 (24.10.94)	US

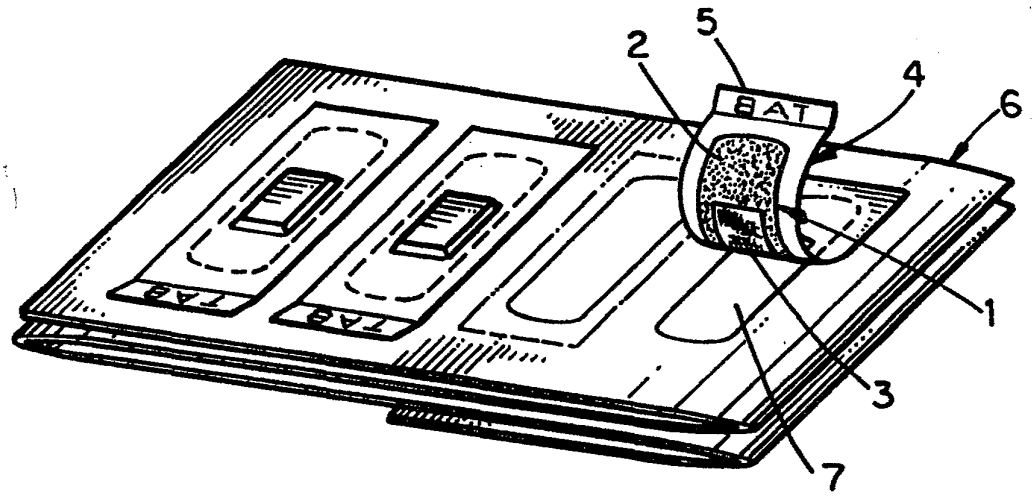
(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ).

(71)(72) Applicant and Inventor: FRANK, Richard, D. [US/US]; 11909 South Lake Drive, Houston, TX 77077 (US).

(74) Agent: CAGLE, Stephen, H.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

Published
With international search report.

(54) Title: PAKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES



(57) Abstract

The present invention provides an encased article combination that includes a support member (100, 6, 53, 71), a cover member (104, 4, 50, 72), and an encased article (101, 1, 52, 70). The encased article is in the form of adhesive bandages (1), chemical applicator pads (52), and doses of medicine (70). In particular, the invention in part allows access to and use of such items with a single hand.

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PACKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES

This invention relates to a dispensing device for sterile articles such as adhesive bandage strips, chemical applicator pads, and medication. More particularly, this invention permits one-handed access, removal, and application or use of adhesive bandages, chemical substances, or medication.

While adhesive-backed articles such as adhesive bandage strips are known in the art, they are commonly sealed in sterile, individual wrappings and packaged within paper or metal boxes. Examples include the well-known "Band-Aid®" brand bandage strips. While popular, these products suffer certain disadvantages such as the fact that the bandages themselves can be difficult to remove from the wrappings and difficult to apply to the desired location. The user generally must remove the bandage from the wrapping, remove the nonstick layers from the

adhesive portion of the bandage and then attempt to apply the bandage to the desired location in its sanitary and sterile condition without the bandage curling or adhering to itself.

Previous attempts to improve upon this concept include U.S. Patent No. 4,993,586 to Taulbee, et al., which discloses a bandage dispenser device in which a continuous strip is grasped with one hand and a bandage is removed with the other hand. This is accomplished by the use of a continuous strip with a first and second layer. Bandages are placed on sterile mounting pads affixed to the first layer. The bandages and the first layer are then enclosed by a second layer and stacked or rolled within a container. In use, the sheet is pulled through a splicer attached to the container that cuts the first and second layers. The second layer is then lifted and removed. The first layer is then grasped with one hand and a bandage is removed with the other.

U.S. Patent No. 5,133,477 to Etheredge, et al. also discloses a bandage dispensing device employing the use of a continuous strip. The strip has a nonstick coating upon which one end of a bandage is affixed. The other end of the bandage and the cotton gauze area of the bandage are covered with a release sheet. In use, the continuous sheet is grasped with one hand the bandage is grasped and removed with the other hand. The bandage is then applied to the desired location by affixing the exposed half to the skin. Once applied, this end of the bandage is held in place while the release sheet is removed from the bandage and the other end of the bandage is applied to the skin.

Despite these and other prior art devices, there remains a need for a packaging and dispensing device for adhesive-coated articles, such as adhesive bandage strips, by which the article may be grasped with one hand from the front of dispenser and then applied, also one-handedly, to the desired location without the article curling or adhering to itself. Both Taulbee and Etheredge require the use of two hands to remove and apply a bandage strip, and neither addresses the

problem of the bandage strip curling or adhering to itself. Further, the device disclosed by Taulbee would entail considerable manufacturing costs due to the splicer structure. Similarly, there is still a need for a packaging and dispensing device that allows convenient, and in some cases, one-handed access to sanitary applicators and doses of medication.

While the prior art has improved upon access to sanitary articles, there is a need for both improved access to the article and improved applicability of the article. As an example, a lab technician who is drawing blood from a patient could use the improved access to such articles to apply an adhesive bandage strip with one hand while maintaining pressure on the puncture with the other.

Similarly, there remains a need for a device used for the application of chemical substances such as alcohol, makeup, sunscreen and other lotions, antiseptics and medicaments to the skin of the human body in a sterile and sanitary fashion with the use of a single hand. Additionally, there is also a need for convenient, and in some cases, one-handed access to doses of medicine.

The encased article combination of this invention includes a support member, a cover member and an encased article. The encased articles may be packaged either individually, as an assemblage of articles, or as an assemblage of articles in a dispensing device. In one embodiment of this invention the encased article is an adhesive coated article such as a conventional adhesive bandage or other form of wound dressing. In other embodiments of this invention the article is an applicator for chemicals, such as medicines, cosmetics, ointments, salves and the like. In yet another embodiment of this invention pills, capsules, or capelets, or other forms of medicinal dosage units are enclosed for dispensing.

The support member of this invention may take the form of a continuous sheet, coated or uncoated, or a series of molded housings for the articles to be

dispensed. In the most preferred embodiments the support member is flexible so that it can be loaded into a dispensing device in folded or rolled form.

The cover member of this invention is typically adhered to the support member to form the encasement for the article. In certain preferred embodiments the cover member has either one or two adhesive coatings for releasable adherence to the support member and to the encased article. In another preferred embodiment the cover member includes means for gripping the cover member for removal to enable one-handed application or use of the encased device.

In the practice of this invention it is important that the assembly of the support member, the cover member and the encased article form bonds of appropriate adhesive strengths to ensure correct release characteristics. A first adhesive bond is typically formed between the support member and the adhesive surface of the encased article. Such a first bond is typically found in the adhesive bandage encasement embodiment of this invention. A second adhesive bond is formed between the support member and the cover member. A third adhesive bond is formed between the cover member and the encased article. It is important that the third adhesive bond (between the cover member and the encased article) be adhesively stronger than either the first or second adhesive bond. This relationship of the first, second, and third adhesive bonds is important to the practice of this invention. Likewise, it is important that the third adhesive bond be weaker than the bond between the adhesive surface of the encased article and the surface to which it is ultimately applied (recipient surface).

Generally, the present invention comprises an apparatus for packaging and dispensing a sterile article such as an adhesive bandage, a swab-type or sponge-like applicator that may be pretreated with the substance to be applied, or a dose of medicine.

In the present invention, adhesive-coated items are encased within self-contained, sanitary packaging. The adhesive-coated item, such as an adhesive bandage usually has two substantially flat sides. The bottom (or adhesive) side or surface, which is the side applied to the skin in the case of standard adhesive bandages, is coated at least in part with a first adhesive and typically has a sanitary pad affixed thereto.

The adhesive-coated article such as an adhesive bandage is packaged by sandwiching the item between a dispensing support structure, layer, or sheet and a cover layer or strip. The adhesive-coated article is removably adhered to the support sheet by the first adhesive, which forms a first bond with the support sheet. The length and width dimensions of the support sheet exceed those of the adhesive-coated article. Alternatively, sterile, nonstick mounting pads may be affixed to the support sheet and an adhesive-coated article such as an adhesive bandage may instead be removably adhered to each of the mounting pads. If the support sheet is made of suitable material, then nonstick mounting pads are not necessary.

The packaging or encasement is further accomplished by forming or removably adhering a cover structure or layer, which also exceeds the dimensions of the adhesive-coated article, both to the top surface of the adhesive-coated article and to an additional peripheral area of the support sheet surrounding the article. A second adhesive may be used to removably adhere the cover layer to the top surface of the adhesive-coated article by forming a second bond therebetween. The second adhesive forms an additional bond between the peripheral area of the cover strip extending beyond the edges of the adhesive-coated article and the corresponding peripheral area of the support sheet. The second bond, that formed between the adhesive-coated article and the cover strip, is of greater strength than the first bond, that between the adhesive-coated article and the support sheet, so that when the cover strip is removed, usually by grasping a tab portion of the cover strip or any other suitable gripping means attached to the cover strip, the

adhesive-coated article is detached from the support sheet, while the top surface of the adhesive-coated article remains removably attached to the cover strip.

The adhesive-coated article can then be transported to and applied to the receiving surface, such as the human skin, with single handed use of the cover strip. Once the bottom surface of the adhesive-coated article, containing the first adhesive, is applied to the receiving surface, the first adhesive forms a strong bond between the receiving surface and the bottom surface of the article such that the strength of this bond with the receiving surface exceeds that of the bond between the cover layer and the top surface of the article so that subsequent pulling force exerted upon the cover layer will cause the cover layer to become detached from the top surface of the article, thereby leaving the article suitably applied to the receiving surface.

In another form, the present invention comprises an apparatus for packaging and dispensing a swab-type or sponge-like applicator, which is packaged by sandwiching it between a support structure, layer, or sheet and a cover structure, layer, or strip. In this application, the swab-type or sponge-like applicator, such as a piece of gauze, cotton, cloth, sponge, or other material is attached to a cover strip having length and width dimensions that exceed those of the applicator. The cover strip is attached to the applicator with an adhesive or some other suitable means of attachment. A peripheral area of the cover strip surrounding the applicator is coated with an adhesive which forms a temporary bond between the peripheral area of the cover strip extending beyond the edges of the applicator and the corresponding peripheral area of the support sheet. When the cover strip is pulled, the applicator is removed with the cover sheet, thereby exposing the applicator so that it may be moved to the receiving surface. The applicator can be pretreated with antiseptics, lotions, sunscreens, makeup or any medicament or other chemical to be applied, but does not necessarily have to be pretreated.

In yet another form, the present invention comprises an apparatus for packaging and dispensing doses of medicine such as capsules, capelets, pills, or other units of medicine. In this embodiment, capsules, for example, are packaged in trays which function as the support member and which contain troughs for holding the capsules. The capsules are further packaged with the use of a cover sheet which is removably adhered to at least the peripheral area of the trays. The package may or may not include an additional, protective, thin burstable film between the cover sheet and the capsules. The inner dimensions of the troughs may or may not be slightly smaller than the outer dimensions of the capsules in at least one dimension. If the troughs are slightly smaller than the capsules, then the user must exert force on the troughs to eject the capsules once the troughs have been removed from the cover layer with the use of a tab or other suitable gripping means attached to or formed as part of the tray. If the troughs are of the same or equal size as the capsules, then a portion of the underside of the cover layer may be coated with a temporary adhesive that removably adheres the capsules to the cover layer and removes the capsules from the troughs when the cover layer is removed.

Embodiments of this invention include the individual packaging and dispensing of individual or multiple adhesive bandages of virtually any shape, or applicators as well as the packaging and dispensing of multiple bandages, applicators, or doses of medicine positioned on individual or continuous sheets or rolls or in trays packed within a dispenser.

The dispenser itself may be a desktop or wall-mounted refillable container constructed of metal, plastic or paper. The dispenser has an opening or a window to provide access to sterile, individually wrapped adhesive bandages or applicators affixed to single or continuous sheets or rolls, or doses of medicine in trays formed from single or continuous sheets or rolls. A continuous support sheet of bandages or applicators may be layered or rolled in the bottom of the dispenser and fed across the dispenser window so that the leading end of the sheet either

exits through one end of the dispenser or is attached to a spool. As the bandage strips or applicators are removed via the access window and used, the support sheet may be pulled through the aperture or the spool may be turned, thus exposing additional bandages or applicators in the dispenser window. If medicine is dispensed then single sheets or multiple layers of single sheets of trays of medicine may be loaded into the dispenser and the trays may be accessed through the access window for use.

An aperture may be in addition to or instead of the access window. The aperture allows single or multiple packaged bandages, applicators or packets of medicine to be dispensed from one side of the dispenser for immediate or subsequent use. In a dispenser containing both an access window and an aperture, the aperture also allows the packaging material remaining from bandages, applicators, or pills accessed through the access window to be removed and discarded.

Thus, it is an object of the present invention to provide an improved package and dispenser for sterile articles such as adhesive bandages, chemical applicators, and doses of medicine.

It is also an object of present invention to provide a device that allows the user to apply a common sterile adhesive bandage or chemical substance using only one hand in the process of removing the bandage or substance applicator from the dispenser and applying it to the desired location.

It is a further object of this invention to provide an apparatus for application of a bandage strip to its desired location with the use of a single hand without the bandage strip curling or adhering to itself.

Yet another object of this invention is to provide an apparatus for the application of a chemical substance to a surface with the use of a single hand.

It is still a further object of the invention to provide a convenient dispenser which displays several adhesive bandages or substance applicators for immediate use, eliminates the handling of individually wrapped bandages or substance applicators, and reduces the amount of immediately discarded wrapping material.

Other objectives, features and advantages of the present invention will become apparent upon reading the following specification, when taken in conjunction with the drawings and the claims.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 3 is a side view conceptually showing the layers and adhesives of an adhesive coated article encased according to the present invention.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 5 is a side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention.

FIG. 6 is a perspective view showing an adhesive bandage strip removably adhered to a cover strip containing a pull tab.

FIG. 7 is a perspective view showing the positioning of adhesive bandage strips and non-continuous cover strips on a continuous support layer.

FIG. 8 is a perspective view showing the positioning of adhesive bandage strips and continuous cover strips on a continuous support layer.

FIG. 9 is an exploded perspective view of a single adhesive bandage strip encased according to the present invention.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip with a cover strip to a recipient's skin.

FIG. 11 is an exploded perspective view of one embodiment of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 12 is a side cut away view showing the dispenser of FIG. 11 packed with a fan folded continuous member of adhesive bandage strips.

FIG. 13 is a perspective view of the dispenser of FIG. 11.

FIG. 14 is a perspective cut away view of one embodiment of a dispenser for adhesive bandages packaged on continuous support member.

FIG. 15 is a perspective view of a portion of a dispenser for adhesive bandages packaged on a continuous support member.

FIG. 16 is a cut away perspective view of a wall mounted dispenser containing a spool for dispensing adhesive-coated bandages packaged on a roll according to the present invention.

FIG. 17 is a cut away perspective view of a wall mounted dispenser containing a roll of adhesive coated bandages on a roll packaged according to the present invention.

FIG. 18 is an exploded perspective view showing an applicator packaged according to the present invention.

FIG. 19 is an exploded perspective view showing a plurality of applicators packaged on a single support member according to the present invention.

FIG. 20 is a perspective view showing one embodiment of a dispenser for a plurality of applicators packaged on a single support member according to the present invention.

FIG. 21 is a perspective view of one embodiment of a dispenser for dispensing the applicators shown in FIG. 19.

FIG. 22 is an exploded perspective view of one embodiment of capsules packaged according to the present invention.

FIG. 23 is an exploded perspective view of another embodiment of capsules packaged according to the present invention.

FIG. 24 is a bottom perspective view of the packaged capsules shown in FIG. 23.

FIG. 25 is a perspective view of a user ejecting capsules packaged according to the present invention.

FIG. 26 is a cut away perspective view of one embodiment of a dispenser for dispensing
medicine packaged according to the present invention.

FIG. 27 is an exploded cut away perspective view of another embodiment of a dispenser for dispensing medicine packaged according to the present invention.

FIG. 1 is an exploded side view conceptually showing the layers and adhesives of an adhesive-coated article encased according to the present invention. FIG. 1 shows adhesive-coated article 101 having first adhesive surface 102 encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by the second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween.

FIG. 2 is an exploded side view conceptually showing the layers and adhesives of another embodiment of an adhesive-coated article encased according to the present invention. Adhesive-coated article 101 having first adhesive surface 102 is encased between support member 100 and cover member 104. A first adhesive bond removably adheres the first adhesive surface 102 and support member 100 by first adhesive coating 103 disposed on first adhesive surface 102. Cover member 104 is removably adhered to support member 100 by second adhesive coating 105 disposed therebetween and which forms a second adhesive bond therebetween. Cover member 104 is also removably adhered to the adhesive-coated article 101 by third adhesive coating 106 which forms a third adhesive bond therebetween which is stronger than the second adhesive bond.

FIG. 3 further shows the encased adhesive-coated article of FIG. 2 with the addition of contact between the appropriate layers and adhesives, and also shows the addition of means for gripping 107 to facilitate removal of cover member 104.

FIG. 6 shows an application of the present invention to the packaging of an adhesive bandage strip. The adhesive bandage strip 1 is the adhesive-coated

article. The cover member in this embodiment is cover strip 4, as these terms may be used interchangeably in this configuration. The support member in this embodiment is support sheet 4. FIG. 6 shows a perspective view of an adhesive bandage strip 1 joined to a cover strip 4 with a pull tab 5. The adhesive bandage strip 1 is generally constructed of plastic, paper, or cloth material with an adhesive substance applied to the adhesive side 2 of the strip and a cotton gauze area 3 in the middle of this adhesive side 2 of the strip 1. A conventional adhesive bandage strip, such as the "Band-Aid®" brand bandage strip, may be used.

The adhesive bandage strip 1 is joined to a cover strip 4 by a temporary adhesive. Examples of the temporary adhesive substance include "DryLine™" temporary adhesive made by the Gillette Company. The cover strip 4 may be constructed of any suitable material, including paper or plastic. The temporary adhesive used to join the cover strip 4 to the adhesive bandage strip 1 forms a stronger bond between the cover strip and the bandage than the bond formed by the adhesive substance between the adhesive side 2 of the adhesive bandage strip 1 and the support sheet 6 of FIG. 7. The cover strip 4 also contains a suitable means for gripping, such as pull tab 5, for ease of removal, as explained below.

FIG. 7 is a perspective view showing the positioning of the adhesive bandage strips 1 and non-continuous cover strips 4 on a continuous support sheet 6. The continuous support sheet 6 may be constructed out of any suitable material, including paper or plastic. The support sheet 6 can be of any suitable length and can be fan folded as shown in FIG. 7, or rolled as shown in FIGS. 16 and 17.

FIG. 8 shows a perspective view of an embodiment of the invention in which adhesive bandage strips are dispensed on a fan folded continuous support sheet 6 and covered and dispensed with the use of continuous cover strips 18 formed by the perforation or cutting of a continuous cover layer 19.

In the embodiments utilizing either continuous or non-continuous cover strips, a variable number of sterile, nonstick mounting pads 7, as shown in FIG. 7, may be permanently affixed to or incorporated into the continuous support sheet 6. The sterile, nonstick mounting pads 7 are generally constructed out of paper, such as the release liner-type paper manufactured by Rhinelander Paper Company. The adhesive bandage strips 1 are positioned on the sterile, nonstick mounting pads 7 such that the adhesive side 2 of a bandage strip 1 is in contact with the sterile, nonstick mounting pads 7. Alternatively, the continuous support sheet 6 itself can be treated with a nonstick substance such that the adhesive bandage strips 1 may be placed directly on the support sheet 6.

If non-continuous cover strips 4 are used as shown in FIG. 7, then a cover strip 4 is joined to each of the adhesive bandage strips 1 as discussed above. The cover strip 4, covers the adhesive bandage strip 1 and adheres to that area of the support sheet 6 immediately surrounding the adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed within the cover strip 4 and the support sheet 1. This enclosure ensures that the adhesive bandage strips 1 remain sterile until use. The support sheet 6 may be scored or perforated between a predetermined number of packaged bandages so that individual or groups of packaged bandages may be torn off for immediate or subsequent use as shown in FIGS. 14 and 15. This also allows the user to remove and discard portions of the support sheet 6 remaining after any number of bandages has been used.

If continuous cover strips 18 are used, as shown in FIG. 8, then a continuous cover sheet 19 covers any number of adhesive bandage strips 1 and adheres to the area of the continuous support sheet 6 immediately surrounding each adhesive bandage strip 1, such that each adhesive bandage strip 1 is sealed between a portion of the continuous cover sheet 19 and the continuous support sheet 6, maintaining sterility. The continuous cover sheet 19 is cut or perforated into individual cover strips 18 so that bandages 1 can be removed and applied individually.

In this embodiment, the continuous support sheet 6 and continuous cover sheet 19 may both be scored or perforated between any number of adhesive bandages 1 as shown in FIGS. 8 and 13, thereby allowing any number of packaged bandages to be removed individually or in groups and also allowing removal of portions of the continuous support sheet 6 after any number of bandages 1 has been used.

FIG. 9 shows an exploded perspective view of an individual, packaged adhesive bandage that has been removed from a continuous support sheet of adhesive bandages having perforations between bandages and that also has cover strips cut or perforated from a continuous cover sheet.

Referring to FIG. 7, in operation, the cover strip 4 is grasped via the pull tab 5. When the pull tab 5 is pulled, the adhesive bandage strip 1 and the cover strip 4 are peeled together from the continuous support sheet 6, or from alternative, nonstick mounting pad 7 and the continuous support sheet 6. The temporary adhesive joining the bandage strip 1 and the cover strip 4 is of sufficient strength to overcome the bond between the adhesive side 2 of bandage strip 1 and sterile, nonstick mounting pad 7 or the support sheet. The adhesive bandage strip 1, still backed by cover strip 4, is then applied to the desired location on the recipient's skin.

FIG. 10 is a perspective view showing the typical application of an adhesive bandage strip 1 with a cover strip 4 to a recipient's skin. Once the adhesive bandage strip 1 is applied, because the temporary adhesive joining the adhesive bandage strip 1 and the cover strip 4 forms a bond that is weaker than the bond formed between the adhesive side 2 of bandage strip 1 and the recipient's skin, the cover strip 4 is peeled away from both the adhesive bandage strip 1 and the recipient's skin, thereby leaving the adhesive bandage strip 1 applied to the recipient's skin. The cover strip 4 may then be discarded.

FIG. 11 is an exploded perspective view showing the elements of a dispenser 10 for the packaged bandages described. The dispenser 10 consists of a top half 11 defining an access window 12, a bottom half 13, a support ledge 14, a spool 15, and a knob 16. As shown, the support ledge 14 is positioned within top half 11 directly underneath access window 12 and is supported by bottom half 13. The bottom half 13 is generally hollow so as to provide space for the packing of the continuous sheet 6. The spool 15 is generally located on one end of the lower half 13 and communicates with knob 16 on the exterior of the dispenser 10. Optionally, the dispenser 10 may also contain an aperture through which prepackaged bandages, or portions of support sheet remaining from bandages accessed through the access window 12, may pass for use or discarding.

The dispenser 10 can be manufactured out of any suitable material including metal, plastic or paper. The dispenser 10 may be refillable and may be used on a desktop or mounted to a wall.

FIG. 12 is a side cut away view showing a dispenser 10 packed with a fan folded continuous support sheet 6 of adhesive bandage strips 1. The continuous support sheet 6 is fed through and across support ledge 14 such that the adhesive bandage strips 1 are exposed through access window 12. The leading end 8 of continuous support sheet 6 is attached to spool 15 such that the continuous support sheet 6 can be advanced by rotating knob 16 as the adhesive bandage strips 1 are removed. Alternatively, the leading end 8 of continuous support sheet 6 may be fed through optional aperture 15a so that either packaged bandages can be removed for subsequent use, or portions of continuous support sheet 6 that remain after bandages have been removed via access window 12 may be removed and discarded.

FIG. 13 is a perspective view of the dispenser of FIGS. 11 and 12, showing the optional dispensing aperture.

FIG. 14 shows an alternate embodiment of a dispenser for packaged bandages or other adhesive-coated articles, in which the dispenser contains an access window 12 and a dispensing aperture 15a, but does not contain a spool and knob. The continuous support sheet 6 may be pulled through the aperture 17 so as to advance the continuous support sheet 6 after adhesive bandage strips 1 are removed through the access window 12. Alternatively, the dispenser 10 may allow bandages packaged on the continuous support sheet 6, and which were not removed while exposed in the access window 12, to pass through the aperture 17 and be removed at perforations in the continuous support sheet 6 either individually or in groups for later use.

FIG. 15 shows a perspective view of a portion of yet another embodiment of a dispenser for packaged bandages or other adhesive-coated articles. In this embodiment, multiple adhesive-coated articles are visible on access shelf 20.

FIG. 16 shows a perspective cut away view of a wall-mounted dispenser for bandages or other adhesive-coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled.

FIG. 17 shows a perspective cut away view of yet another embodiment of a dispenser for adhesive coated articles packaged according to the present invention, in which the assemblage of adhesive-coated articles is rolled. In this configuration, the dispenser contains no spool for coiling the remaining portions of the support sheet after removal of adhesive-coated articles.

While the invention has been disclosed with respect to an adhesive bandage strips, it will be appreciated that the invention is equally well suited for other shapes of adhesive bandages as well as other types of adhesive-backed articles such as bumper stickers, adhesive-backed name tags, and the like.

FIG. 4 is an exploded side view conceptually showing the layers and adhesives of a sterile article encased according to the present invention. A sterile article 133 is effectively encased for dispensing or distribution by its attachment to cover member 132. The sterile article 133 is further encased by removably adhering cover member 132 to support member 130 with first adhesive coating 131 to form an adhesive bond therebetween.

FIG. 5 is a conceptual side view of another embodiment of the present invention, showing a sterile article adhered to cover member 132 by second adhesive 134, forming a second bond therebetween. As in the embodiment of FIG. 4, the sterile article 133 is encased by removably adhering cover member 132 to support member 130 with the use of first adhesive coating 131 to form a first bond therebetween and functionally encase the sterile article 133.

FIG. 18 shows an exploded perspective view of an embodiment of the invention in which the sterile article is a chemical substance applicator 52 such as a cotton swab, a portion of gauze, sponge, cloth, or other material and is affixed to a cover 50 which serves as the cover member. The applicator 52 is further packaged by placement of the applicator 52 on a support sheet 53 which serves as the support member. The portion of the cover 50 extending beyond the periphery of the applicator 52 is coated with a temporary first adhesive which removably adheres that portion of the cover 50 to a corresponding region of the continuous support sheet 53, thereby sealing the applicator 52 in a sanitary package. The adhesive surrounding the applicator 52 used to removably adhere the periphery of the applicator 52 to the support sheet 53 may also be used to adhere the cover 50 to the applicator 52.

Multiple covers may be formed from a continuous sheet that is cut, scored, or perforated between adjacent applicators or they may formed from separate pieces of material. The covers 50 may contain a corner-type tab 54 as shown in 18, an edge-type tab 55 as shown in FIG. 19, or any other means for gripping that

facilitates the removal of the cover 50 and applicator 52 from the support sheet 53. The cover 50 may contain an additional handle or gripping device on its surface to further assist the user in removing or holding the cover 50.

The applicator 52 may be pre-treated with any chemical substance to be applied such as antiseptics, makeup, lotions, medicaments or any other suitable substance for application. Alternatively, the applicator 52 may not be pre-treated. If the applicator 52 is pre-treated, then the user will pull the tab 55, thereby removing the applicator 52 from the support sheet 53, and exposing the applicator 52 for application to the recipient surface such as human skin. If the applicator 52 is not pre-treated, then after removal from the support sheet, the applicator 52 may be used as a sanitary wipe, or the user may apply any suitable substance such as bottled alcohol, makeup, or lotion, or any other suitable substance to the applicator and then apply the applicator to a recipient surface. In this embodiment, it is contemplated that both pretreated and non-pretreated swabs will have application beyond the medical field and will provide a convenient swab or applicator for the application of any number of chemical substances in any number of commercial or household applications.

Applicators of this embodiment may be dispensed from single or continuous sheets or rolls. FIG. 19 shows an embodiment in which multiple applicators 52 are packaged on a single support sheet 53. The encased, or packaged, applicators of FIGS. 18 and 19 may be dispensed with the use of the dispensers of FIGS. 20 and 21 respectively. Alternatively, the encased articles may be dispensed with dispensers not shown in the figures, but which may be similar or identical to the dispensers of FIGS. 14 and 15 in which any such articles may be dispensed via the aperture at the end of an access shelf of the dispenser. In yet another configuration not shown, such encased sterile articles may be dispensed on rolled sheets with dispensers similar or identical to the dispensers of FIGS. 16 or 17.

FIG. 22 shows another embodiment in which the invention is used to dispense doses of medication such as capsules, capelets, pills, or other units of medicine. In this embodiment, a dosage of medicine, such as capsule 70, is packaged in dispensing tray 71 which functions as the support member and which contains holding troughs 73. In one embodiment, the size of the capsule 70 exceeds the interior size of the holding trough 73 in at least one dimension so that some pressure may be required for the removal of capsules 70 from the trough 73. The capsules 70 are further packaged with the use of a cover sheet 72 which functions as the cover member and which is coated in part on one side with an adhesive that removably adheres peripheral and central portions of the cover sheet 72 to corresponding portions of the dispensing tray 71 so as to retain the capsules 70 in a completely enclosed sanitary package. The tray 71 may contain a suitable means for gripping, such as pull tab 75 in one or more corners or along one or more edges for ease in removing the tray 71 from the cover sheet 72.

In this embodiment, filled packages may be dispensed through a dispenser such as that shown containing a spool and aperture in FIG. 27 or an aperture only as in FIG. 26. Trays 71 may be pulled with tab 75 through access window 81. Alternatively, complete, unused packages may be dispensed through an aperture 82 for immediate or subsequent use and are perforated or scored between single or multiple packages. If complete, unused packages are dispensed through an aperture, then, the user removes capsule 70 by peeling back the tray 71 with the use of tab 73 or a suitable handle or grasping device affixed to the exterior of the tray 71. The user then squeezes the trough 73 to eject the capsule 70 therefrom, as shown in FIG. 25.

In another embodiment, as shown in FIGS. 23 and 24, a thin, burstable film 74, made of paper, plastic, metal foil, or any other suitable material, is adhered to the top surface of dispensing tray 71 so as to form an intermediate layer between cover sheet 72 and dispensing tray 71. In this embodiment, the cover sheet 72 is removably adhered to the film 74. Once the cover sheet 72 is

removed, the user must then squeeze the trough 73 to force the capsule 70 to penetrate or break through the film 74 and eject the capsule 70 from the package for use.

For any of the embodiments used in dispensing medication, the dispensing trays may be formed individually or from single or continuous sheets of material. The cover sheets may be spaced or may be formed by cutting, perforating, or scoring of a continuous sheet of material. If multiple dispensing trays are formed from a single piece of material, the material may be perforated or scored between adjacent packages or at other regular or varying intervals to allow dispensing or single or multiple packages of medication.

In any of the embodiments for dispensing medication, dosage information may be printed on the surfaces of the cover sheet or dispensing tray. This allows the manufacturer or user to label particular doses. For example, with certain medications, a particular dosage must be taken on each day of the week such that the dosages for different days will differ. In this case, a particular dosage can be labelled for "Monday," "Tuesday," and so forth. These embodiments allow the user to see quickly whether the dosage for a particular day has already been dispensed. This may be particularly helpful in the case of forgetful patients.

While the invention has been disclosed with respect to particular embodiments, the applicant does not regard the invention as being limited to such embodiments or applications. It is also understood that this description is not meant to be limiting because further modifications may now suggest themselves to those skilled in the art and is intended to cover such modifications as fall within the scope of the following claims.

CLAIMS:

1. An encased adhesive-coated article combination comprising:

a. a support member;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a second adhesive coating covering at least a portion thereof, said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and said cover member forming a second adhesive bond.

2. The encased adhesive-coated article combination of claim 1, wherein said second adhesive bond is weaker than the first adhesive bond.

3. The encased adhesive-coated article combination of claim 2, wherein said support member further comprises a nonstick mounting pad.

4. The encased adhesive-coated article combination of claim 1 further comprising a means for gripping attached to said cover member.

5. The encased adhesive-coated article combination of claim 4, wherein said adhesive-coated article is an adhesive bandage.

6. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-coated article being removably adhered to said support member by contact of said first adhesive coating, the first adhesive coating between said support member and said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a second adhesive coating covering at least a portion thereof, each said cover member being removably attached to said support member by contact of said second adhesive coating with said support member, the contact between said support member and each said cover member forming a second adhesive bond.

7. The assemblage of encased adhesive-coated articles of claim 6, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

8. The assemblage of encased adhesive-coated articles of claim 6 wherein the support member further comprises a plurality of nonstick mounting pads.

9. The assemblage of encased adhesive-coated articles of claim 7, wherein said adhesive-coated articles are adhesive bandages.

10. The assemblage of encased adhesive-coated articles of claim 8, wherein said adhesive-coated articles are adhesive bandages.

11. The assemblage of encased adhesive-coated articles of claim 7, wherein said support member is a sheet.

12. The assemblage of encased adhesive-coated articles of claim 11, wherein said sheet is a continuous sheet.

13. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a folded configuration.

14. The assemblage of encased adhesive-coated articles of claim 12, wherein said assemblage is contained in a dispensing unit in a rolled configuration.

15. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated at predetermined intervals.

16. The assemblage of encased adhesive-coated articles of claim 12, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

17. The assemblage of encased adhesive-coated articles of claim 11, wherein said adhesive coated articles are adhesive bandages.

18. The assemblage of encased adhesive-coated articles of claim 12, wherein said adhesive coated articles are adhesive bandages.

19. The assemblage of encased adhesive-coated articles of claim 6, wherein each said cover member is dimensioned to extend beyond the peripheral edges of a respective adhesive-coated article.

20. An encased adhesive-coated article combination comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. an adhesive-coated article, said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, said adhesive-

coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and the first adhesive surface forming a first adhesive bond; and

c. a cover member removably attached to said support member to releaseably encase said adhesive-coated article, said cover member including a third adhesive coating thereon, said cover member being removably attached to said support sheet by contact of said patterned second adhesive coating with said cover member, the contact between said support member and said cover member forming a second adhesive bond, said cover member further being removably attached to said adhesive-coated article by said third adhesive coating, the third adhesive coating forming a third adhesive bond between said cover member and said adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

21. The encased adhesive-coated article combination of claim 20, wherein said second bond is weaker than said first bond.

22. The encased adhesive-coated article combination of claim 20, wherein said support member further comprises a nonstick mounting pad.

23. The encased adhesive-coated article combination of claim 20 further comprising a means for gripping attached to said cover member.

24. The encased adhesive-coated article combination of claim 23, wherein said support member further comprises a nonstick mounting pad.

25. The encased adhesive-coated article combination of claim 23, wherein said adhesive-coated article is an adhesive bandage.

26. The encased adhesive-coated article combination of claim 24, wherein said adhesive-coated article is an adhesive bandage.

27. An assemblage of encased adhesive-coated article combinations comprising:

a. a support member having a patterned second adhesive coating applied thereto;

b. a plurality of adhesive-coated articles, each said adhesive-coated article including a first adhesive surface, said first adhesive surface having a first adhesive coating covering at least a portion thereof, each said adhesive-coated article being removably adhered to said support member by said first adhesive coating, the first adhesive coating between said support member and said first adhesive coating, the first adhesive coating between said support member and each said first adhesive surface forming a first adhesive bond; and

c. a plurality of cover members, each said cover member being removably attached to said support member to releaseably encase a respective adhesive-coated article, each said cover member including a third adhesive coating thereon, each said cover member being removably attached to said support sheet by contact of said second

adhesive coating with said support member, the contact between said support member and each said cover members forming a second adhesive bond, each said cover member further being removably attached to a respective adhesive-coated article by a third adhesive coating, the third adhesive coating forming a third adhesive bond between said each said cover member and a respective adhesive-coated article, said third adhesive bond being stronger than said second adhesive bond.

28. The assemblage of encased adhesive-coated articles of claim 27, further comprising a plurality of means for gripping, each said means for gripping attached to a respective cover member.

29. The assemblage of encased adhesive-coated articles of claim 27, wherein said support member further comprises a plurality of nonstick mounting pads.

30. The assemblage of encased adhesive-coated articles of claim 28, wherein said adhesive-coated articles are adhesive bandages.

31. The assemblage of encased adhesive coated articles of claim 30, wherein said support member further comprises a plurality of nonstick mounting pads.

32. The assemblage of encased adhesive-coated articles of claim 28, wherein said support member is a sheet.

33. The assemblage of encased adhesive-coated articles of claim 32, wherein said sheet is a continuous sheet.

34. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is folded.

35. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is rolled.

36. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated at predetermined intervals.

37. The assemblage of encased adhesive-coated articles of claim 33, wherein said continuous sheet is perforated between each adhesive-coated article and an adjacent adhesive-coated article.

38. The assemblage of encased adhesive-coated articles of claim 33, wherein said adhesive coated articles are adhesive bandages.

39. The assemblage of encased adhesive-coated articles of claim 37, wherein said adhesive coated articles are adhesive bandages.

40. The plurality of encased adhesive-coated articles of claim 27, wherein each said cover member is dimensioned to extend beyond the peripheral edges of said adhesive coated articles.

41. An encased sterile article combination comprising:

a. a support member;

b. a sterile article; and

c. a cover member removably attached to said support member to functionally encase said sterile article, said sterile article being removably adhered to said cover member.

42. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator.

43. The encased sterile article combination of claim 41 wherein said sterile article is a medical applicator that includes a dispensable medicament.

44. The encased sterile article combination of claim 41 wherein said sterile article is a unit of medicine.

45. The encased sterile article combination of claim 41 wherein said sterile article is a pill, capelet, or capsule.

46. The encased sterile article combination of claim 41 wherein said support member comprises a continuous sheet of molded housings adapted to fittably receive said sterile article.

47. The enclosed sterile article combination of claim 41 wherein said cover member further includes gripping means.

48. The encased sterile article combination of claim 41 further comprising a non-adhesive, burstable film disposed between said support member and said cover member, said film being functionally effective to protect the sterility of said sterile article after the cover member has been removed.

49. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a folded configuration.

50. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit in a rolled configuration.

51. An assemblage of encased sterile article combinations wherein said assemblage is contained in a dispensing unit as individual encased units.

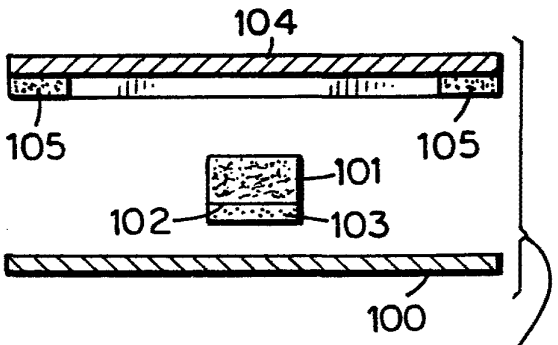


Fig. 1

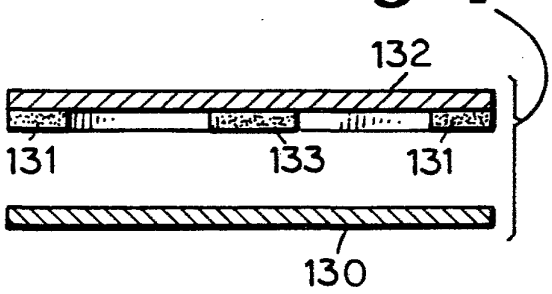


Fig. 4

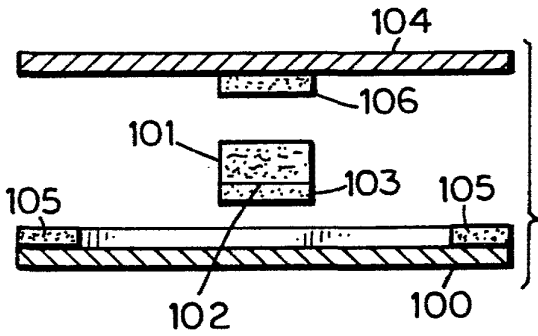


Fig. 2

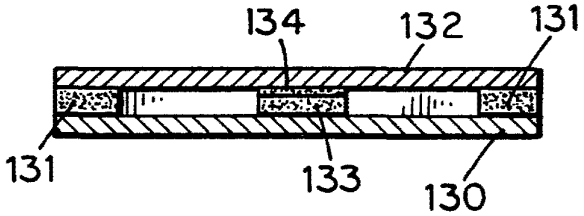


Fig. 5

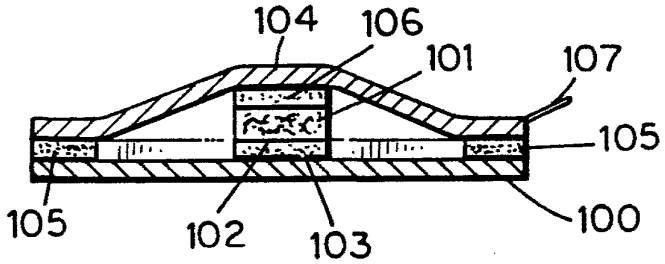


Fig. 3

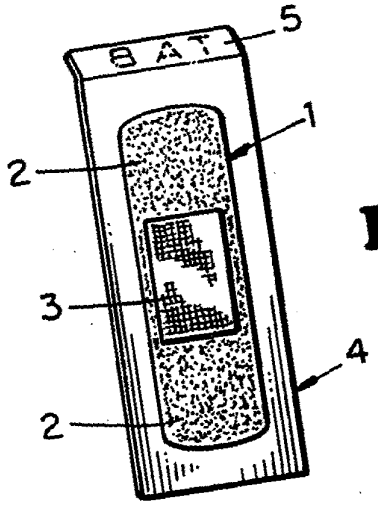


Fig. 6

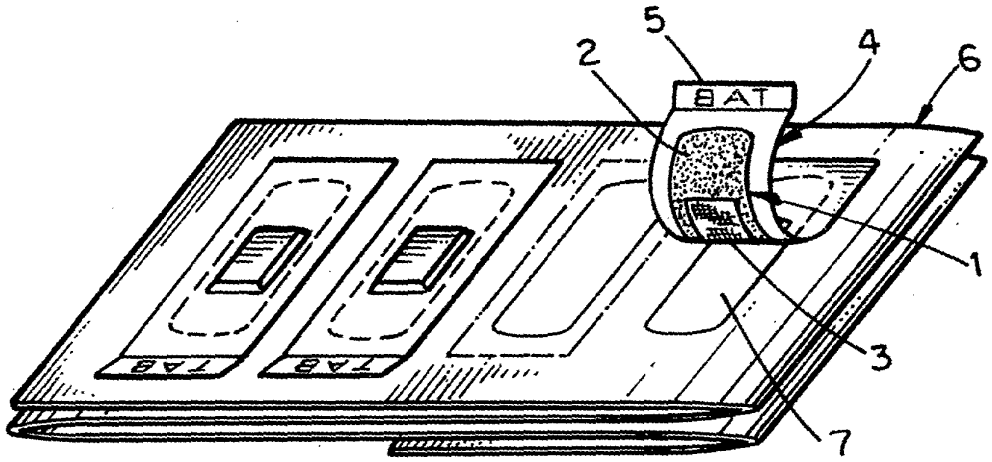


Fig. 7

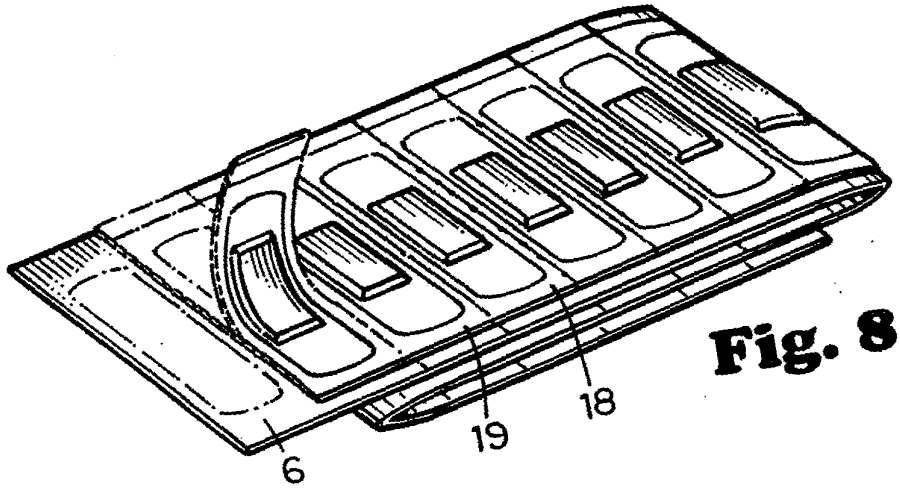


Fig. 8

Fig. 11

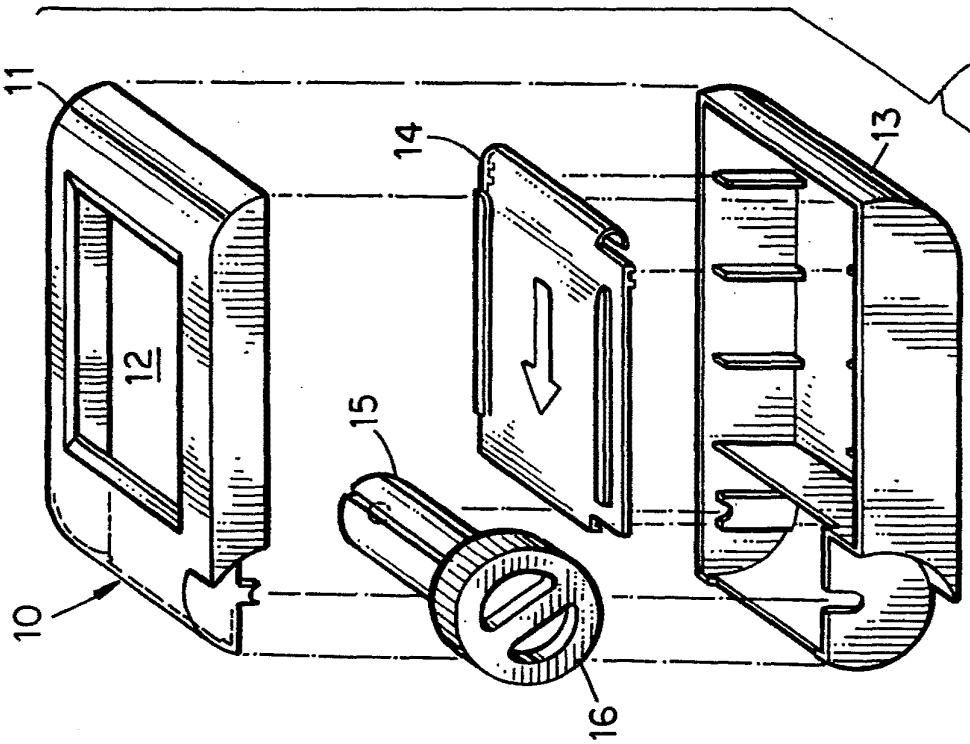


Fig. 9

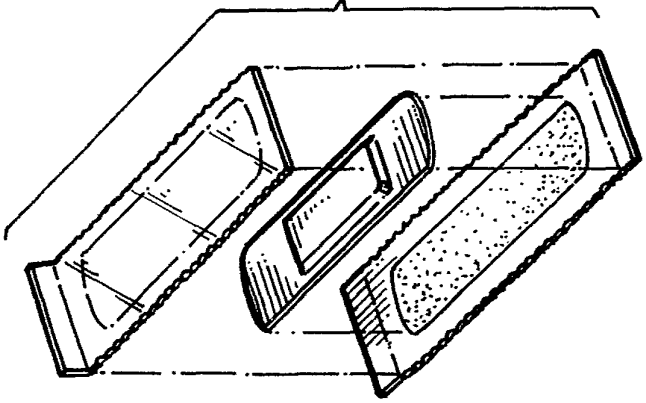
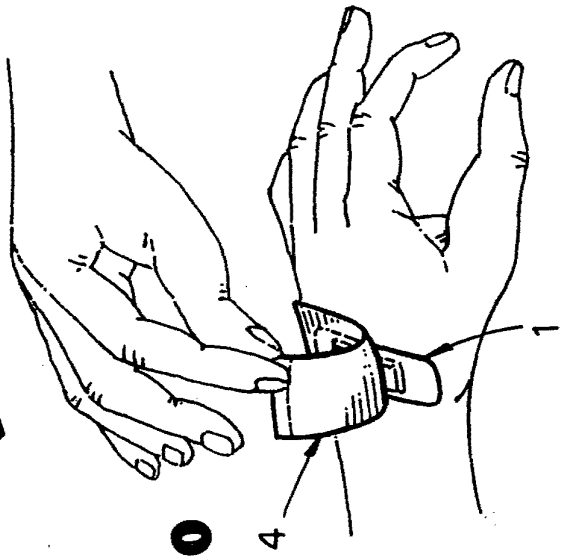


Fig. 10



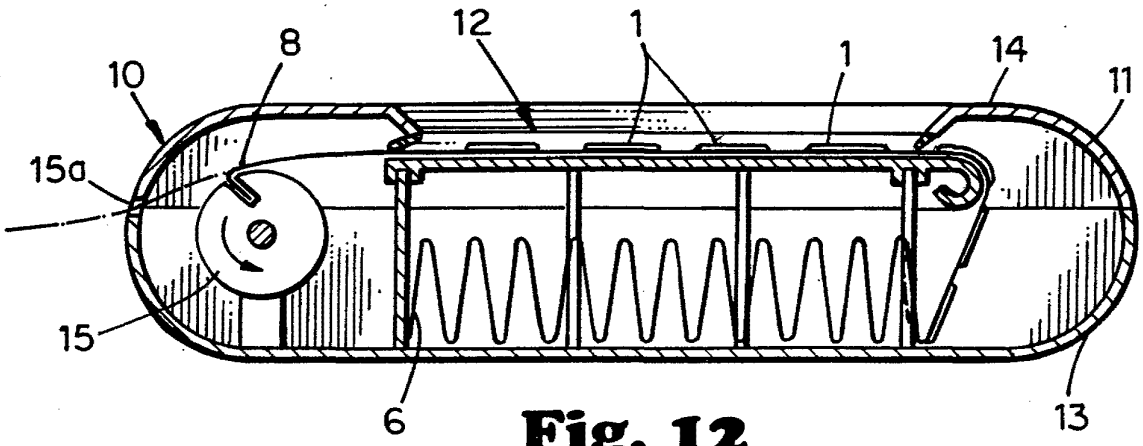


Fig. 12

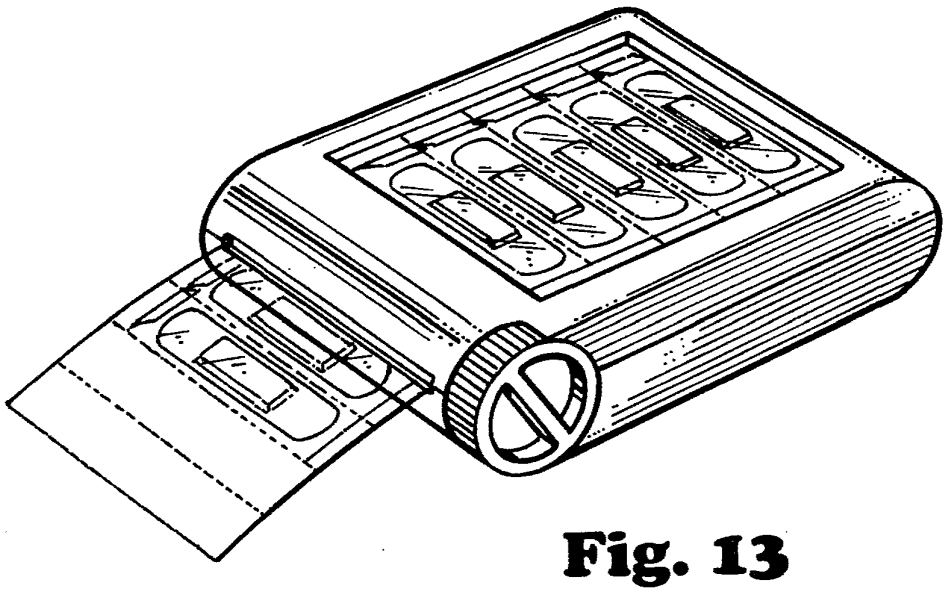


Fig. 13

Fig. 14

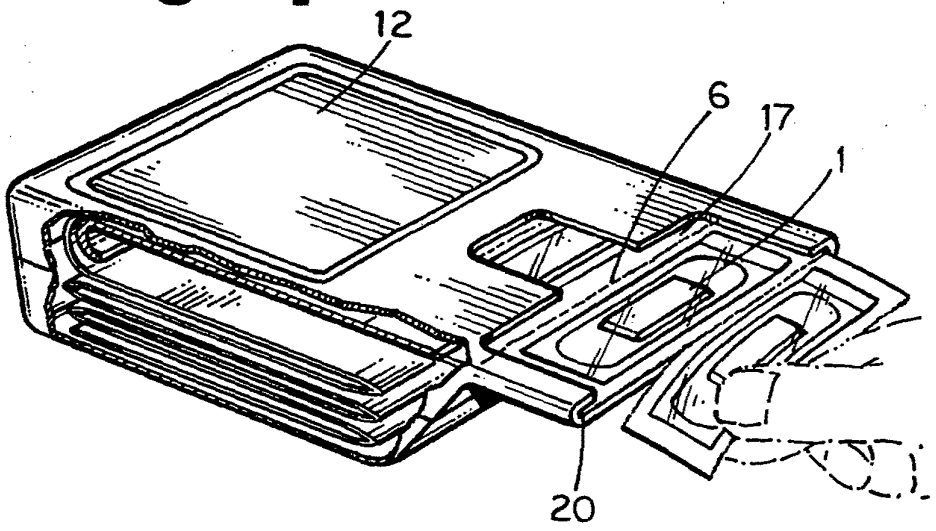


Fig. 15

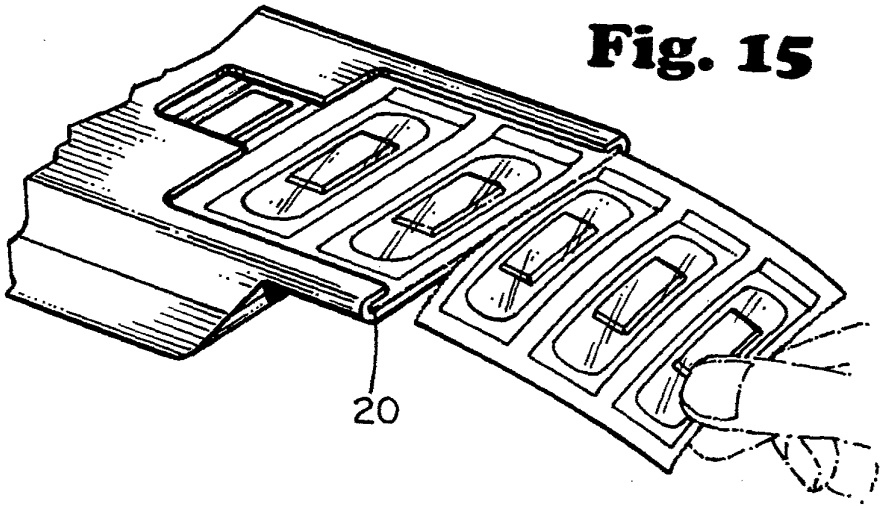
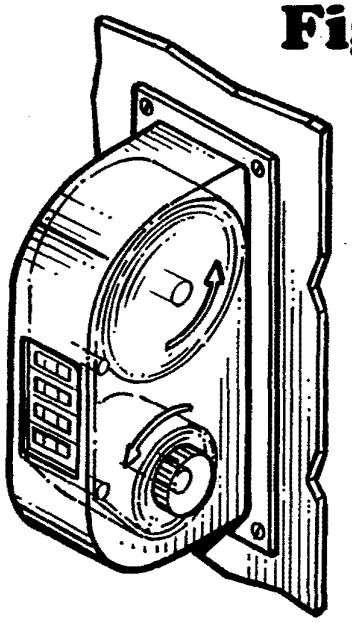


Fig. 16



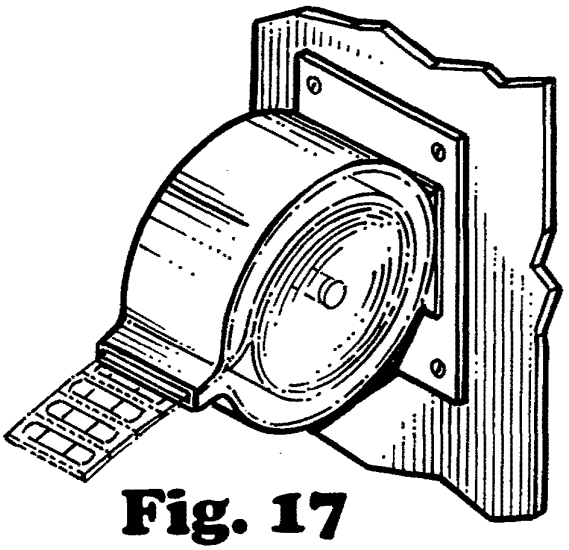


Fig. 17

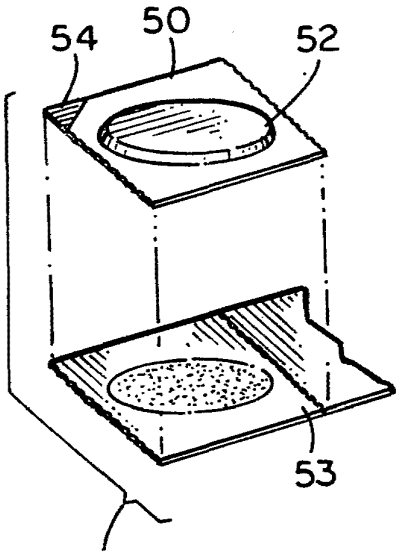


Fig. 18

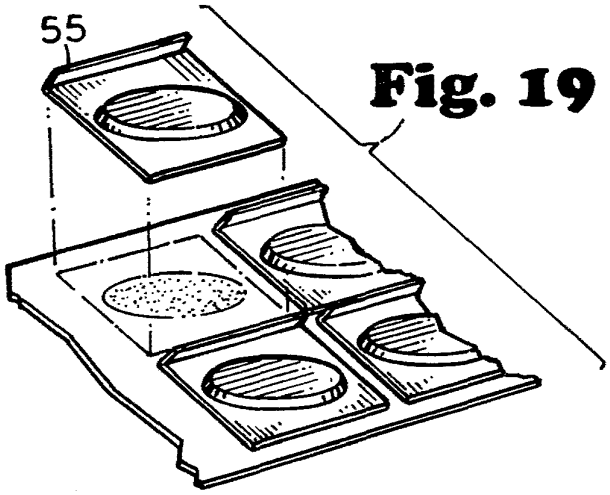


Fig. 19

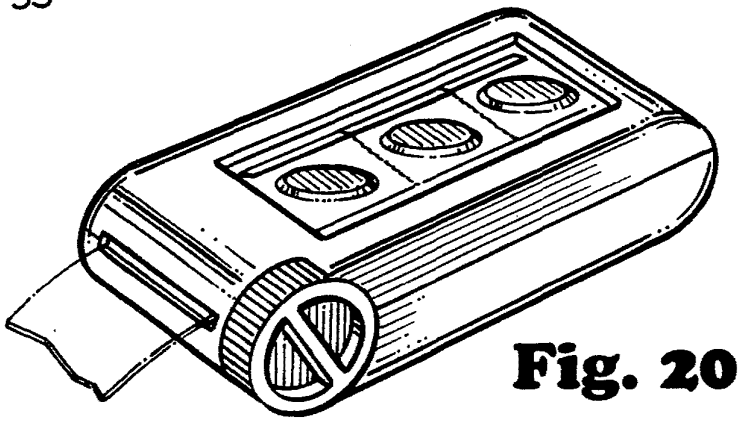
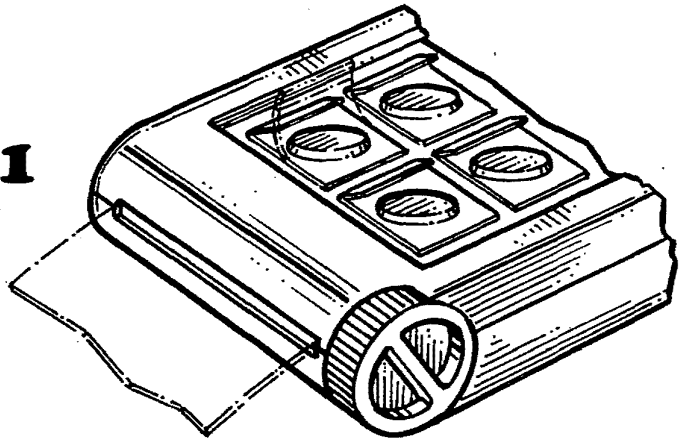


Fig. 20

Fig. 21



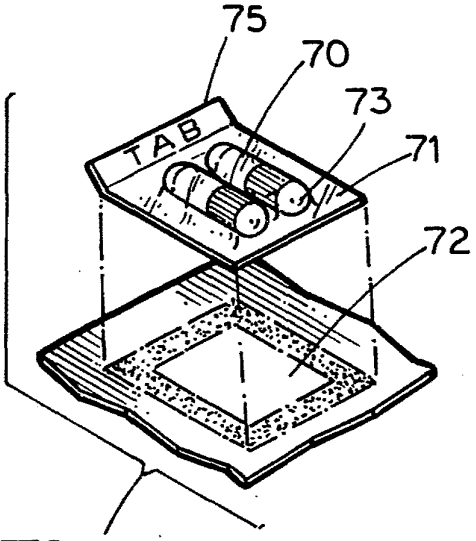


Fig. 22

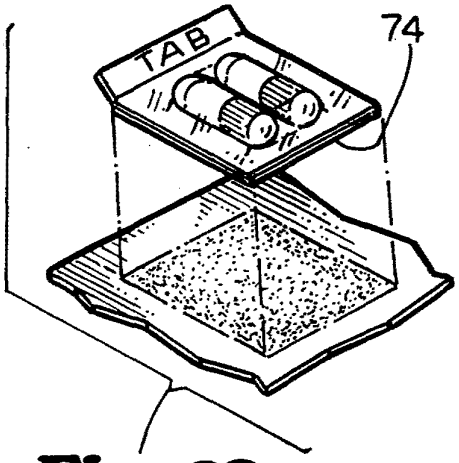


Fig. 23

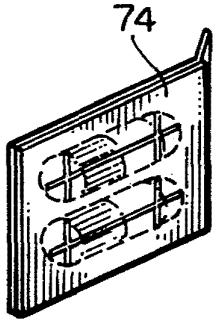


Fig. 24

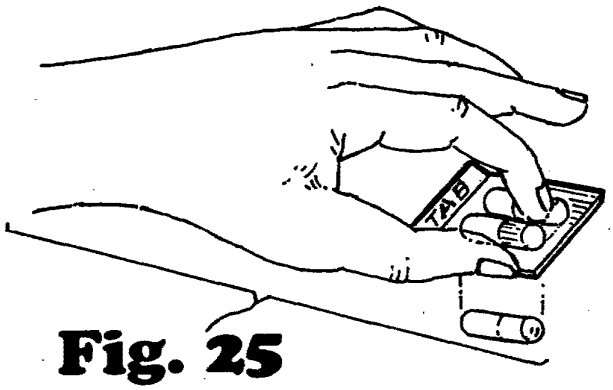


Fig. 25

Fig. 26

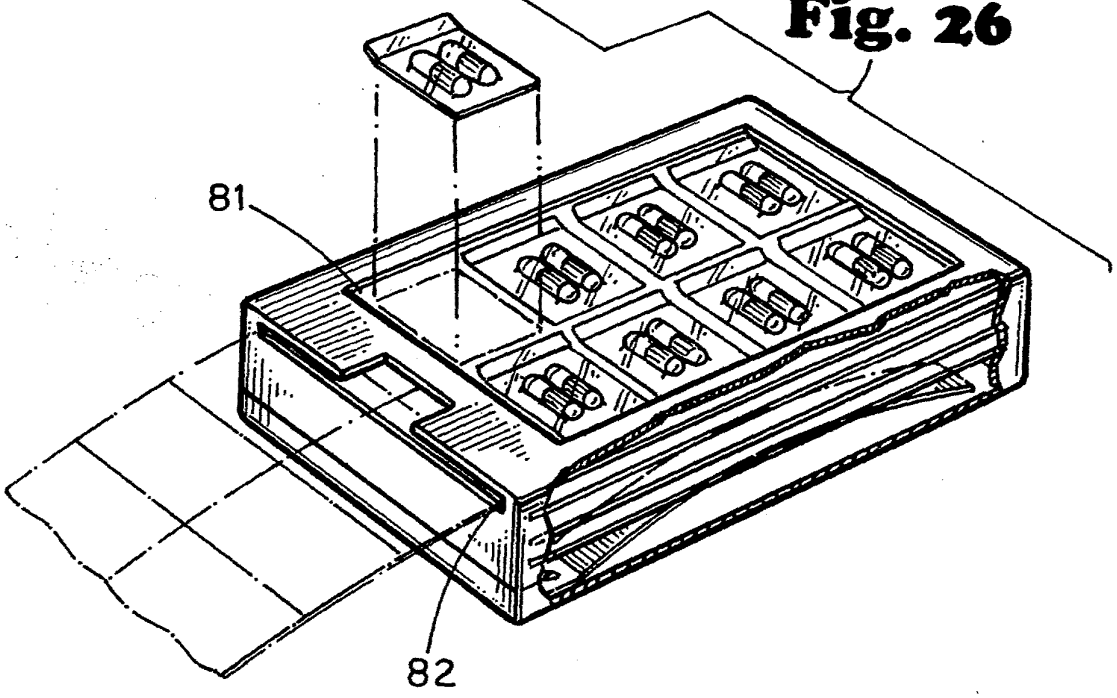
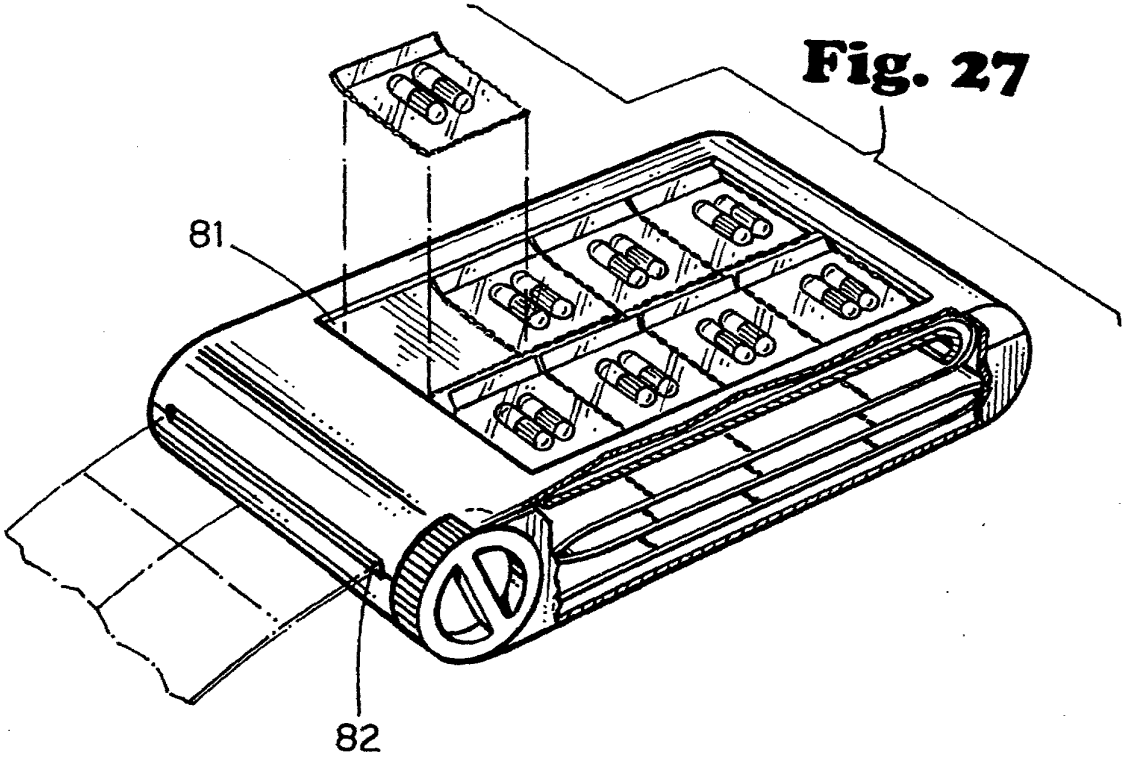


Fig. 27



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OE SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :206/528, 440, 441
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 206/528, 440, 441, 820, 534.1, 538

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 4,265,234 (SCHAAR) 05 May 1991, See the entire document.	1-5, 20-26 ---- 6-19, 27-41
X ---- Y	US, A, 4,807,753 (GOLDSTEIN) 28 February 1989, See the entire document.	50 ---- 6-12, 14, 17-19, 27-33, 35, 38, 40

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"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
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 03 MARCH 1995	Date of mailing of the international search report 22 MAR 1995
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 FOR STEVE MEYERS Stella M. Veney Paralegal Specialist Group 2400 Telephone No. (703) 308-0771

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	US, A, 4,993,586 (TANLBEE, DECEASED ET AL.) 19 February 1991, See the entire document.	49 ---- 6-13, 17-19, 27-34, 38, 40
X ---- Y	US, A, 4,666,040 (MURATA) 19 May 1987, See the entire document.	51 ---- 6-12, 15, 16-19, 27-33, 36-40
X	US, A, 3,809,221 (COMPERE) 07 May 1974, See the entire document.	41-48
X	US, A, 3,630,346, (BURNSIDE) 28 December 1971, See the entire document.	41-48

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

B65D 1/09; A61B 19/08

Form PCT/ISA/210 (extra sheet)(July 1992)

(19) Europäisches Patentamt
European Patent Office
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(11) EP 0 514 691 B1

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(45) Date of publication and mention of the grant of the patent:
03.01.1996 Bulletin 1996/01

(51) Int Cl.[6]: **C08J 5/18**, A61L 15/32, A61L 27/00, A61L 25/00, C08L 89/06

(21) Application number: **92107249.2**

(22) Date of filing: **29.04.1992**

(54) Non-porous collagen sheet for therapeutic use, and the method and apparatus for preparing it

Nichtporöse Kollagenfolie zur therapeutischen Verwendung, und Verfahren und Vorrichtung zu ihrer Herstellung

Feuille non poreuse de collagène à usage thérapeutique, et procédé et appareil pour sa préperation

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE

(30) Priority: **23.05.1991 IT MI911423**

(43) Date of publication of application:
25.11.1992 Bulletin 1992/48

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(74) Representative: **Gervasi, Gemma, Dr. et al**
I-20122 Milano (IT)

(56) References cited:
EP-A- 0 376 931
DE-A- 1 945 072
FR-A- 2 160 462
US-A- 4 948 540

Remarks:
The file contains technical information submitted after the application was filed and not included in this specification

EP 0 514 691 B1

Description

Collagen is a scleroprotein widespread in nature. It represents about one third of the total proteins of the human body.

Medical practice has recently seen the introduction of the use of collagen as a stimulating agent in the cicatrization process involving an interaction effect with various growth factors, because of its capturing action on fibronectin, a glycoprotein which promotes cell attachment and the migration and replication of the resultant cells (see "I1 collageno nella cicatrizzazione" by B. Palmieri, publ. Artestampa, January 1990, pp. 40-42) and other actions which are still not totally clear. The known collagen product, using a particular non-denaturing process, is prepared in stable form by a process of extraction from animal organs rich in this scleroprotein, purification and subsequent lyophilization. The final product is in the form of mats of greater or lesser thickness, characterised by high absorbent power (exudates and liquids in general) because of its structure in the form of fibres which are spaced apart and branched in such a manner as to make a large specific surface available for absorption (up to 50 times its weight). The hydrophilic nature of collagen also greatly favours this absorbent power.

In addition to the aforesaid function, the role of collagen in cicatrization is characterised by collagen/platelet interaction and the formation of a bond between the collagen, the fibronectin and the growth factors, molecules which are known to be implicated in regulating the cicatrization process (see pages 45-46 of the aforesaid text).

There are however cases in which the absorbent formation of the collagen sponge and its hydrophilic nature lead to an excessive loss of physiological liquids. It is well known that an evaporation process normally occurs through the undamaged skin, and this increases considerably in the case of skin lesion, resulting in dehydration of the underlying layers. The phenomenon is accentuated for example in burn cases, when large skin portions are damaged traumatically. In this case the absorbent effect of lyophilized collagen further increases the process of evaporation, with consequent damage to the underlying structure.

Another kind of known collagen-based medicament useful for wound healing is represented by the collagen membranous material disclosed by EP-A-0376931, which is prepared by disrupting and centrifuging a collagen gel matrix so to precipitate collagen, homogenizing the precipitated material in the form of a paste, casting and drying the paste.

The present invention provides a product which while maintaining the rapid cicatrization characteristics of collagen, at the same time prevents excessive evaporation, allows constant inspection of the bed of the wound without having to be removed (transparency), is simple and practical to use, adheres satisfactorily to the injured surface, does not require frequent replacement, can transpire to allow oxygenation of the bed of the wound while preventing its contamination by bacteria, is absorbable but not soluble in the biological liquids with which it comes into contact, unless by specific enzymatic action, and is structurally homogeneous.

Another important characteristic of the collagen according to the invention is that of being suitable as interposition material for preventing accretions in the internal surgery operations.

To obtain a product with these characteristics, type I collagen was used as defined in Table 1 on page 3 of the aforestated text, that is having molecular structure $[\alpha 1(I)_2]\alpha 2(I)$, this having the characteristic of being insoluble in the various types of biological liquids. Type I collagen present in the skin represents about 80% of the total located in the deep dermis, 90-95% in the tendons and 100% in the bones. Type I collagen is therefore the most biologically similar to that present in the human skin.

Because of its insolubility, in order to obtain a product of homogeneous structure, use was made of the known method of dispersing fibrous collagen in a dilute acetic acid solution of about pH 2.5 and maintaining agitation until a good dispersion of the collagen fibres in the liquid is obtained. At this pH value the fibres swell to form a gel. The gel obtained, still comprising fibre fractions which have not completely gelled and possibly corpuscles of extraneous substances, is further diluted with an acetic acid solution of pH 2.5-3.5 until a sufficiently fluid mass is obtained, which is then filtered.

The filtering, which is done under vacuum, uses a special filter, indicative (but not limitative) characteristics of which are given hereinafter, and allows practically total elimination of the inevitable air bubbles which form during gelling and are difficult to eliminate given the viscosity of collagen gel.

By the effect of the vacuum, which has to be of the order of 3999 Pa residual pressure, these bubbles increase their volume, the passage through the mesh then breaks down and eliminates them. It has been found experimentally that the best filtration conditions to achieve the described phenomenon are a gel temperature of 10-30°C, preferably 25-28°C, and a residual vacuum of 2666-7998 Pa (20-60 mmHg), preferably about 3999 Pa (30 mmHg).

These data are indicative and have been found experimentally to be the most effective, although not representing a limitation on the operating conditions of this process.

The filtered gel is collected in a closed vessel maintained under vacuum and constructed in such a manner that the filtered gel runs along vessel partition walls located below the filter mesh and structured to produce a continuous liquid film which does not allow further air absorption after filtration, following inclusion of air bubbles.

The filtered gel is further maintained under vacuum

at 2666-3332.5 Pa (20-25 mmHg) for a further hour to allow total elimination of any air bubbles which may still be present in the gel.

FILTER APPARATUS

The filter required for filtering the collagen gel, which besides eliminating the solid particles, which are retained on the mesh, also eliminates the air bubbles contained in it, consists of an upper cylindrical stainless steel shell provided with a scraping stirrer to keep the collagen gel mixed and to remove solid particles from the mesh so that they do not clog it. The bottom of the cylindrical shell houses a stainless steel mesh with a mesh size of less than 0.1 mm (Taurail meshes have been found to be particularly effective).

The lower part (below the mesh) consists of a cylindrical shell in which vacuum can be generated by a suitable pump. The air bubbles contained in the gel which filters through the mesh increase considerably in volume because of the vacuum.

At about 3 mm below the filter mesh there is a device consisting of a series of stainless steel plates which are vertically or raking placed and parallel between them. The filtered gel descends along these plates in the form of a continuous liquid film and runs by gravity towards the bottom of the vessel.

Those air bubbles which do not break down by the effect of the reduced pressure remain mainly in the upper part of the device whereas the gel, now free or almost free of air, runs to the bottom of the vessel. Any very small bubbles still present in the filtered gel decrease considerably in volume when returned to atmospheric pressure, so that they become practically absent.

In this respect, during filtration because of the difference between the pressure of the gel environment before filtration and the residual pressure below the mesh (about 3999 Pa), the bubble volume increases more than 25 times. Likewise, on passing from vacuum to the environmental pressure the bubble volume decreases 25 times. Hence the air bubbles of diameter less than 0.100 mm (advisable mesh passage size) have a diameter of less than 0.034 mm when returned to atmospheric pressure, ie are practically invisible. During drying, these residual bubbles are eliminated without leaving appreciable craters in the structure of the obtained sheet.

This means that extremely uniform thicknesses can be obtained over the entire sheet surface, so avoiding any porosity which could represent a point of preferential attack by enzymatic action, which would annul the protective effect against invasion by micro-organisms.

DRYING

The filtered gel obtained as described, free from extraneous particles and air bubbles and perfectly clear and transparent, can then be used for preparing films of desired thickness and diameter. For this, after analysis to exactly determine the concentration of the filtered gel, exactly measured quantities for obtaining films with the desired collagen thickness must be metered into suitable containers. This metering is generally effected by a suitable peristaltic pump which prevents incorporating air into the gel while at the same time preventing heating or friction which could damage the structure of the collagen protein. The containers are of tray shape and are formed of antiadherent material.

The described trays loaded with the gel in a controlled environment (relative humidity 60-80%, temperature 20-22°C, environment class 10,000 or less) are placed in a suitable controlled drying oven where they are left to stand for at least two hours to obtain perfect gel thickness uniformity. The oven is purged with a nitrogen stream for about 30 minutes to totally eliminate air and remove oxygen, in order to ensure constant operating conditions and prevent possible oxidation.

This operation has also been shown to practically totally block the growth of micro-organism colonies, which sometimes occurs if the procedure is carried out with air present in the environment. Drying is effected in a nitrogen stream under closed cycle.

The drying, being the critical stage for obtaining films with the desired characteristics, is conducted under particular conditions in an appropriate oven shown schematically in Figure 1.

In this, the reference numeral 1 indicates the drying trays resting on perforated side walls, V indicates the fan for circulating nitrogen through the apparatus, N_2 indicates the nitrogen feed valve, GF indicates the refrigeration unit with coil, S represents a parallel plate device for separating condensate droplets, T_1 indicates a first thermometer, SC indicates the condensed water discharge, R indicates the heating device, T_2 indicates a second thermometer, I_1 indicates a first hygrometer, MO indicates an oxygen meter (analyzer), Sg indicates the gas discharge, Tr indicates an overpressure trap and I_2 indicates a second hygrometer.

The oven is arranged in this manner to satisfy the following requirements:

1) the facility for eliminating air by purging with nitrogen to a residual oxygen content of less than 2%;

2) the facility for varying the nitrogen cooling and heating temperature to a maximum of 30°C, to control the relative humidity in the drying chamber and the water evaporation rate;

3) the facility for regulating the rate of nitrogen circulation through the chamber so as not to create high flow points and hence maintain a uniform drying rate over the entire surface and prevent the formation of creases which, besides being undesirable from the appearance aspect, are an indication of different collagen concentrations and poor homogeneity of drying (localized drying).

The H_2O content of the product must not be higher than 20% by weight. It is preferable to achieve a higher level of drying (down to 2% or 3% of H_2O), in particular to ensure proper elimination of the acetic acid present in the initial gel. The dried product obtained easily reabsorbs moisture from the environment, while being maintained within the maximum limit of 20%.

EXAMPLE

The conditions found experimentally to be most appropriate for conducting a drying cycle are given below by way of non-limiting example.

1st stage:

Nitrogen purging until the oxygen content is less than 1%, standing for two hours to come to equilibrium, loaded gel level 10 mm, gel collagen concentration 0.5%.

2nd stage:

Starting of nitrogen circulation by fan.
Nitrogen temperature after cooling -5°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 12-14%.
Relative humidity exit of drying region (point I_2) 70-80%.

3rd stage:

Nitrogen temperature after cooling -15°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.
Relative humidity entry to drying region (point I_1) 6-7%.
Relative humidity exit of drying region (point I_2) 45-50%.

4th stage:

Final drying

Nitrogen temperature after cooling -40°C (T_1).
Nitrogen temperature after heating 26-28°C (T_2).
Time about 12 hours.

5th stage:

Product discharge, preparation of a new load. Complete removal of water from the cooling coil and purging the oven by nitrogen circulation at 70-80°C for two hours, cooling to 20°C and loading new product.

The nitrogen flow rate through the drier is adjusted on the basis of the required degree of drying.

A semi-transparent film with a thickness of about 200 micron is obtained. The thickness can vary in general between 0.02 and 2 mm. This represents a non-specific item for the purposes of the therapeutic application as it determines only the product absorption time but not its specific characteristics. The degree of drying can also vary as stated.

The characteristics of the film obtained are:

- maintaining of the "native" structure of collagen fibre (the classical triple spiral structure of collagen has been demonstrated by the electron microscope)
- absence of degradation products such as monomers or dimers of collagen not organized into fibrils, or gelatin, an indication of potential allergenicity
- high protein nitrogen content (exceeding 90%)
- high hydroxyproline content (exceeding 12%)
- low absorbent power (about 10-15 times its weight against 50 times for the lyophilized product of the known art)
- high resistance to enzymatic attack
- good product transparency
- excellent plasticity after immersion in physiological solution.

The product obtained in this manner is sterilized by irradiation with gamma rays and used in the treatment of burns and generally all cases of skin removal or damage.

The result is excellent both in terms of tolerance (no case of allergenicity or hypersensitivity to the medicament has been recorded, the native characteristic of the product remaining unaltered during the process) and in terms of pain attenuation. The cicatrization time is very rapid and product absorption considerably longer compared with equivalent treatment using lyophilized collagen (sponge) and consequently there is lesser need to replace it. Exudate loss is very low, and much lower than that when using lyophilized collagen.

The transparency of the product means that the progress of the injury can be viewed without the need to remove the collagen sheet (generally a painful procedure).

The product can be presented in the form of sheets of different dimensions (square, rectangular, round, elliptical or others) supported or not supported by adhesives (such as plasters) or by sheets of inert substances such as nylon, polyurethane, polyethylene etc., or associated during the drying process, or subsequently, with pharmacologically active substances.

Claims

1. A sheet of type I collagen gel, having molecular structure $[\alpha 1(I)]_2\alpha 2(I)$, suitable for the therapeutic cicatrizing treatment of wounds and burns, said sheet being free from native collagen degradation products, having an H_2O content not exceeding 20% by weight, a uniform thickness, comprised between 0.02 and 2 mm, said sheet being characterized in that it is of transparent structure, it has an homogeneous structure, it has the classical triple-helical structure of native collagen, it comprises gas bubbles with a diameter of less than 0.034 mm under atmospheric pressure, it has a capacity for absorbing aqueous biological liquids limited to a maximum of 15 times its weight and a high resistance to enzymatic attack.

2. A method of preparing a sheet of type I collagen as claimed in claim 1 from aqueous diluted collagen gel of pH 2.5-3.5, comprising filtering the gel through a filter surface with a passage size of less than 0.1 mm, the lower part of filtering apparatus being under a vacuum of 2666-7998 Pa and provided in the region immediately below the filter mesh with a device consisting of a series of plates vertically or raking placed and parallel between them, then drying the liquid gel contained in trays by purging with nitrogen to a residual oxygen content of less than 2%, at a temperature of 20-22° C and with a relative humidity of 60-80%.

3. A device suitable for filtering under vacuum the collagen gel in accordance with claim 2, comprising an upper shell provided with a scraping stirrer, a metal mesh with a mesh size of less than 0.1 mm placed at the bottom of the upper shell, a lower shell connected with a vacuum pump, and provided in the region immediately below the filter mesh with a pack of plates vertically or raking placed and parallel between them for the purpose of conveying the filtrate constitued by the said collagen gel as a continuous liquid film.

4. Use of the sheet of type I collagen as claimed in claim 1, for the preparation of a medicament useful for the treatment of wounds and burns and as interposition material for preventing accretions in the internal surgery operations.

Patentansprüche

1. Folie aus Typ I-Kollagengel, das die Molekularstruktur $[\alpha 1(I)]_2\alpha 2(I)$ hat und für die therapeutische Narbenbildungsbehandlung geeignet ist, wobei die Folie von Abbauprodukten natürlichen Kollagens frei ist, einen Wassergehalt hat, der 20 Gew.-% nicht übersteigt; eine gleichmäßige Dicke zwischen 0,02 und 2 mm hat,
dadurch gekennzeichnet, daß
die Folie eine transparente Struktur aufweist, eine homogene Struktur hat, daß sie die klassische Dreifachhelix-Struktur von natürlichem Kollagen hat, bei atmosphärischem Druck Gasblasen mit einem Durchmesser von weniger als 0,034 mm enthält, ihre Kapazität zur Absorption wäßriger biologischer Flüssigkeit auf ein Maximum des 15-fachen ihres Gewichts limitiert ist, und sie eine hohe Beständigkeit gegenüber einem enzymatischen Angriff hat.

2. Verfahren zur Herstellung einer Folie aus Typ I-Kollagengel nach Anspruch 1 aus wäßrigem verdünntem Kollagengel mit einem pH von 2,5 bis 3,5, umfassend

   - Filtrieren des Gels durch eine Filteroberfläche mit einer Durchgangsgröße von weniger als 0,1 mm, wobei der untere Teil der Filtrierapparatur unter einem Vakuum von 2666 bis 7998 Pa steht und in dem Bereich unmittelbar unter dem Filtersieb bereitgestellt ist, mit einer Vorrichtung, die aus Reihen von Platten besteht, welche senkrecht oder schräg und zueinander parallel angeordnet sind;

   - Trocknen des flüssigen Gels, das in Schalen enthalten ist, durch Spülen mit Stickstoff bis zu einem Restsauerstoffgehalt von weniger als 2%, bei einer Temperatur von 20 bis 22° C und einer relativen Feuchtigkeit von 60 bis 80%.

3. Vorrichtung, die zum Filtrieren des Kollagengels nach Anspruch 2 geeignet ist, und die aus einem oberen Mantel, der mit einem Shabrührer ausgestattet ist; einem Metallsieb mit einer Maschengröße von weniger als 0,1 mm, das am Boden des oberen Mantels angeordnet ist; einem unteren Mantel, der mit einer Vakuumpumpe verbunden ist, besteht, und die im Bereich unmittelbar unter dem Filtersieb mit einer Reihe von Platten, die vertikal oder schräg und zueinander parallel angeordnet sind, zum Zwecke eines Beförderns des Filtrats, das aus dem Kollagengel besteht, als kontinuierliche flüssige Folie, versehen ist.

4. Verwendung der Folie aus Typ I-Kollagengel nach Anspruch 1 zur Herstellung eines Medikaments, das zur Behandlung von Wunden und Verbrennungen sowie als Interpositionsmaterial zur Verhinderung von Verwachsungen bei inneren Operationen verwendbar ist.

Revendications

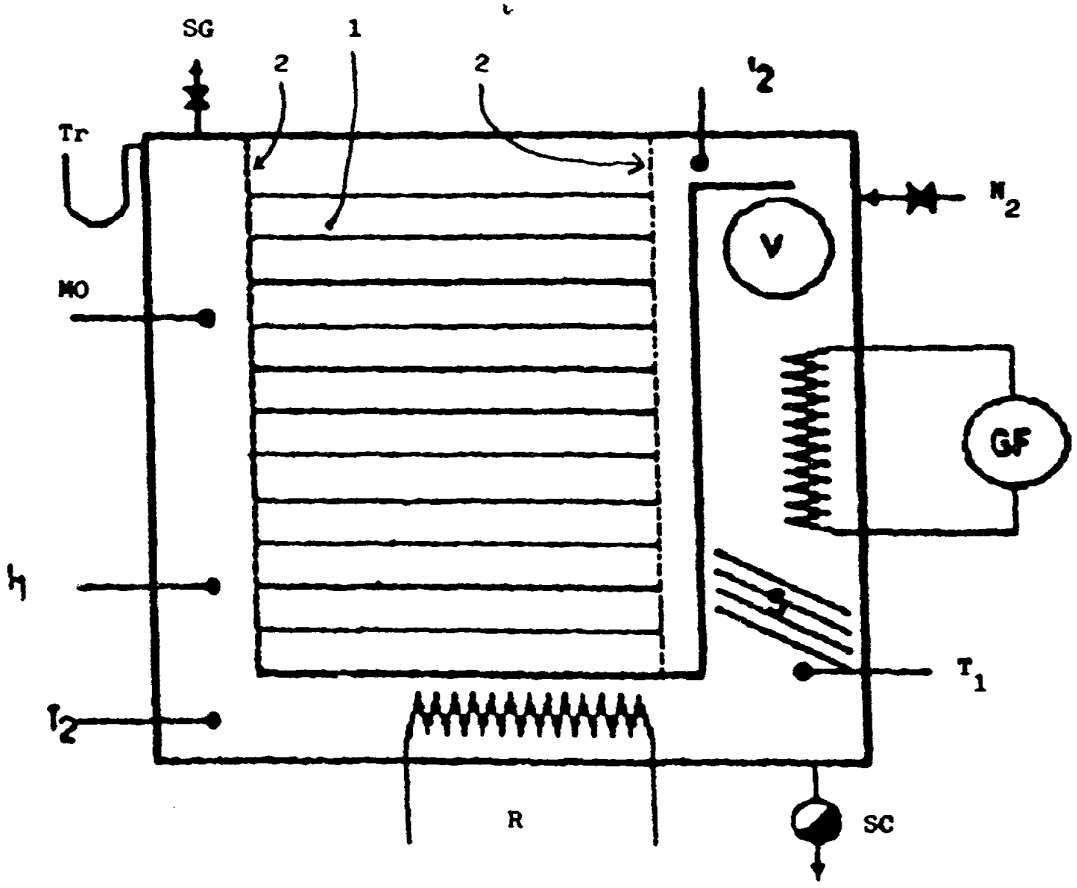
1. Feuille de gel collagène du genre I ayant une structure moléculaire $[\alpha 1(I)]_2\alpha 2(I)$, apte au traitement thérapeutique cicatrisant de blessures et brûlures, la susdite feuille étant sans produits de dégradation du collagène naturel, ayant un contenu de H_2O qui n'est pas supérieur à 20% en poids et une épaisseur uniforme de 0,02-2 mm, la susdite feuille étant characterisée en ce qu'elle a une structure transparente et homogène, la structure typique à triple-hélice de collagène naturel, en ce qu'elle comprend des bulles de gaz ayant un diamètre de moins de 0,034 mm à pression atmosphérique, et en ce qu'elle est capable d'absorber des liquides biologiques aqueux pour un maximum de 15 fois son poids et est très resistante à l'attaque enzymatique.

2. Méthode pour préparer une feuille de collagène du genre I selon la revendication 1 à partir de gel collagène aqueux dilué avec un pH 2,5-3,5, comprenant la filtration du gel à travers une surface filtrante avec un passage inférieur à 0,1 mm, la partie inférieure de l'appareil filtrant étant sous un vide de 2666-7998 Pa et étant pourvue dans la région directement au-dessous du filet de filtration d'un appareil composé par une série de plaques arrangées verticalement ou inclinées et parallèles entre elles, la susdite méthode comprenant ensuite le séchage du gel liquide contenu dans des plateaux en le purgeant avec azote jusqu'à obtenir un contenu en oxygène inférieur à 2% à une température de 20-22°C et avec une humidité relative de 60-80%.

3. Appareil apte à la filtration sous vide du gel collagène selon la revendication 2, comprenant une coque supérieure avec un agitateur raclant, un filet métallique avec une maille inférieure à 0,1 mm placé au fond de la coque supérieure, une coque inférieure liée avec une pompe à vide et pourvu dans la région directement au-dessous du filet de filtration d'une pile de plaques arrangées verticalement ou inclinées et parallèles entre elles pour acheminer le filtrat constitué par le susdit gel collagène comme une pellicule liquide continue.

4. Emploi de la feuille de collagène du genre I selon la revendication 1 pour la préparation d'un médicament utilisé dans le traitement de blessures et brûlures et comme matériel d'interposition pour éviter des excroissances dans les opérations de chirurgie interne.

FIG. 1



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(54) **Title:** FAST DISSOLVING ORALLY CONSUMABLE FILMS

(57) **Abstract**

Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film–forming polymer such as pullulan. Edible films are disclosed that include pullulan and antimicrobially effective amounts of the essential oils thymol, methyl salicylate, eucalyptol and menthol. The edible films are effective at killing the plaque–producing germs that cause dental plaque, gingivitis and bad breath. The film can also contain pharmaceutically acitve agents. Methods for producing the films are also disclosed.

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FAST DISSOLVING ORALLY CONSUMABLE FILMS

SPECIFICATION

FIELD OF THE INVENTION

This invention relates to fast dissolving orally consumable films. The films are used to deliver breath deodorizing agents, antimicrobial agents and salivary stimulants to the oral cavity. The films can also be used to deliver pharmaceutically active agents.

BACKGROUND OF THE INVENTION

In a more perfect world, people would thoroughly cleanse their mouths after each meal as part of their routine oral hygienic practices. Unfortunately, several factors conspire to prevent widespread compliance with this basic requirement of a good oral cleaning regimen.

Oral cleansing can be difficult or inconvenient at times, depending on the nature of the cleansing and the situation in which the cleansing must occur. Brushing, flossing, cleaning your tongue and gargling using a variety of devices and compositions well-suited for the privacy of one's home are common oral care practices. However, the devices and compositions used in oral cleansing practices are less convenient to use away from home, where bathroom facilities might be scarce, unavailable or unsanitary.

As brushing, flossing, cleaning your tongue and gargling in public are not considered to be socially acceptable behaviors in many, if not all cultures, a variety of

less obtrusive oral cleansing products have been developed. These include breath-freshening gums and lozenges. Although gums and lozenges have been formulated to achieve a variety of beneficial effects, they are not always socially acceptable. For example, gum is expressly banned from certain institutions, such as schools as well as in certain countries, such as Singapore. Gums and mints are used over extended periods of time, and they require an amount of sucking or chewing action on the part of the consumer, which can be distracting, tedious and undesirable.

Another portable oral cleansing product is a mouthspray. Like a mouthwash, a mouthspray can provide the consumer with a quick burst of strong breath-freshening action, which might be overwhelming in an extended-consumption product like gum or lozenges. On the other hand, mouthsprays are obtrusive. Spraying a mouthspray typically generates a noise, which undesirably draws the attention of the public to the consumer. Moreover, mouthsprays are typically packaged in relatively expensive and complex metal canisters, which can clog in use and are not environmentally friendly. Furthermore, misdirecting the spray not only wastes the product, but can result in irritated eyes, a sticky face and/or stained clothing.

It has been proposed to use an edible film as a vehicle for unobtrusively delivering breath-freshening agents. See JP 5-236885. This Japanese patent application does not, however, teach the inclusion of antimicrobial agents in the film, using the film to decrease the amount of undesirable bacteria within the oral cavity, or stimulating saliva. Furthermore, this patent application does not disclose employing

its film for purposes other than breath freshening or within cavities other than the mouth.

U.S. Patent No. 5,518,902 to Ozaki et al. (Hayashibara) discloses high pullulan content products, such as edible films, dentifrices and pharmaceuticals (column 3, lines 44-56 and Example B-8). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, polyhydric alcohols, antiseptics and flavor-imparting agents (column 4, line 58 to column 5, line 11). None of the essential oils, such as thymol, eucalyptol, methyl salicylate or menthol, are mentioned as suitable ingredients.

U.S. Patent No. 5,411,945 to Ozaki et al. (Hayashibara) 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). None of the essential oils are mentioned as suitable ingredients.

U.S. Patent No. 4,851,394 to Kubodera discloses glucomannan/polyhydric alcohol edible films, which can comprise pullulan (column 3, line 59 to column 4, line 21). The films are contrasted with existing pullulan-based films, which are said to lack resistance to water (column 1, lines 40-44). None of the essential oils are mentioned as suitable ingredients.

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.

U.S. Patent No. 4,623,394 Nakamura et al. discloses a gradually disintegrable molded article that can be a film made with pullulan. The articles contain a particular heteromannan, which can be locust bean gum.

U.S. Patent No. 4,562,020 Hijiya et al. discloses a process for producing a self-supporting film of a glucan, which can be pullulan.

Japanese Patent Document JP5-1198 discloses films made of polyvinyl alcohol and at least one of carrageenan, water-soluble cellulose alpha-starch and water-soluble polysaccharides.

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.

Despite the existence of rapidly dissolving orally consumable films in the prior

art, there is still room for improvement in such films, and in processes for making them.

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

SUMMARY OF THE INVENTION

The invention provides a physiologically acceptable film, which is particularly well adapted to adhere to and rapidly dissolve in the mouth of a consumer. In a first embodiment of the invention, the film delivers at least one oral care agent, such as antimicrobial agents and salivary stimulants. The antimicrobial agents are effective against germs that cause halitosis, dental plaque, and gingivitis. The salivary stimulants are effective against the condition known as xerostomia or dry mouth. Additionally, the oral care films are a breath freshener effective against oral malodor. The film former used to make the films according to the present invention entraps the oral care agents in the oral cavity to provide extended efficacy.

In a second embodiment of the invention, the rapidly dissolvable film acts as a vehicle for administering a pharmaceutically active agent orally, through a mucous membrane or an open wound of a patient.

The invention is also directed to a method for producing a supple, non-self-adhering film especially suitable for oral delivery. The method comprises mixing a film forming agent and at least one stabilizing agent to provide a film-forming mixture; dissolving water-soluble ingredients in water to provide an aqueous solution;

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 emulsified gel; casting the uniform gel on a substrate; and drying the cast gel to provide a film.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC 25175, and exposed to a film according to the present invention that contains 0.391 mg of essential oils.

Fig. 2 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC 25175, and exposed to drops of an essential oil mixture containing 0.391 mg of essential oils per drop.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Description of Oral Care Film Compositions

The first embodiment of the invention is a physiologically acceptable film that is particularly well adapted to adhere to and dissolve in a mouth of a consumer to deliver an antimicrobial agent that kills germs that cause halitosis, dental plaque and gingivitis. Thus, the film can be an effective tool in the prevention and treatment of halitosis, dental plaque accumulation, dental tartar accumulation and gingivitis. This film preferably comprises pullulan, thymol, methyl salicylate, eucalyptol and menthol.

LISTERINE® brand mouthwash is, perhaps, the most well-known example of an antiseptic oral composition that has proven effective in killing microbes in the oral

cavity that are responsible for plaque, gingivitis and bad breath. LISTERINE® brand mouthwash achieves its antimicrobial effect through a combination of essential oils that penetrate and kill the microorganisms. These essential oils include precisely balanced amounts of thymol, methyl salicylate, menthol and eucalyptol (hereinafter "the essential oils") in a hydro alcoholic solution. Many bad breath bacteria live in pits or fissure on the surface of the tongue. Listerine® Antiseptic mouthwash reduces bad breath because of high concentrations of antimicrobial agents in a liquid medium that can easily penetrate into these pits and fissures. This would not be possible with a solid dosage form containing low amounts of these antimicrobial ingredients. However, the preferred consumable film of the invention captures a significant portion of the hygienic benefits and the consumer appeal of LISTERINE® brand mouthwash, in a more portable and unobtrusively consumed form.

It was a significant challenge to maintain the essential oil interaction and relatively high oil content of LISTERINE® brand mouthwash in a film. However, the inventors have overcome this challenge in providing the film of the invention.

A further aspect of this invention is that while the amounts of LISTERINE® essential oils are relatively high for incorporation in a film, the film according to the present invention still delivers a lower total amount of essential oils per unit dose when compared to that of LISTERINE® mouthwash. Yet the film suprisingly provides antimicrobial efficacy in the oral cavity. The inventors theorize that the preferred film forming ingredient, pullulan, forms a thin layer on the oral surfaces

entrapping the small amount of essential oils which are capable of penetrating into the pits and fissures of the oral cavity to provide sustained antimicrobial efficacy.

Although the inventors are presently unaware of any other breath-freshening consumable film that provides antimicrobial efficacy, they are aware of a consumable film disclosed in JP 5-236885, which is said to possess breath-freshening activity, but is not described as possessing any ingredients having significant antimicrobial activity. Moreover, JP 5-236885 teaches that its film should contain flavor and extract in amounts of 5 to 7 wt %, with the flavor being added as an oil (the essential oils are not disclosed), whereas the film of the invention preferably has an oil content of at least about 10 wt %, more preferably about 15 wt % to about 30 wt %, most preferably about 15 wt % to about 25 wt %. Except as otherwise noted in the examples, the amounts of oils and other ingredients in the film are wt% after the film formulation has been dried to create the film.

The amounts of the specific essential oils used in the film compositions can vary as long as they are in amounts sufficient to provide antimicrobial efficacy. Generally the amount of thymol, methyl salicylate and eucalyptol is from about 0.01 to about 4 wt % of the film composition, preferably about 0.50 to about 3.0 wt % and even more preferably from about 0.70 to about 2.0 wt % of the film. Menthol can be added from about 0.01 to about 15 wt % of the composition, preferably about 2.0 to about 10 wt % and even more preferably from about 3 to about 9 wt % of the film. The amounts added can be readily determined to those skilled in the art and can

exceed these amounts as long as the total oil content does not create sticking or other processing problems. In certain embodiments, the essential oils are combined in amounts synergistically effective to kill the plaque-producing germs that cause dental plaque, gingivitis and bad breath.

A major difficulty in formulating a film having such a relatively high oil content is that simply increasing the amount of oil in the film without determining the precise proportions of the many other ingredients typically results in a film that is too moist and therefore difficult to handle or process. The inventors have discovered how to provide a high oil content film that is moist enough so that it is not brittle, but is not so moist that it feels undesirably slimy or significantly adheres to adjacent films. Thus, a non-self-adhering film according to the invention can be stored in contact with another such film (e.g., in a stack), or can be wound about itself (e.g., around a spool), without having to place a non-stick agent (e.g., a plastic film, paper or other support) between adjacent portions of film.

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.

The film of the invention preferably comprises pullulan as a film-forming agent and the essential oils as antimicrobial/flavoring agents, and can further comprise water, additional antimicrobial agents, additional film-forming agents, plasticizing agents, additional flavoring agents, sulfur precipitating agents, saliva stimulating agents, cooling agents, surfactants, stabilizing agents, emulsifying agents, thickening agents, binding agents, coloring agents, sweeteners, fragrances, and the like.

Due to the relatively high oil content in the oral care film, 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 the film with a plasticizing agent other than glycerin, which is also a humectant, and with a sweetener other than sorbitol, which is a mild humectant.

Sulfur precipitating agents that reduce oral malodor can also be added to the oral care films according to the present invention. These agents bind with, and inactivate, the volatile sulfur compounds that cause a large percentage of oral malodor. Sulfur precipitating agents useful in the present invention include metal salts such as

copper salts and zinc salts. Preferred salts include copper gluconate, zinc citrate and zinc gluconate. The amount of sulfur precipitating agent is from about 0.01 to about 2 wt %, preferably about .15 wt % to about 1.5 wt %, even more preferably about .25 wt % to about 1.0 wt % of the film.

Saliva stimulating agents can also be added to the oral care films according to the present invention. Useful saliva stimulating agents are those disclosed in U.S. Patent No. 4,820,506, which is incorporated by reference herein in its entirety. 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.

Antimicrobial Efficacy of Oral Care Films

The preferred embodiment of the oral care film composition according to the

present invention contains the essential oils used in Listerine® mouthwash to provide antimicrobial efficacy. The films are shaped and sized to be placed in the oral cavity. The film adheres to a surface in the mouth, usually the roof of the mouth or the tongue, and quickly dissolves. The amount of essential oils in one individual film that is a preferred size for placing in the mouth is significantly lower than that in the recommended amount, 20ml, of Listerine® mouthwash.

In a preferred formula according to the present invention, the amount of thymol and eucalyptol in the film is about 70 times less than in the mouthwash. The amount of methyl salicylate in the film is about 46 times less than in the mouthwash. The amount of menthol in the film is about 2.8 times less than in the mouthwash. These figures are based on comparing a 20 ml dose of liquid mouthwash with a 0.0358 gram film.

The inventors have unexpectedly found that the film provides sustained antimicrobial efficacy at these low amounts of oils. The inventors believe that the efficacy of the essential oils is enhanced by the creation of a layer of pullulan in the oral cavity that holds the essential oils. This is unexpected because pullulan is water-soluble and the film dissolves very quickly.

The extended antimicrobial activity is shown in the following experiments.

The purpose of these experiments was to determine the antibacterial efficacy of an application of a breath film on tongue malodor microorganisms thirty, sixty or ninety minutes after use. The thirty minute study also tested the efficacy of using two

films. Subjects' baseline oral malodor microbial recoverable counts were determined by plating the microorganisms recovered from a tongue swab on a selective agar medium. The test product was dispensed and subjects dissolved one or two breath films on their tongue. Subjects remained on the premises and returned for a second tongue swab thirty, sixty or ninety minutes after placement of the test product on their tongue. After a forty-eight hour washout period, subjects returned for a no treatment control.

The thirty minute single film use group showed a reduction in mean log malodor microbial counts compared to the control group. The data was borderline statistically significant ($p=0.052$). The difference between the one film group and the no treatment control group represented a 42.7% reduction in malodor microbial colony counts.

Statistically significant malodor microbial reduction was also observed with the two film use group. A 79.6% reduction in malodor microbial colony counts was obtained ($p<0.001$).

Statistically significant malodor microbial reduction was observed sixty minutes after use of a single breath film. A 69.8% reduction in malodor microbial colony counts was obtained ($p=0.002$).

Significant malodor reduction was also observed ninety minutes after use of a single breath film. A 69.1% reduction in malodor microbial colony counts was obtained ($p=0.006$).

The data from these studies support the following conclusions: (1) Pullulan polymer-based breath film containing essential oils is an effective antibacterial composition against oral malodor causing bacteria and (2) significant *in vivo* bacterial reductions were achieved at thirty, sixty and ninety minutes post use.

Experimental Procedures

The procedures used in these antimicrobial studies were as follows. The subject were required to refrain from all oral hygiene procedures (e.g., toothbrushing, oral lavage) eating or drinking any food, beverage or confectionery products from midnight prior to the study and until the study was completed on each test day. Subjects refrained from smoking on mornings prior to the odor evaluations.

In vivo Germ Kill Assay

1. Materials

Test tubes containing 10 ml of sterile 0.01% peptone

Sterile Swabs

OOPS III Agar (B.-F. Turng, G.E. Minah, and W.A. Falkler. Development of an Agar Medium for Detection of Oral H_2S-producing Organisms. J Dent Res 76 IADR Abstracts 1997.):

Columbia Agar Base (Catalogue # DF0792-17-3)	44 grams
Distilled Water	1 liter
Lead Acetate[a] (Sigma L3396)	0.2 grams
Hemin Solution[b] (Sigma H-1652)	2 ml

Glutathione[c] (Sigma G4251) 1.2 grams

Forty-four grams of Columbia Blood Agar Base was suspended in 1 liter distilled water and boiled to dissolve completely. The media was sterilized at 121-124°C for 15 minutes.

[a] Dissolved 0.2 grams of lead acetate in 1 ml of distilled H_2O and filter sterilized. Added after autoclaving the base media.

[b] Dissolved 50 mg of hemin in 1 ml of 1N NaOH; qs'd to 100 ml with distilled H_2O. Filter sterilized. Added 2 ml per liter of OOPS III after autoclaving base media.

[c] Dissolved 1.2 grams of glutathione in 10 ml of distilled H_2O. Filter sterilized. Added after autoclaving base media.

2. Procedure

a. All media were prereduced in an anaerobic chamber overnight. Plates were loosely wrapped in plastic bags to prevent excessive drying.

b. Panelists refrained from oral hygiene, eating and drinking from midnight prior to the assay and until the assay was complete. Twelve panelists were used for the sixty and ninety minute experiments. Eighteen panelists were used for the thirty minute experiments.

c. Each panelist swabbed the right side of his tongue by placing the swab at the midpoint of the tongue and swiping forward to the tip. The swab was placed in a tube of peptone.

d. The panelist received a film treatment, either a single or double film. Panelists

placed the breath film on the left side of their tongue covering the tongue from the midpoint to the tip and allowed the film to dissolve with the mouth slightly open for thirty seconds to prevent the film from sticking to the palate.

e. After thirty or sixty minutes, panelists swabbed the left side of the tongue by placing the swab at the midpoint of the tongue and swiping forward to the tip. The swab was placed in a tube of peptone.

f. The tubes of peptone were vortexed vigorously for 10 seconds, and serial dilutions were made. The 10^{-4} dilution was plated in duplicate on OOPS III Agar using a Spiral Biotech Autoplate 4000 (Bethesda, MD). All plates were identified with the subject's initials, assay date, sampling time station, and replicate number.

g. The plates were incubated in an anaerobic chamber at 35-37°C for 7 days to permit full development of colonies without overgrowth.

h. After a 48 hour wash out period, panelists returned for the no treatment control. No film was applied, and steps (e) through (g) were followed as described above.

i. After a 48 hour wash out period, the sixty minute panelists returned for another single film application. Steps (a) through (h) were followed, with the exception that panelists returned after 90 min in step e.

j. The dark-pigmented colonies (H_2S-producing organisms) were counted as whole plate counts by hand under appropriate magnification or by Segment

counts using a Spiral Biotech counting template. The appropriate code was entered on the data sheet to permit interpretation of the counts. The CFU's counted were converted to CFU/ml by dividing by the appropriate exponential volume constant listed in Table A and multiplying by 1000. This value was then multiplied by the dilution factor of the plate (10^4).

Table A. Exponential Volume Constants for Segment Pairs

Last Counted Segment	Exponential Volume Constant
8	1.214
9	2.968
10	5.500
11	9.157
12	14.482
13	25.015
Total Plate	50.030

The film used in the *in vivo* germ kill tests was Example 19 as described in Table 2. The films used in the study were approximately 22mm x 32mm, between about 0.0013 and 0.0015 inches thick and weighed between about 35 to about 37 mg.

The enhanced activity of the essential oil containing pullulan film is also shown in Figures 1 and 2. Figure 1 is a photograph of an agar plate spread with *Streptococcus mutans*, ATCC # 25175, to which a piece of an essential oil pullulan

film according to the present invention was added. The piece of film delivered approximately .391 mg of essential oils using Example 15 listed below.

Figure 2 is a photograph of an agar plate spread with Streptococcus mutans, ATCC # 25175 to which drops of essential oils have been added. The drops were 148 ul in volume and contained 0.391 mg of essential oils. The percentages of each essential oil in the drop are 2.200% menthol, 0.186% eucalyptol, 0.186% methyl salicylate and 0.1300% thymol in a hydro alcohol solution.

The area or zone of inhibition around the film in Figure 1 is much larger than the dimensions of the film. This is due to the presence of pullulan because the oils in the pullulan film were spread by the pullulan, diffused outward and did not wash away after repeated rinses. In contrast, the essential oils in Figure 2 did not diffuse away from the droplet, remained as a circle and easily washed off after 1-2 rinses. This shows that the antimicrobial efficacy of the essential oils is enhanced by the presence of pullulan.

Methods For Preparing Essential Oil Containing Films

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.

The aqueous phase can include ingredients such as coloring agent(s), copper gluconate 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.

If sodium saccharin and copper gluconate are both ingredients in the formulation, it is preferable to dissolve them separately in solution to avoid precipitation.

In a preferred method of producing essential oil containing films according to the invention, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. The preferred method of producing films 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, thymol and menthol in the flavor oil to form an oil mixture; adding methyl salicylate; eucalyptol and surfactants to the 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.

The preferred method for making an essential oil containing film hydrates the film-forming ingredients without heating the water. Heating the ingredients increases energy costs in the manufacturing process. Moreover, heating results in undesirable losses of volatile ingredients to evaporation, which also affects the germ killing activity of the composition due to the loss of essential oils. 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.

It is preferable to avoid adding both copper gluconate and saccharin at the same time to the aqueous solution, as a precipitate will form. Thus, it is preferred to combine sweeteners other than saccharin with copper gluconate.

Description of Film Compositions That Deliver Pharmaceutical Agents

A second embodiment of the invention is a fast dissolving film that includes at least one physiologically acceptable, pharmaceutically active agent. 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; and

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,

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

The amount of medicament 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 medicament. Examples of doses for specific medicaments that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table 1.

TABLE 1

MEDICAMENT	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 Hydrochloride	10-20 mg.
Ketoprofen	12.5 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	25 mg.
Pseudoephedrine Hydrochloride	30 mg.

The ingredients used to make the pharmaceutical containing films are similar to those used to make oral care films. Specifically, the plasticizing agents, cooling agents, surfactants, stabilizing agents, emulsifiers, thickening agents, binding agents, film formers, sweeteners, flavors and colors described above can also be used in all of the films according to the present invention.

The films that deliver a pharmaceutical agent 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 that contain pharmaceutical agents also can include a preservative. The preservative is added 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.

The pharmaceutical agent containing 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 pharmaceutical agent containing 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.

The active ingredient used in the film can be coated to mask the taste of the active ingredient or to prevent the active ingredient from numbing the tongue or other surfaces in the oral cavity. The coatings that can be used are known to those skilled in the art. These include polymers such, as Eudragit® E, cellulosics, such as ethylcellulose, and the like.

An additional way to mask the taste of the active ingredient is by using an ion exchange resin such as Amberlite RP-69, available from Rohm and Haas, and Dow XYS-40010.00, available from the Dow Chemcial Co.

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.

Preparation Method I

The following method was used to prepare the films of Examples 1-13.

A. The film-forming ingredients (e.g., xanthan gum, locust bean gum, carrageenan and pullulan) other than Polysorbate 80 and Atmos 300 are mixed and hydrated in hot purified water to form a gel and stored in a refrigerator overnight at a temperature of approximately 4 °C to form preparation A.

B. The coloring agent(s), copper gluconate and sweetener are added to and

dissolved in purified water to form preparation B.

C. Preparation B is added to preparation A and mixed well to form preparation C.

D. The flavoring agent and the oils (e.g., cooling agent, thymol, methyl salicylate, eucalyptol and menthol) are mixed to form preparation D.

E. The polysorbate 80 and Atmos 300 are added to preparation D and mixed well to form preparation E.

F. Preparation E is added to preparation C and mixed well to form preparation F.

Preparation F is poured on a mold and cast to form a film of a desired thickness at room temperature. The film is dried under warm air and cut to a desired dimension, packaged and stored.

Preparation Method II

Examples 14-18 were prepared using a preferred method, which comprised the following steps:

A. dissolve copper gluconate, acesulfame K, aspartame, glycerin, sorbitol and dye in purified water to form an aqueous mixture;

B. mix pullulan, xanthan gum, locust bean gum and carrageenan together in powder form to form a powder mixture;

C. add the powder mixture from step B to the aqueous mixture from step A to form a hydrated polymer gel;

D. stir the hydrated polymer from step C at slow speed (about 50-100 RPM) overnight at room temperature;

E. mix and dissolve cooling agent, thymol and menthol in the flavor oil;

F. add methyl salicylate, eucalyptol, Polysorbate 80 and Atmos 300 to the oil mixture from step E;

G. add the oil mixture from step F to the hydrated polymer gel from step D and mix until uniform;

H. cast the uniform mixture from step G on a suitable backing; and

I. dry the cast mixture to form a film.

Example 1

Example 1 produced a film according to the invention having a blue-green tint, a mint odor and a refreshing mint taste.

Examples 2-4

Examples 2-4 contain sorbitol, glycerin or both. These examples yielded products that easily broke off pieces, or were too moist and/or self-adhering. However they did produce films that rapidly dissolved in the oral cavity with a refreshing mint taste.

Examples 5-6

Examples 5 and 6 removed glycerin and sorbitol. The resultant films did not stick together during processing and packaging and were more moisture stable over a

long time frame.

Examples 7-9

Examples 7-9 were produced to determine the effect of Avicel® on germ killing activity. While Examples 7-9 produced more acceptable films from a processing and handling perspective, they had diminished antimicrobial activity relative to films without Avicel®, such as Example 8.

Examples 10-15

Examples 10 - 15 varied the amounts of aspartame and menthol to alter the sweetness and coolness of the film.

Example 16

Example 16 was prepared by replacing the sorbitol replaced with maltitol, which has less humectant properties. The resultant film was less sticky during processing and long term storage.

Example 17

Example 17 is prepared in which pullulan is replaced with another film former, polyvinyl pyrrolidone, to produce films according to the invention.

Example 18

Example 18 is prepared in which pullulan is partially replaced with another film former, konjac gum, to produce films according to the invention.

Example 19

Example 19 represents a film containing a salivary stimulant, citric acid.

Example 20

Example 20 is the film composition used in the antimicrobial efficacy studies described above.

The formulas for examples 1 - 20 are summarized in Table 2. The amounts in these examples are presented as the actual weight (grams) or w/w %. These formulas create the solution/gel that is cast and dried into a film. The actual amount of each ingredient in the finished, dried film depends upon the amount of relative moisture removed during drying.

Table 2

Ingredient	Ex. 1 w/w%	2 wt (g)	3 wt (g)	4 wt (g)	5 wt (g)	6 wt (g)	7 wt (g)	8 wt (g)	9 wt (g)
Xanthan Gum, Food Grade	0.1070						11.60	12.60	11.60
Xanthan Gum (1% solution)		3.85	3.85	3.85	3.85	3.85			
Locust Bean Gum, Clarified	0.2150						23.40	25.40	23.40
Locust Bean Gum (1% solution)		7.70	7.70	7.70	7.70	7.70			
Polyvinyl Pyrrolidone									
Konjac Gum									
Carrageenan	1.0730						116.60	126.10	116.60
Carrageenan (5% solution)		7.70	7.70	7.70	7.70	7.70			
Avicel							500.00		500.00
Pullulan	51.5780						5604.00	6513.00	5949.00
Pullulan (25% sol)		74	74	74	74	74			
Thymol NF	0.4070	0.146			0.146	0.146	40.70	40.70	40.70
Methyl Salicylate NF	0.4210	0.151			0.151	0.151	58.50	58.50	58.50
Eucalyptol	0.5850	0.21			0.21	0.21	42.10	42.10	42.10
Menthol USP	5.8830	2.23			2.11	2.11	588.00	588.00	588.00
Mint flavor	8.3640	2			3.0	3.0	836.00	836.00	836.00
Citric Acid									
Copper gluconate	1.1150	0.275			0.41	0.14	112.00	112.00	112.00
Purified water, USP/EP	22.32	2	10.22	12.22	8.0	8.0	2230.00	2230.00	2230.00
Sod. saccharin USP granulate	6.6910	1.8	1.4	1.4	2.0	2.4			
Sodium saccharin							609.00	609.00	609.00
Acesulfame-K									
Aspartame									
Cooling agent		0.05			0.05	0.05	13.90	13.90	13.90
Maltitol									
Sorbitol (crystalline)							64.30	64.30	64.30
Sorbitol 70% sol.		4	4.0						
Glycerin		2		2.0			136.00	136.00	136.00
Polysorbate 80 NF/EP	0.5580	0.3	0.2	0.2	0.2	0.2	112.00	112.00	112.00
Atmos 300	0.5580						112.00	112.00	112.00
Atlas 3000		0.3	0.2	0.2	0.2	0.2			
Hi Set C Starch									77.0
FD&C Green # 3	0.0084	0.3	0.3	0.3	0.3	0.3	0.84	0.84	0.84
D&C Yellow #10									

Table 2 cont.

Ingredient	10 wt (g)	11 wt (g)	12 wt (g)	13 wt (g)	14 w/w%	15 w/w%	16 w/w%	17 w/w%	18 w/w%	19 w/w%	20 w/w%
Xanthan Gum, Food Grade	0.0385	0.0385	0.0385	0.0385	0.0342	0.0342	0.0342	0.04	0.04	0.34	0.0342
Xanthan Gum (1% solution)											
Locust Bean Gum, Clarified	0.077	0.077	0.077	0.077	0.0684	0.0684	0.0684	0.07	0.07	0.68	0.0684
Locust Bean Gum (1% solution)											
Polyvinyl Pyrrolidone								16.5			
Konjac Gum									5.0		
Carrageenan	0.385	0.385	0.385	0.385	0.342	0.342	0.342	0.34	0.34	.34	0.342
Carrageenan (5% solution)											
Avicel											
Pullulan	18.5	18.5	18.5	18.5	16.43	16.43	16.43		11.0	16.34	16.43
Pullulan (25% sol)											
Thymol NF	0.146	0.146	0.146	0.146	0.130	0.13	0.13	0.13	0.13	0.129	0.13
Methyl Salicylate NF	0.21	0.21	0.21	0.21	0.186	0.186	0.186	0.186	0.186	0.185	0.18
Eucalyptol	0.21	0.21	0.21	0.21	0.186	0.186	0.186	0.186	0.186	0.185	0.18
Menthol USP	2.11	1.95	2.36	2.36	2.096	2.520	2.096	2.096	2.096	2.084	2.096
Mint flavor	3.0	3.0	3.0	3.0	2.664	2.344	2.664	2.664	2.664	2.649	2.0
Citric Acid											2.5
Copper gluconate	0.4	0.4	0.4	0.4	0.355	0.355	0.355	0.35	0.35	0.353	0.355
Purified water, USP/EP	84.25	84.25	84.25	84.25	74.81	74.63	74.81	75	75	74.39	72.2168
Sod. saccharin USP granulate											
Sodium saccharin											
Acesulfame-K	0.5	0.5	0.5	0.5	0.444	0.444	0.444	0.45	0.45	.04420	0.444
Aspartame	1.30	1.60	1.30	1.60	1.421	1.421	1.421	1.4	1.4	1.413	1.421
Cooling agent	0.10	0.10	0.10	0.10	0.089	0.089	0.089	0.089	0.089	0.088	0.89
Maltitol							2.80				
Sorbitol (crystalline)											
Sorbitol 70% sol.										0.199	
Glycerin										0.418	
Polysorbate 80 NF/EP	0.4	0.4	0.4	0.4	0.355	0.355	0.355	0.355	0.355	0.353	0.355
Atmos 300					0.355	.0355	0.355	0.355	0.355	0.353	0.355
Atlas 3000	0.4	0.4	0.4	0.4							
Hi Set C Starch											
FD&C Green # 3	0.003	0.003	0.003	0.003	0.0026	0.0026	0.0026	0.0026	0.0026		
D&C Yellow #10											

The following examples are films according to the second embodiment of the present invention, in which the rapidly dissolving film contains a pharmaceutical agent. Examples 21A-21E, listed in Table 3, are medicament containing rapidly dissolvable oral film formulas. The amounts in Table 3 are in milligrams.

TABLE 3

Example Number	21A	21B	21C	21D	21E
Dextromethorphan HBr	7.500				
Phenylepherine HCl		10.0000	10.0000		
Chlorpheniramine Maleate			4.0000		
Loperamide HCl				2.0000	
Nicotine					2.0000
Xanthan Gum	0.0818	0.0818	0.0818	0.0818	0.0818
Locust Bean Gum	0.0954	0.0954	0.0954	0.0954	0.0954
Carrageenan	0.4088	0.4088	0.4088	0.4088	0.4088
Pullulan	21.8036	21.8036	21.8036	21.8036	21.8036
Sodium Benzoate	0.0954	0.0954	0.0954	0.0954	0.0954
Acesulfame Potassium Salt	0.6814	0.6814	0.6814	0.6814	0.6814
Aspartame NF	1.9078	1.9078	1.9078	1.9078	1.9078
Purified Water	*	*	*	*	*
Cooling agent	0.1363	0.1363	0.1363	0.1363	0.1363
Menthol	2.7255	2.7255	2.7255	2.7255	2.7255
Polysorbate 80 NF	0.4770	0.4770	0.4770	0.4770	0.4770
Atmos 300	0.4770	0.4770	0.4770	0.4770	0.4770
Propylene Glycol	4.0882	4.0882	4.0882	4.0882	4.0882
Olive Oil	0.6814	0.6814	0.6814	0.6814	0.6814
Titanium Dioxide	0.3407	0.3407	0.3407	0.3407	0.3407
Total Dose Weight	41.5000	44.0000	48.0000	36.0000	36.0000

*Calculated assuming complete evaporation of water from the films after drying

Table 4 summarizes additional films according to the present invention. The amounts in Table 4 are % w/w prior to drying.

Table 4

Examples	22A	22B	22C	22D	22E	22F	22G	22H	22I
Xanthan Gum	.03	.03	.06	.03	.03	.03	.06	.06	.06
Locust Bean Gum	.07	.07	.07	.07	.07	.07	.07	.07	.07
Carrageenan	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3
Pullulan	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Sodium Benzoate	0.1	0.1	0.1	.07	.07	.07	.07	.07	0.7
Acesulfame Potassium	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aspartame	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Water	qs100	qs100	qs100	Qs100	qs100	qs100	qs100	qs100	Qs100
Cooling agent	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Menthol	2.0	2.0	2.0	1.3	2.0	2.0	2.0	2.0	2.0
Polysorbate 80	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Atmos 300	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35	0.35
Propylene Glycol	1.0	1.0	1.0	1.0	1.0	1.0	3.0	3.0	3.0
Peg 1450	-	3.10	-	-	-	-	-	-	-
Olive Oil	-	-	-	1-2	2.0	2.0	.5-2	-	.5
Polyox N-10	-	-	-	-	-	-	-	-	1.0
Titanium Dioxide	-	0.25	0.25	0.25	0.25	-	0.25	-	0.25

Example 22A was used to make films containing a) 7.5 mg of dextromethorphan hydrobromide, b) 2.5 mg of tripolidine, c) 4.0 mg of chlorpheniramine maleate and d) 12.5 mg of diphenhydramine hydrochloride.

Example 22B was used to make a film containing 10 mg of dextrometorphan hydrobromide.

Example 22C was used to make a film containing 10 mg of dextromethorphan hydrobromide.

Example 22D was used to make a film containing a) 10 mg of phenylepherine hydrochloride, b) 10 mg of phenylepherine hydrochloride and 4 mg of chlorpheniramine maleate and c) 10 mg of dextromethorphan hydrobromide.

Example 22E was used to make a film containing 7.5 mg dextromethorphan hydrobromide.

Example 22F was used to make a film containing 20 mg of coated dextromethorphan hydrobromide to provide a 7.5 mg dose.

Example 22G was used to make a film containing a) 7.5 mg dextromethorphan hydrobromide, b) 10 mg phenylepherine hydrochloride and c) 10 mg phenylepherine hydrochloride and 4 mg chlorpheniramine maleate.

Example 22H was used to make a film containing 15 mg of dextromethorphan hydrobromide.

Example 22I was used to make a film containing 15 mg of dextromethorphan

hydrobromide.

Processes For Making Pharmecutical Containing Films

Example 22A was made using the following procedure.

1. Add the sodium benzoate and sweeteners to water.
2. Mix the locust bean gum, xanthan gum and carrageenan together.
3. Add the gum mixture to the mixture of step 1 and mix until dissolved.
4. Mix the active ingredient with either water or propylene glycol. Heat if needed.
5. Add the remaining ingredients to the mixture of step 4 or mix the remaining ingredients in a separate mixture.
6. Add the mixtures of step 4 and step 5 to the mixture of step 3. Cast and dry to make a film and cut to a size to achieve the desired dose.

Examples 22B-22E were made using the following procedure.

1. Add the sodium benzoate to water heated to 50 C. Mix to dissolve.
2. Separately, add the Peg 1450, titanium dioxide and active ingredient to the mixture of step 1, mixing with each addition.
3. Mix the locust bean gum, xanthan gum and carrageenan together.
4. Add the gums to the mixture of step 2 and mix until dissolve.
5. Add the remaining ingredients together with heat if needed.
6. Add the mixture of steps 4 and 5 together. Cast and dry to make a film and cut to a size to achieve the desired dose.

Examples 22F - 22I were made in the same manner as Examples 20B - 20E, except the active was dispersed right before the film was cast.

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 and an antimicrobial effective amount of at least one essential oil selected from the group consisting of thymol, methyl salicylate, eucalyptol and menthol.

2. The consumable film according to claim 1, comprising at least two of said essential oils.

3. The consumable film according to claim 1, comprising at least three of said essential oils.

4. The consumable film according to according to claim 1, comprising thymol, methyl salicylate, eucalyptol and menthol.

5. The consumable film according to claim 4, further comprising a salt of gluconic acid.

6. The consumable film according to claim 4, further comprising copper gluconate.

7. The consumable film according to claim 1, wherein said water soluble polymer is 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.

8. The consumable film according to claim 7, wherein said water soluble polymer is pullulan.

9. The consumable film of claim 8, comprising:

about 40 to about 80 wt % pullulan;

about 0.01 to about 4 wt % thymol;

about 0.01 to about 4 wt % methyl salicylate;

about 0.01 to about 4 wt % eucalyptol; and

about 0.01 to about 15 wt % menthol.

10. The consumable film according to claim 7, 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 8 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; and

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

11. The consumable film according to according to claim 10, wherein said least one stabilizing agent is selected from the group consisting of xanthan gum, locust bean gum and carrageenan, and said at least one sweetening agent is selected from the group consisting of saccharin, aspartame and acesulfame K.

12. The consumable film according to claim 1, wherein said film does not substantially adhere to itself.

13. The consumable film according to claim 1, wherein said film is free of glycerin and sorbitol.

14. The consumable film according to claim 1, wherein said film is free of humectants.

15. The consumable film according to claim 1, wherein the essential oils comprises at least about 10 wt % of the film.

16. The consumable film according to claim 15, wherein the essential oils comprises at least about 15 wt % of the film.

17. The consumable film according to claim 1, further comprising water in an amount from about 3 wt % to about 8 wt %.

18. A method for preparing a physiologically compatible film, said method comprising:

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

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

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.

19. The method according to claim 18, wherein at least one surfactant is mixed into said oil mixture.

20. The method according to claim 18, wherein the total amount of said oils in said oil mixture is at least about 5 wt % of the total weight of ingredients in said method.

21. The method according to claim 20, wherein said total amount of oils is at least about 15 wt %.

22. The method according to claim 18, wherein said drying is conducted until said film has a moisture content of about 3 wt % to about 8 wt %.

23. The method according to claim 18, wherein, prior to being combined with said aqueous solution, said film-forming mixture is hydrated with water at a temperature of about 25 to about 50°C and subsequently chilled to a temperature of about 4 to about 30°C for about 2 to 48 hours.

24. The method according to claim 18, wherein said film-forming mixture is

a powder, which is directly combined with said aqueous solution.

25. The method according to claim 24, wherein said hydrated polymer gel is formed without heating.

26. The method according to claim 25, wherein said hydrated polymer gel is stirred at room temperature for about 2 to about 48 hours.

27. The method according to claim 26, wherein said oil mixture is prepared by mixing thymol and menthol in a flavor oil, and subsequently adding methyl salicylate and eucalyptol.

28. A non-self-adhering film produced according to the method of claim 18.

29. The method according to claim 18, wherein the water soluble film former is 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.

30. The method according to claim 29, wherein said water soluble polymer is pullulan.

31. A consumable film adapted to dissolve in the mouth of a consumer,

wherein said film comprises a single layer including pullulan and at least one pharmaceutical agent.

32. The consumable film according to claim 31, wherein said pharmaceutical agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory agents, anti-tussives, decongestants, anti-histamines, expectorants, anti-diaherrals, H_2 –antagonists, proton pump inhibitors, central nervous system agents, analgesics. and mixtures thereof.

33. The consumable film according to claim 32, wherein the antimicrobial agent is 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.

34. The consumable film according to claim 32, wherein the non-steroidal anti-inflammatory agent is selected from the group consisting of aspirin, acetaminophen, ibuprofen, diflunisal, fenoprofen calcium, naproxen, tolmetin sodium, indomethacin, and mixtures thereof.

35. The consumable film according to claim 32, wherein the anti-tussive is selected from the group consisting of benzonatate, caramiphen edisylate, dextromethorphan hydrobromide, chlophedianol hydrochloride and mixtures thereof.

36. The consumable film according to claim 32, wherein the decongestant is selected from the group consisting of pseudoephedrine hydrochloride, phenylepherine, phenylpropanolamine and mixtures thereof.

37. The consumable film according to claim 32, 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.

38. The consumable film according to claim 32, wherein the expectorant is selected from the group consisting of guaifenesin, ipecac, potassium iodide, terpin hydrate and mixtures thereof.

39. The consumable film according to claim 32, wherein the anti-diarrheal is loperamide.

40. The consumable film according to claim 32, wherein the H_2 –antagonist is selected from the group consisting of famotidine, ranitidine and mixtures thereof.

41. The consumable film according to claim 32, wherein the proton pump inhibitor is selected from the group consisting of omeprazole, lansoprazole, and mixtures thereof.

42. A method for delivering and enhancing the retention of an effective amount of an antimicrobial agent to the oral cavity comprising introducing in the oral cavity a rapidly dissolving film comprising pullulan and an antimicrobial agent comprising menthol and at least one of methyl salicylate, eucalyptol and thymol, wherein said pullulan enhances the retention of the antimicrobial agent in the oral

cavity.

43. The method according to claim 42, wherein the antimicrobial agent comprises menthol, methyl salicylate, eucalyptol and thymol.

44. The method according to claim 42, wherein the amount of pullulan in the film is from about 40 wt% to about 80 wt %.

45. The method according to claim 42, wherein the amount of antimicrobial agent in the film is from about 5 wt% to about 12 wt%.

46. The method according to claim 43, wherein the amount of antimicrobial agent in the film is from about 5 wt % to about 12 wt%.

47. A method for delivering and enhancing the retention of an effective amount of an antimicrobial agent to the oral cavity comprising introducing in the oral cavity the consumable film according to claim 9.

FIG-1

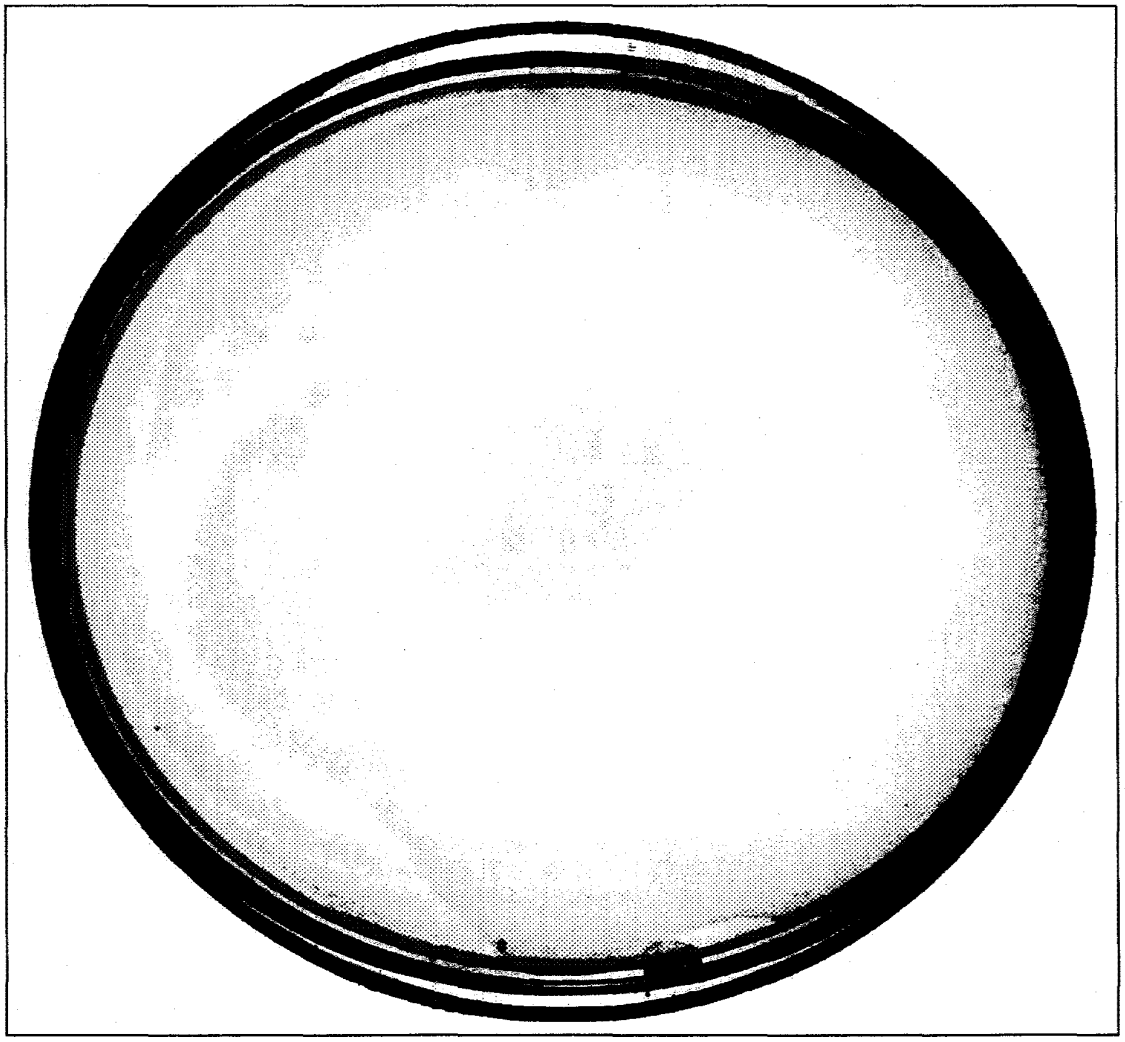
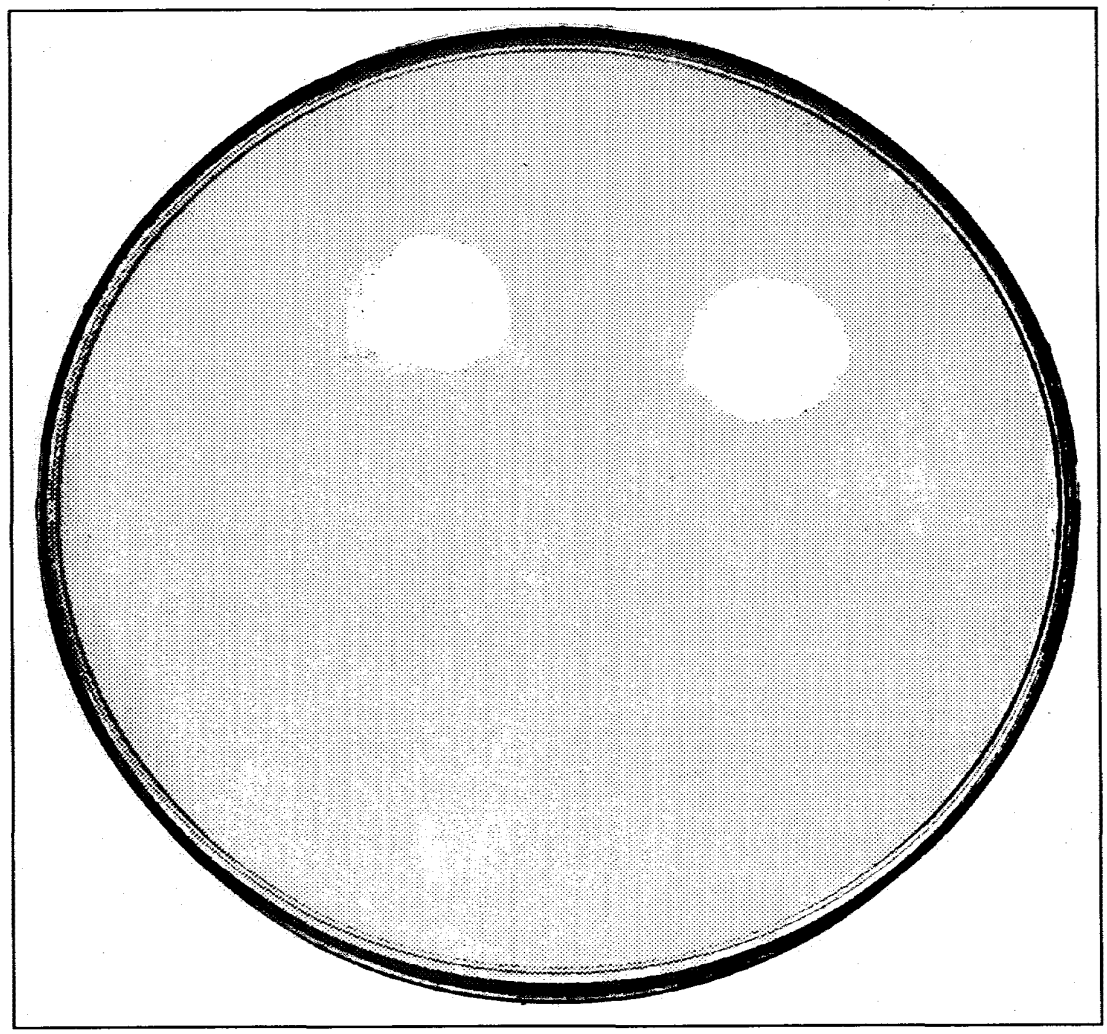


FIG-2



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(51) International Patent Classification 7 : A61K 7/16, 9/70, 7/22, 7/18, 7/26, A61L 15/28, 15/60, 15/44, 26/00, A61K 31/00, A61P 29/00, 31/04, 11/14, 37/00, 11/10, 1/12, 1/04	A3	**(11) International Publication Number:** **WO 00/18365** **(43) International Publication Date:** 6 April 2000 (06.04.00)

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(71) Applicant: WARNER–LAMBERT COMPANY [US/US]; 201 Tabor Road, Morris Plains, NJ 07950 (US).

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(74) Agents: RYAN, M., Andrea; Warner–Lambert Company, 201 Tabor Road, Morris Plains, NJ 07950 (US) et al.

(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, TZ, UA, UZ, VN, YU, ZA, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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16 November 2000 (16.11.00)

(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS

(57) Abstract

Physiologically acceptable films, including edible films, are disclosed. The films include a water soluble film–forming polymer such as pullulan. Edible films are disclosed that include pullulan and antimicrobially effective amounts of the essential oils thymol, methyl salicylate, eucalyptol and menthol. The edible films are effective at killing the plaque–producing germs that cause dental plaque, gingivitis and bad breath. The film can also contain pharmaceutically acitve agents. Methods for producing the films are also disclosed.

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 99/22115

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K7/16 A61K9/70 A61K7/22 A61K7/18 A61K7/26
A61L15/28 A61L15/60 A61L15/44 A61L26/00 A61K31/00
A61P29/00 A61P31/04 A61P11/14 A61P37/00 A61P11/10

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IPC 7 A61K A61L

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26 July 2000	11.08.00

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Cielen, E

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/US 99/22115

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61P1/12 A61P1/04

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Cielen, E

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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national Application No
PCT/US 99/22115

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Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

International application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [ ] Claims Nos.:
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:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-17,42-47

   A consumable film adapted to adhere and dissolve in a mouth of a consumer comprising (a) at least one water soluble polymer and (b) at least one essential oil. A method for delivering and enhancing the retention of the essential oils.

1.1. Claims: 1-17,42-47 (partially)
The subject matter as defined in Subject 1, wherein the essential oil is thymol.

1.2. Claims: 1-17,42-47 (partially)
The subject matter as defined in Subject 1, wherein the essential oil is methyl salicylate.

1.3. Claims: 1-17,42-47 (partially)
The subject matter as defined in Subject 1, wherein the essential oil is eucalyptol.

1.4. Claims: 1-17,42-47 (partially)
The subject matter as defined in Subject 1, wherein the essential oil is menthol.

2. Claims: 18-30

   A method for preparing a physiologically compatible film and the film prepared according to this method.

3. Claims: 31-41

   A consumable film adapted to dissolve in the mouth of a consumer comprising a single layer including pullulan and at least one pharmaceutical agent.

Please note that all inventions mentioned under item 1, although not necessarily linked by a common inventive concept, could be searched without effort justifying an additional fee.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
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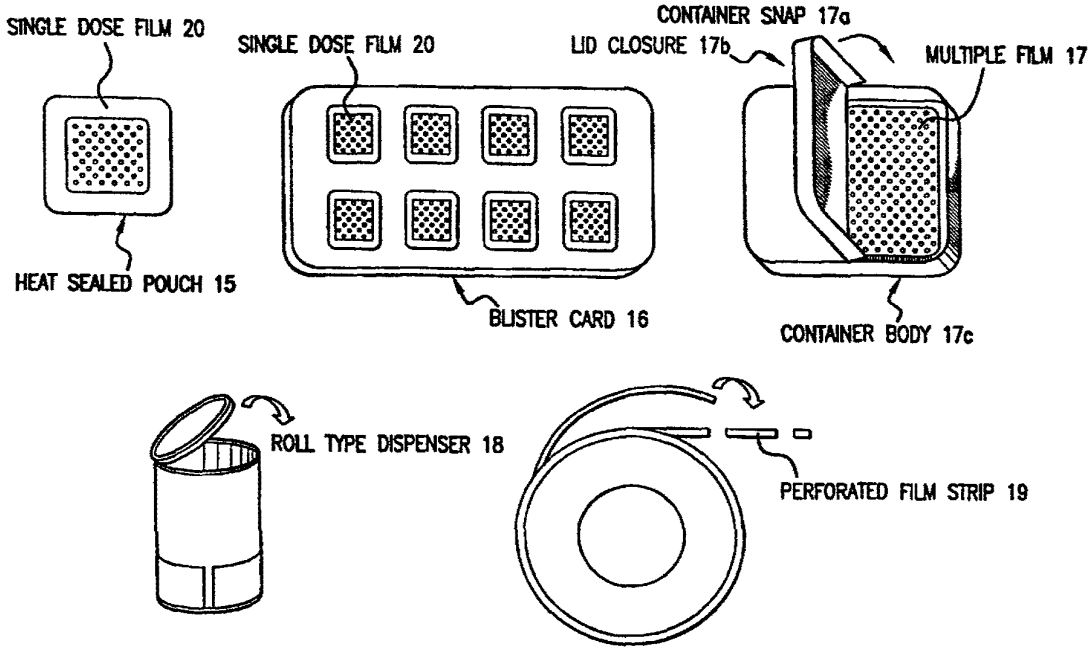

(57) Abstract

A dosage unit comprising a water–soluble hydrocolloid and a mucosal surface–coat–forming film, such film including an effective dose of active agent. In the dosage unit slidenafil citrate, nicotine, hydromorphone, oxybutynine or estradiol are used as active agents.

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COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY

Technical Description

The present invention is directed to a device and method for administering agents in a dissolving film configuration.

Background to the Invention

Many pharmaceutical dosage forms are administrated orally in the form of solid shaped articles such as tablets, pills, caplets and capsules that retain their shape under moderate pressure. Generally these dosage forms are designed to be swallowed whole or chewed to deliver the medication with adequate amounts of liquid. Some patients, particularly pediatric and geriatric patients, have difficulty swallowing or chewing solid dosage forms. Certain patients such as children or animals resist taking medication, and may try to hide a solid pill in order to spit it out later. In addition, many pediatric and geriatric patients are unwilling to take a solid dosage form because the active agent is difficult to swallow or is retained in the pharynx or gullet even when liquids are consumed with the dosage unit. Furthermore, the availability of liquids at the time of administering medications may be limited for certain patients and may be restricted for certain diseases and/or treatments. Chewable tablets provide some advantages over the conventional tablets. However, they are not suitable for children wearing braces and the taste of the medication may be unpleasant and difficult to mask in a chewable tablet. At the same time, water may be still required for the administration of chewable tablets.

In addition, the standard oral dosage forms, such as tablets, pills, caplets, and capsules, are designed for short residence time in the mouth. Absorption of the agent from these dosage forms occurs in the gastrointestinal (GI) tract, after the agent has separated from the dosage form and dissolved in the gastric fluids. For some active agents, it is desirable to achieve absorption through the oral mucosal tissues in order to accelerate onset of the therapeutic effect.

Many active agents are poorly absorbed, even after they are dispersed in the stomach, because of low solubility or slow dissolution rate in the gastric fluids. Tablets may be formulated so as to be quick dissolving. These tablets are commonly placed on the tongue and disintegrate rapidly in the oral cavity. However, these dosage units are

not fixed to a mucosal surface and may move around in the mouth. Consequently, they do not overcome a risk associated with choking or gagging that occurs with subjects having limited control of their swallowing reflexes. However, once placed in the mouth, these tablets dissolve rapidly in the saliva to provide a liquid formulation which is then swallowed. Quick dissolving tablets may be formed from a particulate support matrix containing the therapeutic agent, where the particulate support matrix is a protein (US 5,807,576, US 5,635,210, US 5,595,761). Alternatively, the tablet may be formed from a laminate with several layers and an outer coating (JP 100535518). Tablets have also been manufactured from shearform matrices which are substantially amorphous sugar formed when crystalline sugar is subjected to heat and shear (WO 95/07194; WO 95/35293). Other methods of forming quick dissolving tablets include wet granulation methods (EP 0627 218) and dry granulation methods (EP 0124027A1) and by freeze-drying techniques (EP 0084705A2). Generally, quick dissolving tablets are formed using complex multi-step manufacturing processes. In addition, these tablets may have poor mechanical strength, are fragile and friable and have insufficient holding capacity for active ingredients (US 5,720,974) and may be difficult to store and handle.

Therapeutic compounds are sometimes provided as powders or granules which may be difficult to swallow and cause unpleasant sensations in the mouth. Furthermore, many quick dissolving tablets contain particulates (>25 microns) which leave a "gritty" and unpleasant taste in the mouth. In the elderly, powders may cause choking and discomfort associated with trapping of granules in dentures. Powders and granules are generally packaged in a sealed pouch which requires tearing before use. This causes problems for geriatric patients and those suffering from arthritis in the fingers as well as for children. Consequently, problems of spillage of the contents arise in this group of patients. Furthermore, these oral preparations should be taken with water which for certain patients are inconvenient and may cause reduced patient compliance.

Liquid, syrups or suspensions are an alternative to solid dosage forms and are considered desirable for pediatric and geriatric patients who have problems in swallowing tablets. However, these dosage forms are often difficult to measure accurately and administer easily. Liquid formulations deteriorate rapidly upon exposure to heat or atmosphere and consequently have a relatively short shelf life. Furthermore, liquid formulations require a relatively large volume and are bulky to store.

In addition to solid and liquid dosage forms, rapidly dissolving buccal/oral delivery systems have been developed. These systems are commonly freeze dried preparations which are more expensive to manufacture as compared to tablets (US 5,648,093). Furthermore, freeze dried preparations are brittle and fragile when handled and must be kept in dry conditions to avoid disintegration. The instability of freeze-dried preparations has been reduced somewhat by the addition of mannitol (US 4,946,684). WO 9820862 reports a film that is formed according to a method that does not utilize freeze drying and avoids problems described in the art such as rigidity of the films, delayed softening and poor solubility in the mouth (US 4,876,092; EP 0200508; EPO 381194; CA-PS 1-26331; DE 2449865.5; DE 3630603; EP 0452446 and EP 0219762). However, the film described in WO 9820862 relies on the use of at least two different non-ionic surfactants to achieve immediate wettability.

It is desirable that a dosage unit should provide a non-invasive, effective and economic means to deliver an active agent to the target site. Where the target site is the plasma, additional issues arise concerning the rate of delivery of the active agent to that site as measured by bioavailability. For many types of active agent, fast onset of the therapeutic effect is desirable. Traditional oral dosages, such as tablets, are limited in onset time by the rate of absorption in the gastro-intestinal tract. Formulations have been developed which, when applied in the mouth, lead to faster onset that the traditional oral dosages because they target the oral mucosa. These formulations include dosage units containing 75%-90% polyethylene glycol that melt at body temperature, in the mouth.(US 5,004,601 and 5,135,752) Other formulations include liquid forms, lozenges or tablets that are administered sublingually or by a sweetened matrix on a stick. (US 5,770,606, Streisand et al. and Zhang et al., Christie et al., Sasaki et al.). Whereas the above references address the delivery route, they do not address the problems of bioavailability that arise from poor solubility or low dissolution rate.

A delivery device that addresses the above limitations would represent a desirable improvement on existing delivery systems.

Summary of the Invention

A novel dosage unit and its method of manufacture and use is provided. In an embodiment, the dosage unit includes a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent.

In an embodiment of the invention, the hydrocolloid includes a polymer selected from the group consisting of a natural, semi-natural and synthetic biopolymer being exemplified by a polysaccharide and a polypeptide. In addition to the hydrocolloid, the film may further include one or more of an emulsifier, a plasticizer, a taste modifying agent, a water soluble inert filler, a preservative, a buffering agent, a coloring agent, a permeation enhancer, and a stabilizer. The film may further include an active agent selected from the group consisting of a therapeutic agent, a dietary supplement and a hygiene aid. Embodiments of the invention utilize effective amounts of sildenafil citrate, nicotine, hydromorphone , oxybutynine or estradiol as active agents in the dosage unit. The active agent may be encapsulated within a second polymer having dissolution properties that are different from those of the hydrocolloid. More than one active agent may be included in the film. In an embodiment of the invention, the emulsifier may have a concentration of 0.1-10%w. The water inert filler may include a concentration range of 0.5-50% and the preservative may include a concentration range of 0.01-10%. A mucosal adhesion enhancer such as starch graft copolymer may be included in the dosage unit.

In embodiments of the invention, the dosage unit may further include any of the following features: a dry film thickness in the range of 1-20 mil, more particularly less than 10 mils, a dry tack value of less than 3.5g, more particular less than 2 g, a wet tack value of greater than 35g, a tensile strength greater than 1500psi, a modulus in the range of 35,000-300,000 psi, a tear propagation resistance in the range 0.001N-1N, a disintegration time in a range from 1-300 seconds, a dissolution time in a range from 10-600 seconds, and a percentage elongation less than 20%.

In embodiments of the invention, methods are provided for making a dosage unit, that include in one embodiment, dissolving a hydrocolloid in a solvent so as to form a substantially homogeneous preparation; 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 mixture; and forming a mucosal surface-coat forming film from the mixture for packaging as a dosage unit. The method may further include the step of coating the mixture onto a backing film. In a further embodiment, the reagents including: 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, may be combined in any order in a vessel having a heating source and a mechanical mixing device, the combined ingredients being mixed during and after the addition of the ingredients to the vessel, an effective amount of heat being applied for melting a substantial portion of the mixture. The mixture may then be formed into a film in a dry extrusion process.

In an embodiment of the invention, a method is provided for administering an active agent to a subject, that includes obtaining a water-soluble hydrocolloid, mucosal surface-coat-forming film, such film including an effective dose of an active agent; and placing the film on a mucosal surface coat forming film in the subject; so as to release the active agent.

In a further embodiment of the invention, a dosage unit is provided that includes a water soluble hydrocolloid and an effective dose of sildenafil citrate in a mucosal-surface contacting film. More particularly, an effective dose of sildenafil citrate is formed into a solid dispersion with xylitol for treating erectile dysfunction. The sildenafil/xylitol dispersion may be mixed with 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. The solid dispersion of sildenafil and xylitol may arise at a ratio of 9 parts sildenafil to one part xylitol. According to embodiments of the invention directed to a dosage unit and method of making a dosage unit suitable for erectile dysfunction, the water solubility of sildenafil in the solid dispersion is at least 20 mg/ml, more particularly about 50mg/ml. More particularly, the film may be capable of completely dissolution at the oral mucosal surface within 10-600 seconds.

Brief Description of the Figures

Figure 1 shows possible application sites in the oral cavity for the inventive dosage unit. (**1**) is the upper lip; (**2**) is the gingiva; (**3**) is the hard palate; (**4**) is the cheek; (**5**) is the lingual; (**6**) is the sublingual; (**7**) is the lower lip.

Figure 2 illustrates one manufacturing process for the dosage unit. (**8**) is the

mixing and degassing tank; (**9**) is the coating slot with thickness controller; (**10**) is the polyester backing belt; (**11**) is the drying oven with aeration controller; (**12**) is the intraoral film; (**13**) is the die cutting and (**14**) is the intraoral unit dose.

Figure 3 shows examples of packaging and dispensing devices for the intraoral delivery system. (**15**) is a heat sealed single pouch; (**16**) is a multi-unit blister card; (**17**) is a multi-unit dispensing pack, **17(a)** the container snap and **17(b)** the lid closure; (**18**) is a multi-unit roll-type dispenser cylinder; (**19**) is a perforated film strip; and (**20**) is a single dose film.

Figure 4 demonstrates the disintegration and dissolution time of the intraoral delivery system as a function of thickness.-- • -- is disintegration time and -- ○ -- is dissolving time.

Figure 5 shows the release profiles of -- ▾ -- nicotine, -- ▽ -- oxybutynin, -- • -- hydromorphone and -- ○ -- estradiol.

Figure 6 shows the pharmacokinetics in six subjects after administration of a dissolving film sildenafil formulation and after administration of the commercial tablet containing the same dosage of sildenafil. Sildenafil film -- ○ -- Viagra -- ▽ --.

Detailed Description of Invention

Delivery of active agents in solid form via the mouth causes problems to patients who may choke on the dosage unit. This effect is caused at least in part by the mobility of the dosage unit within the mouth. We have developed a new class of dosage units which are not mobile in the mouth because on contact with the moist mucosal surface, the film becomes a coating that adheres to the mucosal surface and then disintegrates and dissolves over a time frame controlled in the design of the dosage. The dosage unit, in an embodiment of the invention, is in the form of a flexible, non-tacky, dry conveniently packaged film. Once removed from the package and placed on a mucosal surface, the mucosal surface-coat-forming film hydrates substantially immediately to form a coating on the moist surface of the mucous membrane and then disintegrates and dissolves to release the active agent from the film.

The dosage unit may release the active agent over a period of time that is determined by a number of different factors. These factors include the dimensions of the

film, the concentration of the active agent, the solubility of the agent at the mucosal surface and how the agent is dispersed throughout the film. The thickness of the film is a factor in determining the rate of dissolution. A thick film will dissolve more slowly than an otherwise similar thin film. A thick film may be desirable for its holding capacity for active agents that are required in high dosages. Although the surface area of a film can be adjusted up to about 5 square centimeters, increased thickness may also be desirable for purposes of achieving effective active agent dosages. The active agent can form a solid dispersion with a water soluble inert filler for purposes of increasing the solubility of the agent when released from the film thereby enhancing bioavailability of the active agent. This is exemplified here by sildenafil which is incorporated in a film with a water soluble inert filler, for example, xylitol, which has been found here to enhance the bioavailability of this agent. Solubilizing agents that are well known in the art may be included in the film. The extent of uptake of the active agent from the dosage unit at the mucosal surface can be controlled by the dissolution rate of the film. A dissolving film will release the active agent and this in turn will cause the active agent to be swallowed and taken up in the GI tract. In contrast, slow release of the active agent at the mucosal surface will give rise to increased uptake by the mucosal surface. A further parameter governing the release of an active agent at the mucosal surface is the manner in which the agent is dispersed in the film. For example, the agent may be dispersed as colloidal particles or microencapsulated within the film or alternatively may be mixed throughout the film as a reagent during casting.

The dosage unit of the invention may be used as a vehicle for delivering a wide range of active agents. For example, the active agent may be a small molecule, a protein, a nucleic acid including antisense molecules or other biological or synthetic molecules.

The term "mucosal surface-coat-forming" as applied to a film as used in this description and in the following claims unless specified otherwise , means a film that coats the mucosal surface on contact, and may not thereafter be manually recovered or moved from the contact site; and subsequently disintegrates and dissolves so as to release the active agent. It should be noted that for purposes of the description of the invention and the claims,

"mucosal surface" refers to any moist surface of the body. This includes the surfaces identified in Figure 1. It further includes a wound surface where lymph fluid bathes the

tissue surface.

Embodiments of the present invention include a process, composition and method of use for a quick dissolving film for local and systemic delivery of pharmaceutical agents to a mucosal surface in a subject. In the following text, specific reference may be made to the oral cavity by way of example. However, it is not intended to limit the scope of the invention to the oral cavity. The dosage unit of the invention may be applied to any mucosal surface as deemed appropriate for the systemic or local delivery of an active agent including vaginal, rectal, and ocular surfaces. For purposes of oral delivery, the films may be applied on lingual, sub-lingual, buccal, gingival, and palatal surfaces (Figure 1).

For vaginal delivery of such agents as contraceptive agents including nonoxynol or anti-infectives including antifungal agents, antibacterial agents and anti-viral agents, or fragrant or hygiene agents; the film should be non-sticky when removed from the packaging but should have mucoadhesive properties when applied in the vagina. Although films containing active agents for use in the vagina have been used, they appear to have some significant drawbacks most particularly the lack of adhesive properties at the mucosal surface. This makes these films impractical to administer. (US 5,380,529; 5,595,980 and 5,529,782).

Embodiments of the invention provide improved dosage forms to deliver active agents that are appropriate for all age groups and that physician, parents, patients and family members can administer easily. These dosage forms are economical to prepare and have an extended shelf life. They are easy to handle and non-tacky before administration so as to avoid disintegration prior to use and are conveniently packaged for shelf life, ease of storage and distribution. The dosage form may be administered to the subject by placing the film on a mucous surface, at which time the film becomes a mucoadhesive coating, characterized by the property that it can no longer exist in an independent form and is subsequently dispersed in solution.

Embodiments of the invention provide a delivery system for active agents and other active agents that will dissolve and completely release their contents on a moist mucosal surface -for example in the oral cavity. The release of the active agent occurs without mastication or the need for intake of water. With particular reference to the oral cavity, an embodiment of the invention provides active agents that remain in the oral

cavity for treatment or modification of the oral environment; for example, for periodontal disease treatment or breath-odor control. Furthermore, embodiments of the invention further provide improvements that include: improved organoleptic properties (smell and taste), and texture and feel of dosage forms intended to be placed in the oral cavity; a dosage form which "melts" in the mouth and leaves a smooth pleasant after feel following dissolution; and a prolonged retention of the active agent in the mouth following dissolution of the quick dissolving dosage form to extend the residence time of the active agent cleared from the mouth by the production of saliva and subsequent swallowing. Depending on the optimal program for a specific application of the invention, the disintegration time and the dissolution time can be controlled within a prescribed range by adjustment of the formulation and the thickness of the film. In some cases, it is desirable for release of the active agent to occur after dissolution of the film. For these applications, the active agent may be encapsulated in a material with dissolution properties that are different from those of the hydrocolloid. Encapsulation of the active agent also may be utilized to achieve masking of taste for active agents that are bitter. In some cases, two or more different active agents may be included in the film. An example where multiple active agents frequently are administered is cold medications, which often contain several active agents.

"Coating solution" is defined here and in the claims as a viscous and homogeneous mixture of hydrocolloids, active agents and other additives in a solvent. The coating solution is treated according to the method of the invention to form a film.

"Subject" is defined here and in the claims as a human or animal species.

"Thickness" is defined here and in the claims by measurements in mil (a mil = one thousandth of an inch) determined when a film is placed between two microscopic slides.

"Permeation enhancer" as defined here and in the claims is a natural or synthetic molecule which facilitates the absorption of an active agent through a mucosal surface.

"Enzyme inhibitor" as defined here and in the claims is a natural or synthetic molecule which inhibits enzymatic metabolism of an active agent in the saliva or in a mucosal tissue.

"Water Content" is defined here and in the claims as % residual water content per unit dose as measured according to the Karl Fisher method and expressed as percent of

the dry weight of the film.

"The hydration rate" is defined here and in the claims as the speed of absorbing water at 25°C. and 75% relative humidity in 24 hours.

"Percentage of swelling" is defined here as a percentage of the initial volume that is increased before dissolving. In an embodiment of the invention, the percentage of swelling is less than 10% in 60 seconds.

Taste modifying agents include flavoring agents, sweetening agents and taste masking agents and are exemplified by: the essential oils or water soluble extracts of menthol, wintergreen, peppermint, sweet mint, spearmint, vanillin, cherry, chocolate, cinnamon, clove, lemon, orange, raspberry, rose, spice, violet, herbal, fruit, strawberry, grape, pineapple, peach, kiwi, papaya, mango, coconut, apple, coffee, plum, watermelon, nuts, durean, green tea, grapefruit, banana, butter, camomile, sugar, dextrose, lactose, mannitol, sucrose, xylitol, malitol, acesulfame potassium, talin, glycyrrhizin, sucralose, aspartame, saccharin, sodium saccharin, sodium cyclamate and honey.

Emulsifying agents include solubilizers and wetting agents and are exemplified by polyvinyl alcohol, sorbitan esters, cyclodextrins, benzyl benzoate, glyceryl monostearate, polyoxyethylene alkyl ethers, polyoxyethylene stearates, poloxamer, polyoxyethylene castor oil derivatives, hydrogenated vegetable oils, bile salts, polysorbates and ethanol.

Plasticizers may include glycerin, sorbitol, propylene glycol, polyethylene glycol, triacetin, triethyl citrate (TEC), acetyl triethyl citrate (ATEC) and other citrate esters.

Active agents (for human and veterinary applications) include therapeutic agents, nutritional supplements and hygiene aids. The therapeutic agents are exemplified by analgesics, a-adrenergic receptor blockers, anti-Alzheimer's disease medication, antianginal, antianxiety, antiarrythmics, antiarthritics, antibiotics, anticoagulants/thrombolytics, anticonvulsants/anti-Parkinson medication, anti-depressants, anti-diabetics, anti-diarrheal, anti-epileptics, anti-fungal, anti-gout, anti-heartworm medication for dogs, anti-histamines, anti-hypertensives, anti-inflammatories, anti-infectives, antimigraines, anti-nasuants/anti-emetics, anti-neoplastics/anti-tumor active agents, anti-pruitics, anti-psychotics, anti-pyretics, anti-spasmodics, anti-virals, bronchial dilators/anti-asthmatics, calcium antagonists, cardiac agents, cardiotonics, central nervous system actives, contraceptives, coronary vasodilators, cough/cold

remedies, dietary supplements, including vitamins and minerals, diuretics, fertility active agents, flea control agents for animals (Ivermectin), H_2 receptor antagonists, herbal actives, hormones, hypoglycemics, hypolipidemics, muscle relaxants, ovulation stimulators, peptide active agents, polypeptide active agents, proteins such as insulin, calcitonin, LHRH and the like. Sedatives and hypnotics, sexual dysfunction active agents, sleep aids, smoking cessation aids, steroids and steroidals, tranquilizers, laxatives, ophthalmic preparations, nutritional supplements, breath fresheners, breath deodorants, saliva substitutes, antigingivitis agents, anti-cavity agents, anti-plaque agents, diagnostic indicators, and local anesthetics. Also included are active agents for treatment of osteoporosis, hormone replacement, treatment of periodontal disease, antiseptics, corticosteroids, non steroidal anti-inflammatory agents, antiviral agents and vaccines.

Water soluble inert fillers include mannitol, xylitol, sucrose, lactose, maltodextrin, dextran, dextrin, modified starches, dextrose, sorbitol, and dextrates. The water soluble inert fillers may be used in embodiments of the invention as inert carriers to form a high water soluble dispersion with active agents.

Buffering agents include acidulants and alkalizing agents exemplified by citric acid, fumaric acid, lactic acid, tartaric acid, malic acid, as well as sodium citrate, sodium bicarbonate and carbonate, sodium or potassium phosphate and magnesium oxide.

Coloring agents may include FD & C coloring agents, natural coloring agents, and natural juice concentrates, pigments such as titanium oxide, silicon dioxide and zinc oxide.

Stabilizers as used here and in the claims, include anti-oxidants, chelating agents, and enzyme inhibitors as exemplified by ascorbic acid, vitamin E, butylated hyroxyanisole (BHA), butylated hydroxytoluene (BHT), propyl gallate, dilauryl thiodipropionate, thiodipropionic acid, gum guaiac, citric acid, edetic acid and its salts and glutathione.

Preservatives which here include anti-microbial agents and non-organic compounds are exemplified by sodium benzoate, parabens and derivatives, sorbic acid and its salts, propionic acids and its salts, sulfur dioxide and sulfites, acetic acid and acetates, nitrites and nitrates.

The mechanical properties of the film is determined by tensile strength modulus,

percent elongation (ASTM D882, standard test method for tensile properties of thin plastic sheet) and tear propagation resistance (ASTM D1938, standard test method for tear propagation resistance of plastic film and thin sheet by single tear method). The mechanical properties are measured here using standard protocols as described in Annual Book of ASTM Standards, American National Standards Institute, NY 1995.

The "tensile strength" (psi) is the property of film that requires a load to cause load deformation failure of film.

The "% elongation" is measured when the film snaps as sufficient force is applied so as to exceed the elastic limit.

The "release study" is the percentage of active agents released from the film as a function of time in a suitable dissolution vessel and medium under specified conditions of temperature and pH.

"Dry tack" is quantitative values for tackiness (grams) of dry film by Texture Analyzers (Model TA.XT2i with 6mm diameter stainless steel cylinder probe) from Texture Technologies Corp. The tackiness after the addition of 10 ml of water on the same surface area is defined as the wet tack (gram) to simulate the adhesion of film upon the contact with a moist mucosal surface. In an embodiment of the invention, the dry tack ranges from 0.2-3.5grams, with a preferred range of 0.4-2.0grams and the wet tack is in the range of 35-150 grams with a preferred range of 40-100 grams.

"Tear propagation resistance" is defined here and in the claims as the average force (N) necessary to propagate a tear across a film or sheet under a specified rate of extension as defined in ASTM D1938 and is interpreted from the load time chart. In a preferred embodiment of the invention, the tear resistance ranges from 0.001N-1N with a preferred range of 0.01-1N.

"Disintegration time" is defined here and in the claims as the time (second) at which a film breaks when brought into contact with water or saliva. In an embodiment of the invention, the disintegration time ranges from 1-300 seconds.

"Dissolving time" is defined here and in the claims as the time (seconds or minutes) at which not less than 80% of the tested film is dissolved in an aqueous media or saliva. In an embodiment of the invention, the dissolution time ranges from 10-600 seconds.

"Modulus" is a measurement of stiffness of a film.

A factor that plays a significant role in determining the properties of mucosal surface-coat-forming composition is the viscosity of the hydrocolloid. The viscosity of the hydrocolloid depends on its molecular size, derivation, hydrophobicity and hydrophilicity and the presence of other additives in the formulation. A comparison of films formed from the hydrocolloid, hydroxymethylcellulose, having different viscosity values is shown in Table 9a and 9b.

In embodiments of the invention, a hydrocolloid concentration in the range of 5-99% of the dry weight of the films is provided, more particularly greater than 10%. These films have dry tack and wet tack properties that improve ease of handling and use. The low dry tack properties of the film provide for a physically attractive and easily handled film that is neither fragile nor sticky and can be easily removed from packaging and placed on a mucosal surface. The wet tack properties of the film provide the advantage of stickiness of the moistened film such that when the film is placed on the mucosa, it remains attached at that site until it dissolves. In contrast, if the wet tack is too low, the film can move in the mouth and may be swallowed before dissolving and possibly give rise to choking. Furthermore, the low moisture content and low dry tack of the film enhances the shelf-life of the film and the flexibility of the dosage forms. These properties render the films suitable for easy making, packaging, handling and application.

In an embodiment of the invention, a water soluble polymer (2% polymer solution) is selected having a gelation temperature greater than 70°C. The hydration rate of a hydrocolloid having these features is rapid with a percentage moisture absorption of polymers in the range of 5-20% at 75% humidity at room temperature. The hydration rate is selected according to the desired wettability of the film thereby obviating the need for surfactants. The wet tack of the hydrated film ranges from 35-150 grams more particularly 40-100 grams. The percentage swelling may be less than 10% within 60 seconds. The film is cast so as to have a thickness of 1-20mil. The water content of the film ranges from 0.5-10% with a preferred range of 1-5%. In embodiments of the invention, the film may be formed using a mixture of two or more types of the same hydrocolloid that differ only in molecular weights and/or different degrees of substitution. The time of dissolution of the film is in the range of 10-600seconds, (see Figure 4), the time of disintegration of the film may be 1-300 seconds. The active agent

in the film may be encapsulated in a polymer having different chemical or physical properties from the hydrocolloid of the film and having dissolution properties different from those of the hydrocolloid. Examples of the films formed according to the invention having properties that fall into the above ranges are provided in Table 1,3,6 and 7.

The ease of handling is characterized by the dry tack of the film and the flexibility is reflected by the tensile strength, modulus, % elongation and tear resistance of the film. For example, the dry tack is in the range of 0.2-3.5 grams more particularly 0.4-2.0 grams. The tensile strength may be in the range of 1500-10,000 psi, more particularly 2000-8000, more particularly greater than 2000psi, the modulus is in the range of 35,000 -300,000 and the % elongation is less than 20% more particularly 1-10% for a film having a thickness of 2 mil.

In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling (at room temperature) natural polysaccharide or derivatives including pectin and derivatives, guar gum arabic, tragacanth gum, xanthan gum, gellan sodium salt, propyleneglycol alginate, starches (amylose, amylopectin), modified starches, hydroxyethyl starch, pullulan, carboxymethyl starch, gum ghatti, okra gum, karaya gum, dextrans, dextrins and maltodextrins, konjac, acemannan from *aloe*, locust bean gum, tara gum, quince seed gum, fenugreek seed gum, scleroglucan, gum arabic, psyllium seed gum, tamarind gum, oat gum, quince seed gum, carrageenans, scleraglucan, succinoglucan, larch arabinogalactan, flaxseed gum, chondroitin sulfates, hyaluronic acid, curdlan, chitosan, deacetylated konjac, and *rhizobium* gum.

In embodiments of the invention, the hydrocolloid may be a water soluble non-gelling polypeptide or protein exemplified by gelatins, albumins, milk proteins, soy protein, and whey proteins. The hydrocolloid may further be selected from a group of synthetic hydrocolloids exemplified by any of the following: polyethylene-imine, hydroxyethyl cellulose, sodium carboxymethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, methyl cellulose, ethyl cellulose, polyacrylic acids, low molecular weight polyacrylamides and their sodium salts (carbomers), polyvinylpyrollidone, polyethylene glycols, polyethylene oxides, polyvinyl alcohols, pluronics, tetronics, and other block co-polymers, carboxyvinyl polymers, and colloidal silicon dioxide. A preferred embodiment of the invention

utilizes a hydroxypropyl methyl cellulose having a methoxy content of about 19-30% and hydroxypropyl content of 7-12% and a molecular weight of approximately 50,000 - 250,000 daltons (Table 9).

In addition to hydrocolloids and the active agents, the films may contain any or all of the following ingredients: emulsifying agents, solubilizing agents, wetting agents, taste modifying agents, plasticizers, active agents, water soluble inert fillers, preservatives, buffering agents, coloring agents, and stabilizers. In a preferred embodiment, the percentage dry weight concentration of at least single ingredients incorporated in a film in each of the following categories is as follows: emulsifying agent (0.1%-10%), plasticizer (0.5-20%), active agents (0.01-75%), taste modifying agents (0.1-10%), coloring agents (0.01-5%), water soluble inert fillers (0.5-50%), preservatives (0.01-10%), buffering agents (0.1-10%) and stabilizers (0.01-5%).

Methods for manufacturing the dosage unit of the invention include the solvent casting methods as shown in Figure 2 or alternatively extrusion methods as exemplified in Example 11. The extrusion method involves blending ingredients to form a film using mechanical force and moderate heat. Significantly, the above processes do not rely on a freeze drying step. Nor do the above processes rely on extremes of heat or cold during manufacture.

In an embodiment of the invention, the solvent casting method includes a natural or synthetic hydrocolloid that is completely dissolved or dispersed in water or in a water alcoholic solution under mixing to form a homogenous formulation. In addition to the active agent and the hydrocolloid, any of the ingredients listed above may be added and dispersed or dissolved uniformly in the hydrocolloid solution. The active ingredients and flavoring agents can be incorporated before or after film forming. This homogeneous mixture (coating solution) with a solid content of 5-50% and a viscosity of 500-15000cps was degassed (**8**) and coated on the non-siliconized side of a polyester film (**10**) at 5-50mil wet film thickness (**9**), more preferably 5-20mil wet film thickness and dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation (**11**). The manufacturing process for forming the dosage unit is illustrated in Figure 2. The dry film formed by this process is a glossy, stand alone, self supporting, non-tacky and flexible film (**12**). The dry film is

then cut into a suitable shape (**13**) and surface area for active agent delivery at the preferred site. For example, the cast film can be die-cut into different shapes and sizes using a rotary die. The film may be cut into a size that contains for example, a single dosage unit. For example, a dosage unit may include a film size with surface area of $5cm^2$ that contains a dosage of active agent in the range of 20-250 mg (**14**). The size of the film may be varied according to the dosage required. The dosage contained in each square centimeter is selected according to the active agent. Films are then packaged into a single pouch package, multi-unit blister card or multiple unit dispensers (Figure 3).

In contrast to the above method, the dry extrusion method does not rely on placing the hydrocolloid in a solvent. Instead, the ingredients of the dosage unit are mixed together in dry form and heated. The heated blend is then forced through an extrusion die to form a film of selected thickness. The film can then be cut and packaged.

The dry extrusion method has a number of advantages. First, it is an economical process. Second, because there is no drying oven, extrusion of the film is faster than solvent coating. Third, the dry extrusion avoids the step of removing residual solvent. Some residual solvent is generally present in the solvent coating process and can affect the safety or stability of the film. Where a film requires an organic solvent rather than water, removal of the solvent from the film may be required by environmental regulations. The extrusion process avoids any need for recovering solvent and avoids residual solvent in the film.

The dosage unit may be prepared for use by selecting a film that is capable of delivering an effective dose and administering the film to the patient by placing it on a mucosal surface such as the oral mucosa (Figure 1) where it dissolves in the body fluid for example, saliva (0.5-10 minutes) and is swallowed in liquid form. Figure 4 graphically represents the rate of disintegration and dissolution for different thickness films. Figure 5 shows the release profile of four active agents from films according to Examples 5-8. The fraction of the dose absorbed through the mucosal tissue can be facilitated by the use of a permeation enhancer into the film.

The overall bioavailability of the active agent which is absorbed both locally at the mucous membrane and systemically within the gastrointestinal system is improved

compared to the same dose of the active agent given in a conventional oral tablet or capsule dosage form. This is exemplified in Figure 6 and Table 11 which show the improved bioavailability of Sildenafil film over Viagra. The oral retention characteristics, mouth feel properties, flavor and taste of the film can be modified based on the hydrocolloid and other excipients used to prepare the films and the medications.

The invention is illustrated but not meant to be limited to the examples provided below. According to Examples 1-8, the hydrocolloid was dissolved in water under agitated mixing to form a uniform and viscous solution. Additional ingredients were then added sequentially to the viscous solution such as peppermint, aspartame, propyl glycol, benzoic acid and citric acid under agitated mixing until they were uniformly dispersed or dissolved in the hydrocolloid. The resultant mixture was degassed in a vacuum chamber until trapped air bubbles were removed. The viscosity, pH and specific gravity were measured. The formulation was then coated on the non-siliconized side of a polyester film at a wet thickness of 10 mil and dried in a hot air circulating oven at 50°C for 9 minutes. A glossy, substantially transparent, stand alone, self-supporting, non-tacky and flexible film was obtained after drying. The dry film was cut into different shapes for measurement of dry tack, wet tack, tensile strength modulus, elongation, tear resistance, residual water content, disintegration and dissolution. The dosage form was 25-250 mg in various shapes, sizes, and thickness.

Example 9 shows how the properties of dosage units vary when different hydroxymethylcellulose polymers are utilized. Example 10 shows how mucoadhesion can be increased up to at least 84% using an enhancer exemplified by starch graft copolymer. In vivo studies of the dosage unit show that it is well tolerated by patients (Example 12) and shows enhanced bioavailability (Example 13).

Examples

Examples 1-3: Quick dissolving films, compositions and associated properties

The films were prepared as follows: a homogeneous mixture of ingredients was prepared in a coating solution in the amounts indicated in Table 1. The amounts are given as percentage weight of coating solution. The mixture was degassed in a vacuum chamber and coated on the non-siliconized side of a polyester film and dried in a hot air circulating oven to form a self supporting non-tacky and flexible film. The film was then cut into dosage units ready for packaging.

Table 1: Formulation of quick dissolving films using several different hydrocolloids.

Composition: coating solution %	Ex. 1	Ex. 2	Ex. 3
Pullalan (P-20) w%		17.5	
Methocel E5 w%	21.06		
POLYOX WSR N-10 w%			1.8
PVA (Vinol 125) w%		1.5	
Cellulose gum w%			8.1
Propylene glycol w%	1.0		2.5
Aspartame w%	0.8	0.475	0.46
Peppermint w%	1.0	1.0	0.6
Citric acid w%	0.7	0.8	
Cremphor EL40 w%	1.0	1.0	
Benzoic acid w%	0.013	0.1	0.01
FD&C blue #1 w%	qs.		
FD&C yellow #5 w%	qs.		
Ethanol w%		10.6	
Water w%	74.42	67.025	85.6

Table 2: Properties of the film formed from the coating solution of Table 1.

Properties of dry film	Ex. 1	Ex. 2	Ex. 3
Thickness (mil)	2.1	2.5	2.6
Water content %	1.7	8.5	8.0
Dry tack (g)	0.67	0.55	0.60
Wet tack (g)	60.16	86.64	72.27
Tensile strength (psi)	5242	2381	2036
% Elongation (sec)	2.9	4	2.9

Modulus (psi)	266834	272502	44566
Tear resistance (N)	0.02	0.16	0.01
Disintegration (sec)	12	20	12
Dissolving time (sec)	41	60	39

Table 3: Dry weight percentages for components of Example 1 according to Tables 1 and 2.

Ingredients	**Percentage (w/w)**
Methocel E5	82.35
Propylene glycol	3.91
Aspartame	3.13
Citric acid	2.74
Peppermint oil	3.91
PEG-40 Hydrogenated castor oil	3.91
Benzoic acid	0.5
FD&C blue #1	qs.
FD&C yellow #5	qs.

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

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

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

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

Table 5:

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

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

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

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

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

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

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

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

hydroxypropylmethylcellulose polymers

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

Table 9a: Properties of selected commercial hydroxypropylmethylcellulose polymers.

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

* Each value is the mean S±D, n=6

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

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

Example 10: Enhancement of mucoadhesion

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

Table 10

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

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

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

Example 11: Preparation of film using dry extrusion techniques

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

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

Example 12: Human clinical acute irritation study

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

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

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

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

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

dosage unit are described in Table 8.

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

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

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

* Area under the curve

What is claimed:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

time in a range from 10-600 seconds.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(c) forming the mixture into a film.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

58. A method of treating erectile dysfunction; comprising:

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

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

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

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

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

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

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

(c) forming the mixture into a film.

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

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

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

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

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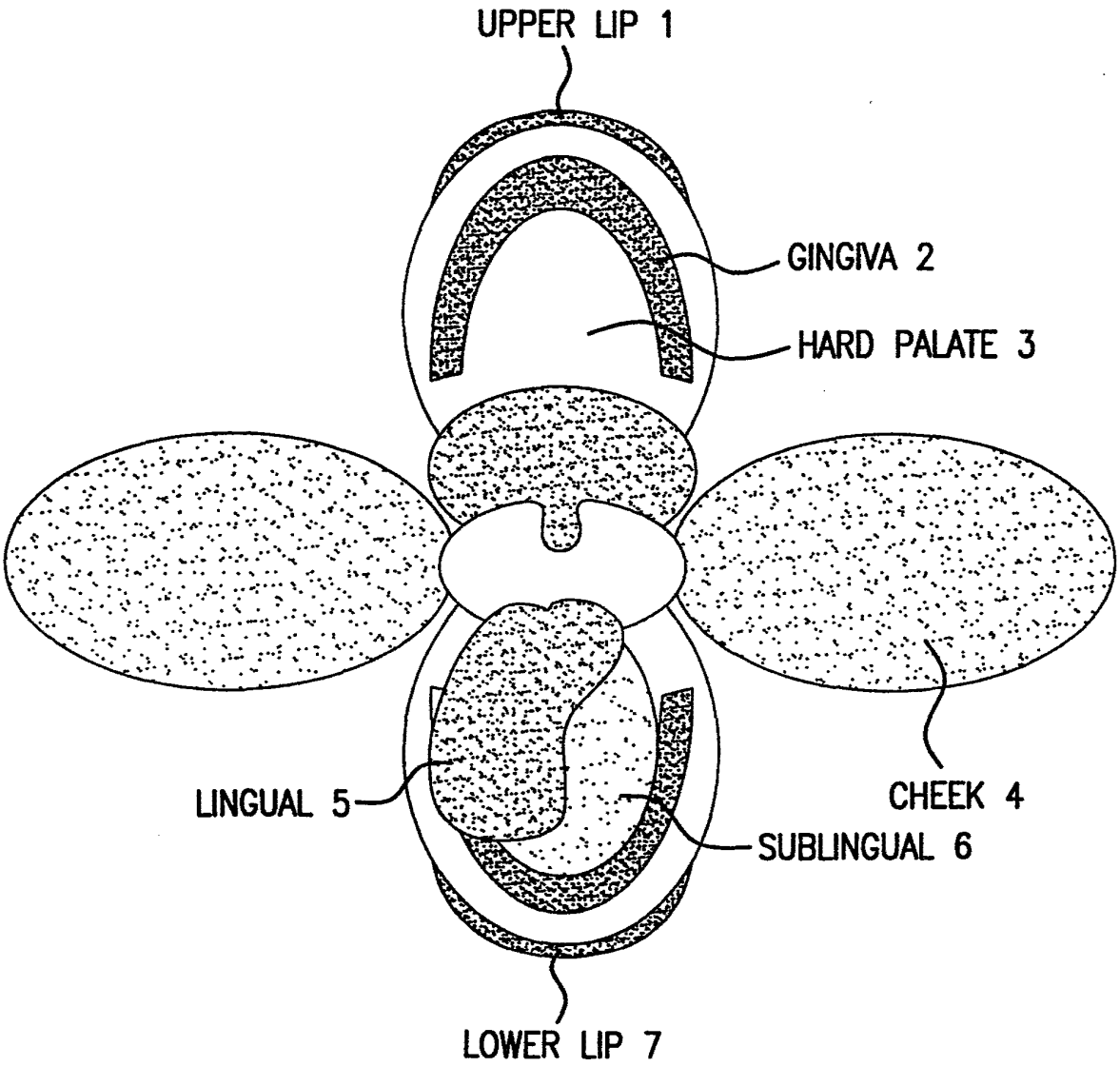

FIG.1

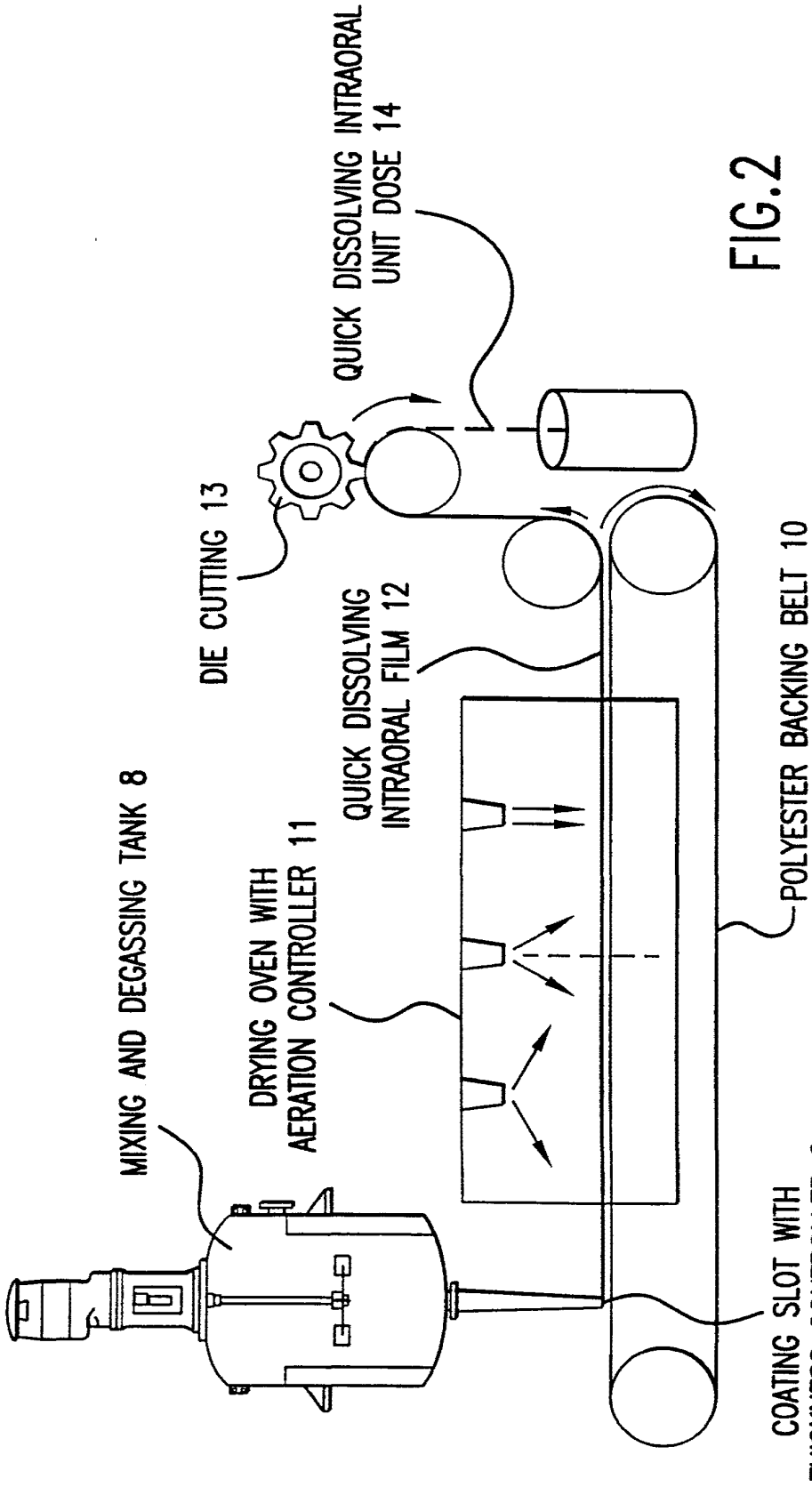

FIG.2

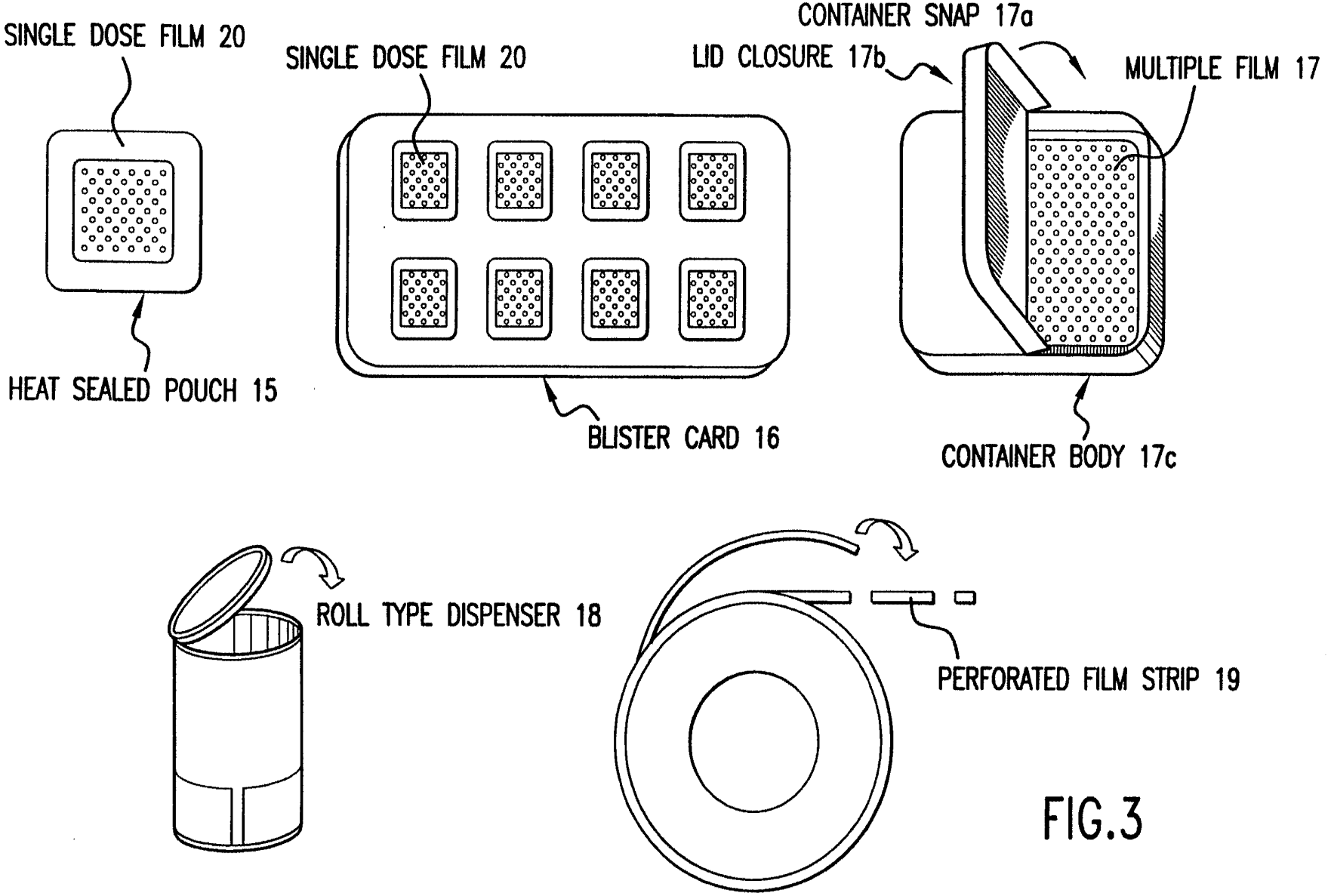

FIG.3

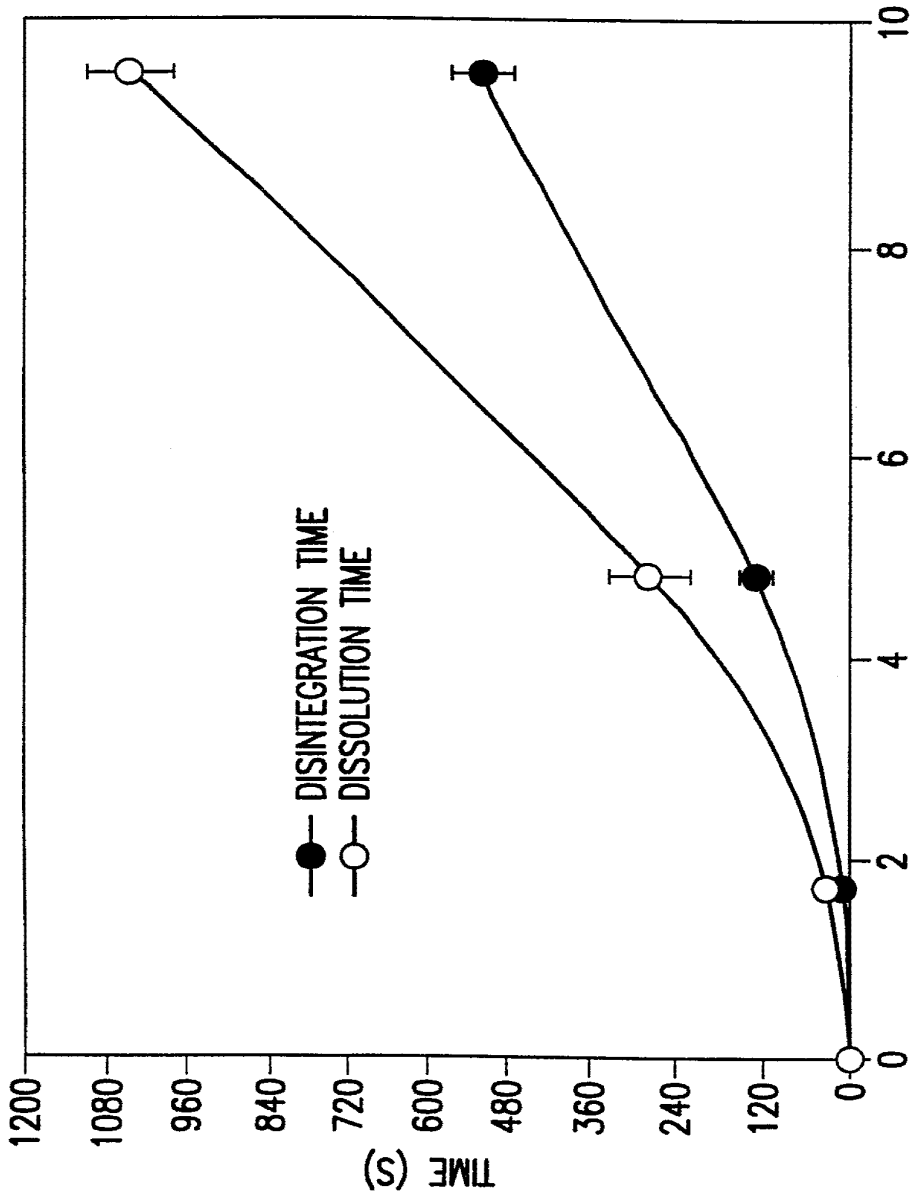

FIG.4

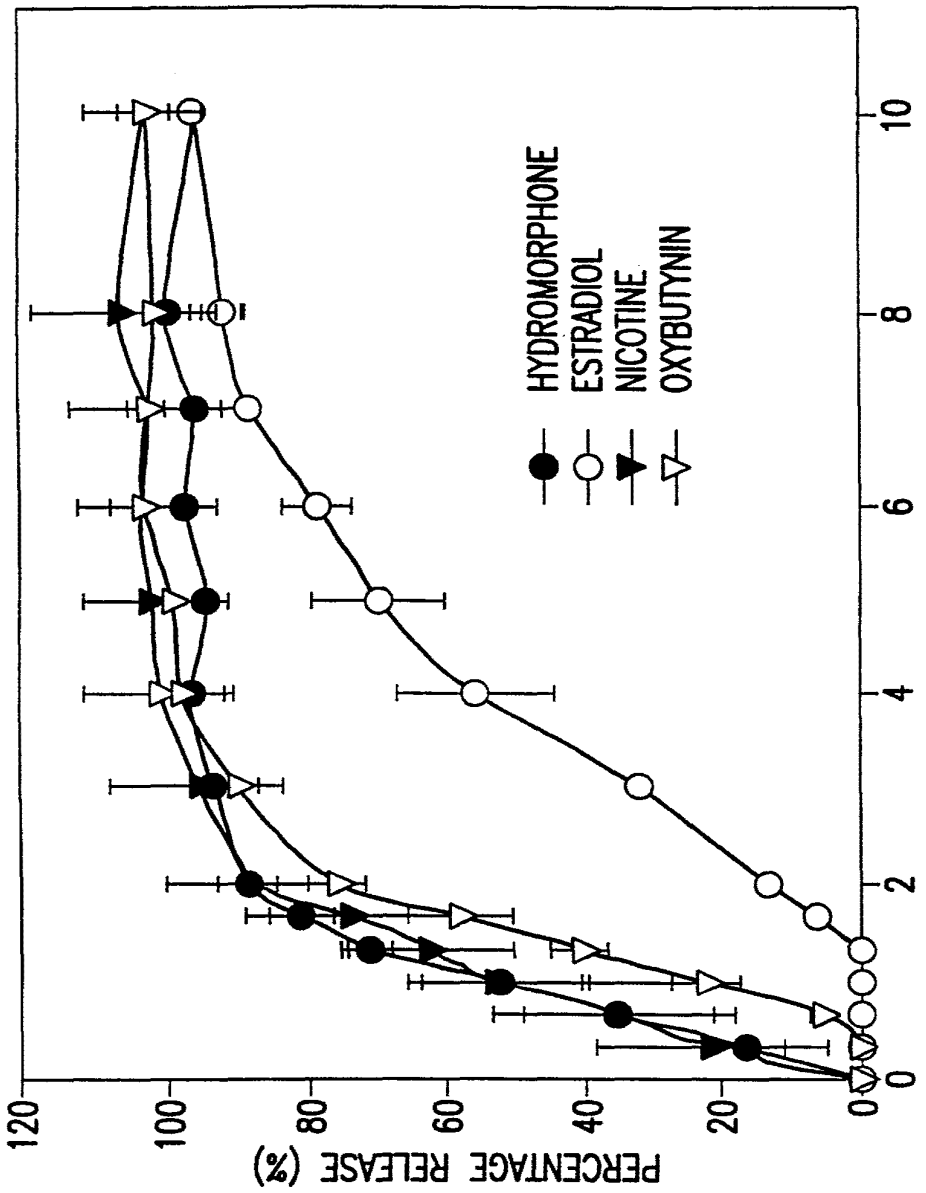

FIG.5

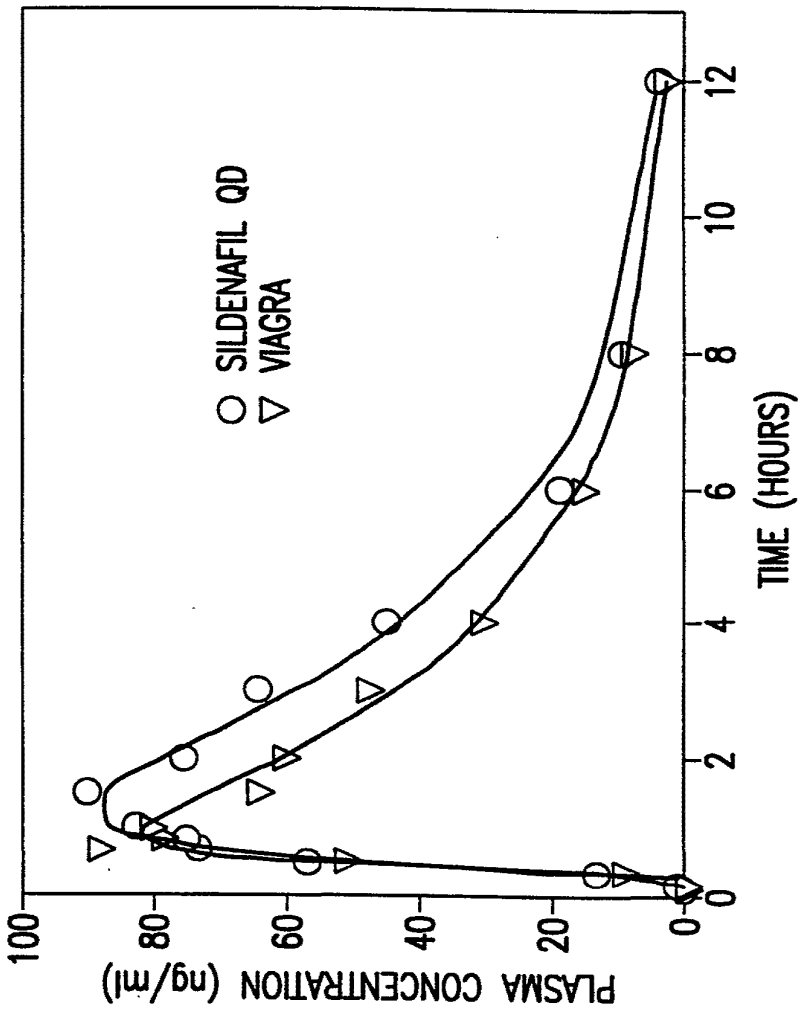

FIG.6

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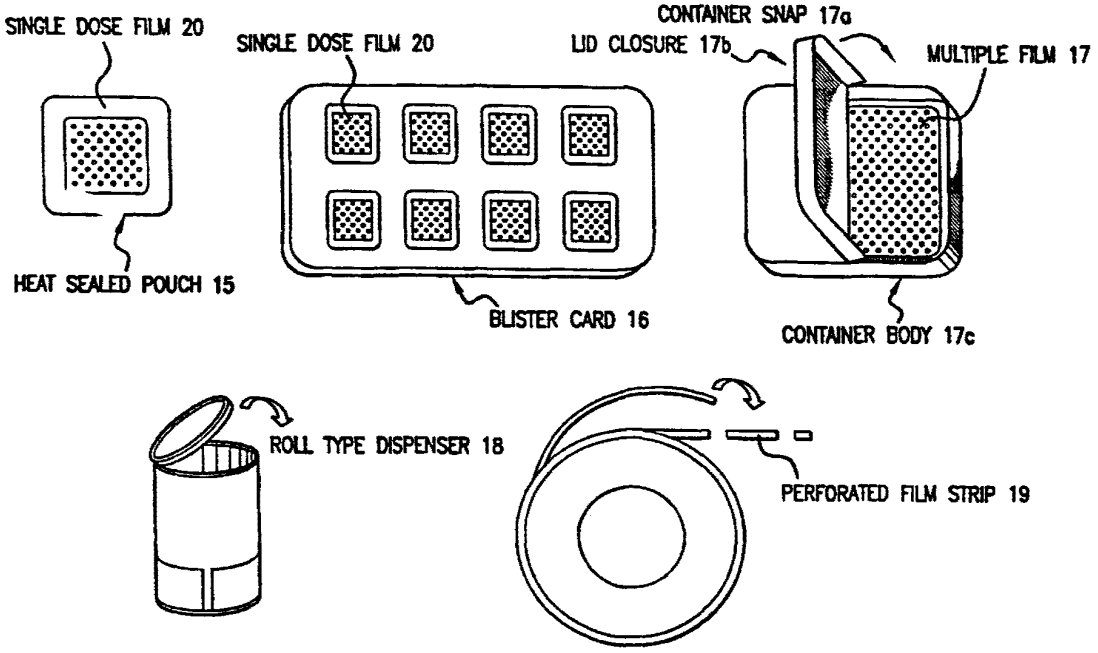

(57) Abstract

A dosage unit comprising a water-soluble hydrocolloid and a mucosal surface-coat-forming, such film including an effective dose of active agent. In the dosage unit slidenafil citrate, nicotine, hydromorphone, oxybutynine or estradiol are used as active agents.

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INTERNATIONAL SEARCH REPORT

In. ational Application No
PCT/US 99/31327

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

Minimum documentation searched (classification system followed by classification symbols)
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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, 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	WO 98 20862 A (LTS GMBH,DE) 22 May 1998 (1998-05-22) cited in the application claims examples page 7, line 1 - line 31	1,4, 10-21, 32,38,39
X	WO 91 06289 A (WATSON LABS. INC.,U.S.A.) 16 May 1991 (1991-05-16) claims 1,3,6,9,20-26,31,32 page 10, line 24 -page 11, line 5 examples 3,5,10,17	1,4, 10-13, 15,20, 21,23, 35,38, 39,43, 45, 50-52,54

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Scarponi, U

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INTERNATIONAL SEARCH REPORT

Int donal Application No
PCT/US 99/31327

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 99 66870 A (LAVIPHARM LABS. INC.,U.S.A.) 29 December 1999 (1999-12-29) claims 1,2,5-8,10,13-16,19,21-24,29-31 page 6, line 2 - line 31	1,4, 10-12, 15, 20-22, 24,34, 38,39,56

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 99/31327

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9820862 A	22-05-1998	DE 19646392 A	14-05-1998
		AU 4868297 A	03-06-1998
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		EP 0452334 A	23-10-1991
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(54) Method of preparing a water soluble film

(57) The present invention provides a method of preparing a water soluble film. The method comprises (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

EP 1 110 546 A1

Description

[0001] This application claims priority from U.S. Serial No. 60/172,085, filed December 23, 1999, which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present invention relates to a method of preparing a water soluble film for use in dosage unit forms, such as tampons and applicators.

BACKGROUND OF THE INVENTION

[0003] Current vaginal dosage forms, except the sponge and film, are messy to use and readily drip out of the vagina. Furthermore, the sponge requires removal after use and is believed to cause infection. Films often cause irritation due to their rigidity and sharp edges.

[0004] U.S. Patent Nos. 5,393,528 and 5,529,782 disclose a device having a dissolvable element for administration of an agent material in an internal body area. The dissolvable element is a film made of polyvinyl alcohol, polyethylene oxide, and/or a complex carbohydrate material.

SUMMARY OF THE INVENTION

[0005] The present invention provides a method of preparing a water soluble film. The method comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and a relative humidity of at least about 30%. The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. The water soluble film of the present invention may be incorporated into vaginal devices, such as tampons and applicators. The formulation of the film may be optimized as known in the art to provide controlled release of the pharmaceutically active agent.

[0006] This method produces a uniform and homogeneous film which is more flexible and drips less than prior water soluble films, especially those incorporated into vaginal dosage forms. As a result, the film is less irritating. Furthermore, unlike most prior art water soluble films, the film may be shaped to provide a larger contact area within a body cavity, such as the vagina, in order to increase drug delivery. The film is also non-messy.

[0007] Another embodiment of the present invention is a dosage unit form, such as a tampon or applicator, comprising a water soluble film prepared by the aforementioned method.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The method of the present invention comprises the steps of (a) preparing a solution comprising a film former, a water soluble plasticizer, a pharmaceutically active agent, and a solvent; (b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and (c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. The inventors have discovered that curing the film under the aforementioned conditions produces a significantly more flexible film which drips less when administered into the vagina and other body cavities than the same film prepared without curing. The film is also non-messy, uniform, and homogeneous.

[0009] The solution may be prepared by mixing the ingredients, if the pharmaceutically active agent is water soluble.

[0010] Water insoluble pharmaceutically active agents may be dispersed, preferably uniformly, in the solvent by any method known in the art. The other ingredients may be added before or after dispersing the pharmaceutically active agent.

[0011] The film former is a polyacrylic acid, cellulose derivative, polyethylene oxide, polyvinyl alcohol, or any combination of any of the foregoing. Suitable cellulose derivatives include, but are not limited to, hydroxyethyl cellulose, carboxymethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, and any combination of any of the foregoing. The film former is preferably polyvinyl alcohol. More preferably, the film former is a partially hydrogenated polyvinyl alcohol, such as Elvanol™ grade 51-05, 52-22, and 50-42 available from DuPont Co. of Wilmington, DE, and Airvol™ grade 205S and 523S available from Air Products & Chemicals, Inc., of Allentown, PA. The viscosity of the polyvinyl alcohol generally ranges from about 3 to about 1000 cps and preferably ranges from about 3 to about 50 cps. The solution typically comprises from about 5 to about 40% by weight and preferably from about 15 to about 35% by

weight of film former, based upon 100% total weight of solution.

[0012] The water soluble plasticizer contains at least one of a hydroxyl, amido, or amino group and has a boiling point greater than about 150° C. Preferably, the boiling point of the plasticizer is greater than about 180° C. Suitable plasticizers include, but are not limited to, polyhydroxy compounds, such as propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing. Other suitable plasticizers include, but are not limited to, fatty acid derivatives having a melting point less than about 45 ° C, such as ehydrogenated vegetable oil available as Wecobee™ from Stepan Company of Northfield, IL, and hydrogenated coco-glycerides available as Witepsol H15™ from Hüls America of Somerset, N.J.; and fatty alcohol derivatives having a hydroxy value of greater than about 30. The solution typically comprises from about 0.1 to about 10% by weight and preferably from about 0.5 to about 5% by weight of water soluble plasticizer, based upon 100% total weight of solution.

[0013] The pharmaceutically active agent may be water-insoluble or water soluble. Suitable pharmaceutically active agents include, but are not limited to, imidazole antifungal agents, such as imidazole antifungal agents include, but are not limited to, miconazole, econazole, terconazole, ketoconazole, saperconazole, itraconazole, clotrimazole, tioconazole, and butaconazole; antibacterial agents, such as nystatin, neomycin, polymycin, tetracycline, clindamycin, and metronidazole; antiseptic agents, such as oxyquinoline benzoate and aminacrine; hormones, such as estrogens, testolactone, androgens, progestins, megestrol acetate, medroxyprogesterone acetate, esterified estrogens, conjugated estrogens, estradiol, polyestradiol, ethinyl estradiol, estropipate, diethylstilbestrol diphosphate, polyestradiol phosphate, and leuprolide acetate; anti-inflammatory agents, hydrocortisone, triamcinolone, betamethasone, flucinonide, and halcinonide; anesthetics, such as lidocaine and benzocaine; spermicides, such as nonoxynol-9 and octoxynol-9; and any combination of any of the foregoing. A preferred imidazole antifungal agent is miconazole nitrate. A preferred antibacterial agent is metronidazole. A preferred spermicide is nonoxynol-9.

[0014] Generally, the amount of pharmaceutically active agent in the solution is an amount effective to accomplish the purpose for which it is being used. The amount of pharmaceutically active agent is typically a pharmaceutically effective amount. However, the amount can be less than a pharmaceutically effective amount when the film is used in a dosage unit form, because the dosage unit form may contain a multiplicity of films or may contain a divided pharmaceutically effective amount. The total effective amount can then be determined in cumulative units containing, in total, a pharmaceutically effective amount of pharmaceutically active agent. The total amount of pharmaceutically active agent may be determined by those skilled in the art. Generally, the solution comprises from about 1 to about 30% by weight and preferably from about 5 to about 20% by weight of pharmaceutically active agent, based upon 100% total weight of solution.

[0015] The solvent may be water, ethanol, glycerin, ethylene glycol, amides, amines, or any combination of any of the foregoing. The solvent is preferably water or a mixture of water and ethanol. Preferably, the mixture comprises less than about 30% by weight of ethanol, based upon 100% total weight of mixture. The solution typically comprises from about 20 to about 90% by weight and preferably from about 40 to about 80% by weight of solvent, based upon 100% total weight of solution.

[0016] According to a preferred embodiment of the present invention, the solution comprises about 26.4% by weight of polyvinyl alcohol, about 2.4% by weight of glycerin, about 11.2% by weight of nonoxynol 9, and about 60% by weight of water, based upon 100% total weight of solution.

[0017] The solution may include other adjuvants, such as surfactants, preservatives, viscosity enhancers, colorants, fragrances, flavorants, lubricants, fillers, binders, wetting agents, penetration agents, pH adjusters, disintegrants, excipients, or any combination of any of the foregoing. Suitable surfactants include, but are not limited to, polyethylene glycol ether of cetearyl alcohol, such as ceteareth-20; hydrogenated coco-glycerides; and any combination of any of the foregoing.

[0018] The solution typically has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying. Generally, the water soluble film prepared by the method of the present invention has a thickness of from about 0.03 to about 0.50 mm. Preferably, the thickness of the film is from about 0.05 to about 0.10 mm.

[0019] The drying step is generally performed at a temperature of from about 50 to about 100° C. Preferably, the drying step is performed in two stages. In the first stage, the solution is heated to from about 50 to about 70° C. The solution in the first stage is typically heated for less than about 5 minutes. The solution is then heated to from about 70 to about 100° C during the second stage. The solution in the second stage is typically heated for less than about 25 minutes.

[0020] The curing step is preferably performed immediately after the drying step. Curing is generally performed at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%. Preferably, the curing step is performed at a temperature of from about 25 to about 60° C. The curing step is preferably performed at a relative humidity of at least about 50% and more preferably at a relative humidity of from about 60 to about 90%. The solution may be dried and cured with a drying tunnel having multiple zones or chambers, such as a 5, 6, or 7 zone drying tunnel.

[0021] A preferred water soluble film prepared by the method of the present invention comprises about 66% by weight of polyvinyl alcohol, about 6% by weight of glycerin, and about 28% by weight of nonoxynol 9, based upon 100% total

weight of water soluble film.

[0022] The water soluble film may be coated or laminated onto a substrate, such as non-woven fiber or cotton, by pouring or casting the solution onto the substrate and then drying and curing the solution as described above. Casting may be performed by any method known in the art, such as with a weigh boat, stainless steel tray, teflon rod, cone shape rod, and reverse roller.

[0023] The water soluble film alone or coated or laminated on a substrate may be incorporated into a dosage unit form for administration into a body cavity, such as the vagina, rectum, and mouth. The dosage unit form may be a tampon or an applicator. For example, the film coated on a substrate may be utilized as a liner for a tampon. The dosage unit form is preferably flexible. The dosage unit form may be any shape, such as a flat sheet or thimble shape. Preferably, the film is contoured to maximize its contact area with the body cavity for which it is intended to be administered.

[0024] According to one embodiment, the outer wrap of the tampon is comprised of non-woven fiber laminiated with the water soluble film. According to another embodiment, the water soluble film is positioned between the inside material of a tampon, such as cotton, and an outer wrap, such as a non-woven fiber material.

[0025] A dosage unit form of the present invention containing an antifungal agent, such as miconazole, may be administered to treat yeast infections. It is possible to treat a yeast infection in 3 days, instead of the common 5 day period, with a dosage unit form of the present invention, since a film prepared by the present method has very little drip and may have controlled release of the antifungal agent.

[0026] The film may be formulated to be puncture resistant and tear resistant. Also, the film may be formulated to achieve desired release rates of the pharmaceutically active agent as known in the art.

[0027] The following examples are intended to describe the present invention without limitation.

Examples 1-32

[0028] Water soluble films having the formulations of Table 1 were prepared as follows. Water was heated to 50-80° C. The film former, *i.e.,* polyvinyl alcohol, is added to the water with constant mixing. The active ingredient, *i.e.,* nonoxynol-9, was added to the solution with constant mixing. The solution was mixed, deaerated, and cooled to room temperature. The solution was coated onto a substrate in the casting device indicated in Table 1 below. The substrate for Examples 1-8 was polypropylene. The substrate for Examples 9-18 and 32 was stainless steel. The substrate for Examples 19-25 was polyester. The substrate for Examples 26-28 was teflon. The substrate for Example 29 was a polyester liner. The substrate for Example 30 was aclar with foil liner. The substrate for Example 31 was a polyethylene and paper liner.

[0029] The solution was dried in a multi-zone drying tunnel to form a film. In Examples 1-28 and 31, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Examples 29 and 30, the solution was first dried at a temperature of about 60-75° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. In Example 32, the solution was first dried at a temperature of about 60-80° C for less than about 5 minutes and then dried at a temperature of about 70-90° C for less than about 25 minutes.

[0030] After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. For examples 29 and 32, the film was cured with moisture at a relative humidity of about 60-90% and at a temperature of about 40-60° C.

[0031] The thickness of the film was measured. The results are shown in Table 1 below.

Table 1

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
1	Weigh Boat	33.33	33.33	-	-	33.33% PG	0.3
2	Weigh Boat	33.33	33.33	-	-	33.33% PEG 300	0.3
3	Weigh Boat	33.33	50.00	-	-	16.67% PEG 300	0.45
4	Weigh Boat	33.33	58.33	-	-	8.33% Glycerin	0.3
5	Weigh Boat	33.33	41.67	-	-	25.00% Glycerin	0.1
6	Weigh Boat	33.33	50.00	-	-	16.67% Glycerin	0.1
7	Weigh Boat	33.33	50.00	-	-	16.67% PG	0.2
8	Weigh Boat	33.33	41.67	-	-	25.00% PG	0.1
9	Stainless Steel Tray	33.00	58.67	-	-	8.33% Glycerin	0.07
10	Stainless Steel Tray	33.33	63.33	-	-	3.33% Glycerin	0.05

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
11	Stainless Steel Tray	33.33	58.33	-	-	8.33% PEG 300	-
12	Stainless Steel Tray	33.33	58.67	-	-	8.33% PG	0.06
13	Stainless Steel Tray	27.78	69.44	-	-	2.78% Glycerin	-
14	Stainless Steel Tray	33.33	-	-	58.33	8.33% Glycerin	0.06
15	Stainless Steel Tray	32.79	-	-	49.18	18.03% Glycerin	0.07
16	Stainless Steel Tray	33.33	-	-	41.67	25.00% Glycerin	-
17	Stainless Steel Tray	33.33	-	-	63.33	3.33% Glycerin	0.07

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
18	Stainless Steel Tray	28.33	-	-	68.00	3.67% Glycerin	-
19	Resource I®	33.33	-	58.33	-	8.33% Glycerin	-
20	Resource I®	33.11	-	62.913	-	3.97% Glycerin	-
21	Resource I®	33.33	-	49.50	-	17.16% Glycerin	-
22	Resource I®	33.33	-	-	63.35	3.33% Glycerin	-
23	Resource I®	33.33	50.00	-	-	16.33% PEG 300	-
24	Resource I®	33.33	58.33	-	-	8.33% PEG 300	-
25	Resource I®	33.33	63.33	-	-	3.33% PEG 300	-
26	Teflon Rod, Thimble	33.33	-	-	63.35	3.33% Glycerin	-
27	Cone Shape Rod, Thimble	31.58	-	-	60.00	3.16% Glycerin & 5.26% H-15	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
28	Cone Shape Rod, Thimble	30.51	-	-	57.97	3.05% Glycerin & 8.47% H-15	-
29	Reverse Roller, Scale-up Run, with Polyester Liner	33.33	-	-	63.33	3.33% Glycerin	-
30	Reverse Roller, Scale-up Run, with Aclar and Foil Liner	33.33	-	-	63.36	3.30% Glycerin	-

Example	Casting Device	Nonoxynol-9 (% by weight)	Polyvinyl alcohol (<60 cps) (% by weight)	Polyvinyl alcohol (<30 cps) (% by weight)	Polyvinyl alcohol (<10 cps) (% by weight)	Plasticizer (% by weight)	Dry Film Thickness (mm)
31	Knife Over Roller, Scale-up Run, with Polyethylene and Paper Liner	28.00	-	-	67.00	5.00% Glycerin	-
32	Extrusion, Scale-up Run, with Stainless Steel Surface Carrier	28.00	-	-	67.00	5.00% Glycerin	-

* - Resource I is a casting device for solutions available from Byk-Gardner Instruments of Silver Spring, MD.

The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

PG is propylene glycol.

PEG 300 is polyethylene glycol having an average of 300 ethylene oxide repeating units.

H-15 is Witepsol H-15, which is hydrogenated coco-glycerides and is available from Hüls America of Somerset, NJ.

[0032] The release rate of nonoxynol-9 from the films prepared and VCF® available from Apothecus Pharmaceutical Corp. of Oyster Bay, NY, in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method

(United States Pharmacopeia Method Section <711>). The results are shown in Table 2 below. The time to plateau is the time after which there is no significant increase in the release rate.

Table 2

Formulation	Time to Plateau (minutes)	Release Rate (% by weight per minute)
VCF®[1]	15-20	5.45
Example 6	50-60	2.59
Example 7	50-60	3.76
Example 9	40-50	2.33
Example 10	40-50	2.97
Example 12	40-50	3.15
Example 14	10-15	6.08
Example 15	10-15	6.66
Example 17	10-15	6.01
Example 19	15-20	5.82
Example 20	30-40	4.33
Example 21	30-40	3.93
Example 22	10-15	6.10
Example 23	40-50	2.34
Example 24	30-40	2.72
Example 25	30-40	2.76
Example 26	10-15	7.23
Example 27	5-10	8.47
Example 28	5-10	8.89
Example 29	<15	>6.0
Example 30	<15	>6.0
Example 31	<15	>6.0
Example 32	<15	>16

Examples 33-42

[0033] Water soluble films having the formulations of Table 3 were prepared as described in Examples 1-32. In Examples 33-41, the solution was dried at a temperature of about 60-90° C for less than about 30 minutes. In Example 42, the solution was first dried at a temperature of about 60-75 ° C for less than about 8 minutes and then dried at a temperature of about 75-90° C for less than about 15 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature.

[0034] The substrate for Examples 33-35 was polyester. The substrate for Examples 36-41 was polyester and non-woven fiber. The substrate for Example 42 was a fiber and polyester liner.

[0035] The release rate of miconazole nitrate from the films prepared in a citrate phosphate buffer having a pH of 4.0 was determined by the USP basket method for Examples 33-35 and by the following modified USP method for Examples 36-38, 40, and 41. A dialysis membrane with known molecular weight cut-off and diameter was used instead of a mesh basket for holding the test samples. The membrane limited the amount of dissolution medium which contacted the release layer or composition. This modified dissolution procedure was designed to mimic a vaginal environment where only limited amounts of a medium are typically in contact with the composition. Each release layer and composition was tested in an aqueous medium and in a buffered aqueous medium, which were maintained at a pH of about 4.

[0036] The results are shown in Table 3 below.

Table 3

Example	Casting Device	Polyvinyl alcohol (<30 cps) (% by weight)	Plasticizer (% by weight)	Miconazole Nitrate (% by weight)	Release Rate
33	Resource I	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.3%/min
34	Resource I	40.0	19.9% Glycerin	40.1	4.7%/min
35	Resource I	38.0	19.0% Glycerin & 4.8% EB2	38.2	4.7%/min
36	Resource I & Fiber	36.2	18.4% Glycerin & 9.2% EB2	36.2	3.50%/hr
37	Resource I & Fiber	34.7	17.3% Glycerin & 13.2% EB2	34.8	3.13%/hr
38	Resource I & Fiber	38.0	19.0% Glycerin & 5.0% EB2	38.0	3.33%/hr
39	Resource I & Fiber	39.6	20.6% Glycerin	39.8	-
40	Resource I, Fiber, & OB Tampon	34.7	17.3% Glycerin & 13.2% EB2	34.8	0.81%/hr
41	Resource I, Fiber, & OB Tampon	38.0	19.0% Glycerin & 5.0% EB2	38.0	1.07%/hr
42	Reverse Roller, Scale-up Run, Fiber & Polyester Liner	38.1	19.1% Glycerin & 4.7% EB2	38.1	-
EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ. The polyvinyl alcohol is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.					

Examples 43-46

[0037] Water soluble films having the formulations of Table 4 were prepared as described in Examples 1-32. In Examples 43-46, the solution was dried at a temperature of about 60-90 ° C for less than about 30 minutes. After drying, the film was cured with moisture at a relative humidity of about 30-60% and at about room temperature. The substrate for Example 43-46 was polyester.

[0038] The time for the dissolution rate to plateau was determined as discussed above.

[0039] The results are shown in Table 4 below.

Table 4

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
43	Resource I	67.2% PVA 52-22	21.7% PEG 400	11.1	20-30
44	Resource I	58.22% PVA 52-22	18.9% PG & 15.7% EB2	7.2	20-30
45	Resource I	34.9% PVA 52-22 and 11.7% PVA 71-30	20.9% PG & 17.5% EB2	15.0	10-15

Table 4 (continued)

Example	Casting Device	Polymer (% by weight)	Plasticizer (% by weight)	Metro-nidazole (% by weight)	Dissolution (Time to Plateau) (min)
46	Resource I	46.6% HPMC E50LV	20.9% PG & 17.5% EB2	15.0	5-10

PG is propylene glycol

PEG is polyethylene glycol.

EB2 is Eumulgin B2, which is ceteareth-20 and is available from Henkel Corp. of Hoboken, NJ.

PVA is a water soluble polyvinyl alcohol, such as Elvanol™ available from DuPont Co. of Wilmington, DE, or Airvol™ available from Air Products & Chemicals, Inc., of Allentown, PA.

HPMC is hydroxypropyl methylcellulose.

Example 47

[0040] A water soluble film having the formulation of Table 5 was prepared as follows. Glycerin and nonoxynol-9 were added into cold water and mixed until uniform. The solution was heated to about 60-80° C and the film former, *i. e.,* polyvinyl alcohol, was added under constant mixing. The solution was mixed, deaerated, and cooled to about room temperature. The solution was coated onto a stainless steel surface with a web thickness of 0.01 to 0.03 cm. The solution was dried in a multi-zone drying tunnel at a temperature of about 60-90° C for less than about 30 minutes to form a film. The film was then cured with moisture at a relative humidity of about 65-90% and at a temperature of about 40-60° C.

Table 5

Ingredient	% by weight
Polyvinyl Alcohol (5 cps)	66.0
Glycerin	6.0
Nonoxynol-9	28.0

[0041] All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

Claims

1. A method of preparing a water soluble film, the method comprising the steps of:

(a) preparing a solution comprising:

(i) a film former selected from the group consisting of polyacrylic acids, cellulose derivatives, polyethylene oxide, polyvinyl alcohol, and any combination of any of the foregoing,

(ii) a water soluble plasticizer having at least one of a hydroxyl, amido, or amino group and a boiling point greater than about 150° C,

(iii) a pharmaceutically active agent, and

(iv) a solvent;

(b) drying the solution at a temperature of from about 50 to about 100° C to form a film; and

(c) curing the film at a temperature of from about 15 to about 60° C and at a relative humidity of at least about 30%.

2. The method of claim 1, wherein the solution has a viscosity of from about 15,000 to about 30,000 cps at room temperature prior to drying.

3. The method of claim 1, wherein the film former is polyvinyl alcohol.

4. The method of claim 1, wherein the film former is a partially hydrogenated polyvinyl alcohol.

5. The method of claim 1, wherein the plasticizer is a polyhydroxy compound.

6. The method of claim 5, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol, glycerin, and any combination of any of the foregoing.

7. The method of claim 1, wherein the pharmaceutically active agent is selected from imidazole antifungal agents, antibacterial agents, antiseptic agents, hormones, anti-inflammatory agents, anesthetics, spermicides, and any combination of any of the foregoing.

8. The method of claim 1, wherein the pharmaceutically active agent is nonoxynol-9.

9. The method of claim 1, wherein the pharmaceutically active agent is miconazole.

10. The method of claim 1, wherein the water soluble film further comprises

(i) a surfactant,
(ii) a preservative,
(iii) a viscosity enhancer,
(iv) a colorant,
(v) a fragrance,
(vi) a flavorant,
(vii) a lubricant,
(viii) a filler,
(ix) a binder,
(x) a wetting agent,
(xi) a penetration agent,
(xii) a pH adjuster,
(xiii) a disintegrant,
(xiv) an excipient, or
(xv) any combination of any of the foregoing.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 31 1610

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X Y	EP 0 466 092 A (LABORATOIRE LUCCHINI) 15 January 1992 (1992-01-15) * claims 1-3 * * page 3; example 1 *	1-3,5-8, 10 9	A61K9/70 A61K9/00
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A	GB 1 108 837 A (ASTRA) * claims 1,3 * * page 4, line 8 - line 15 * * page 4, line 41 - line 53 * * page 6; example 13 * * page 6, line 114 - page 7, line 16 *	1-10	

TECHNICAL FIELDS SEARCHED (Int.Cl.7)
A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	22 February 2001	Ventura Amat, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 31 1610

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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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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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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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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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.

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Information on patent family members

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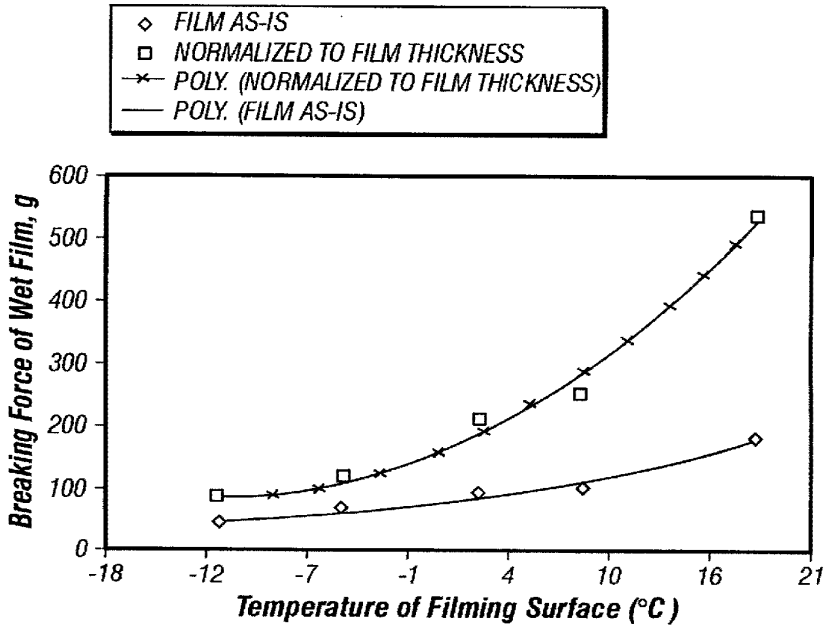

(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1,25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which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

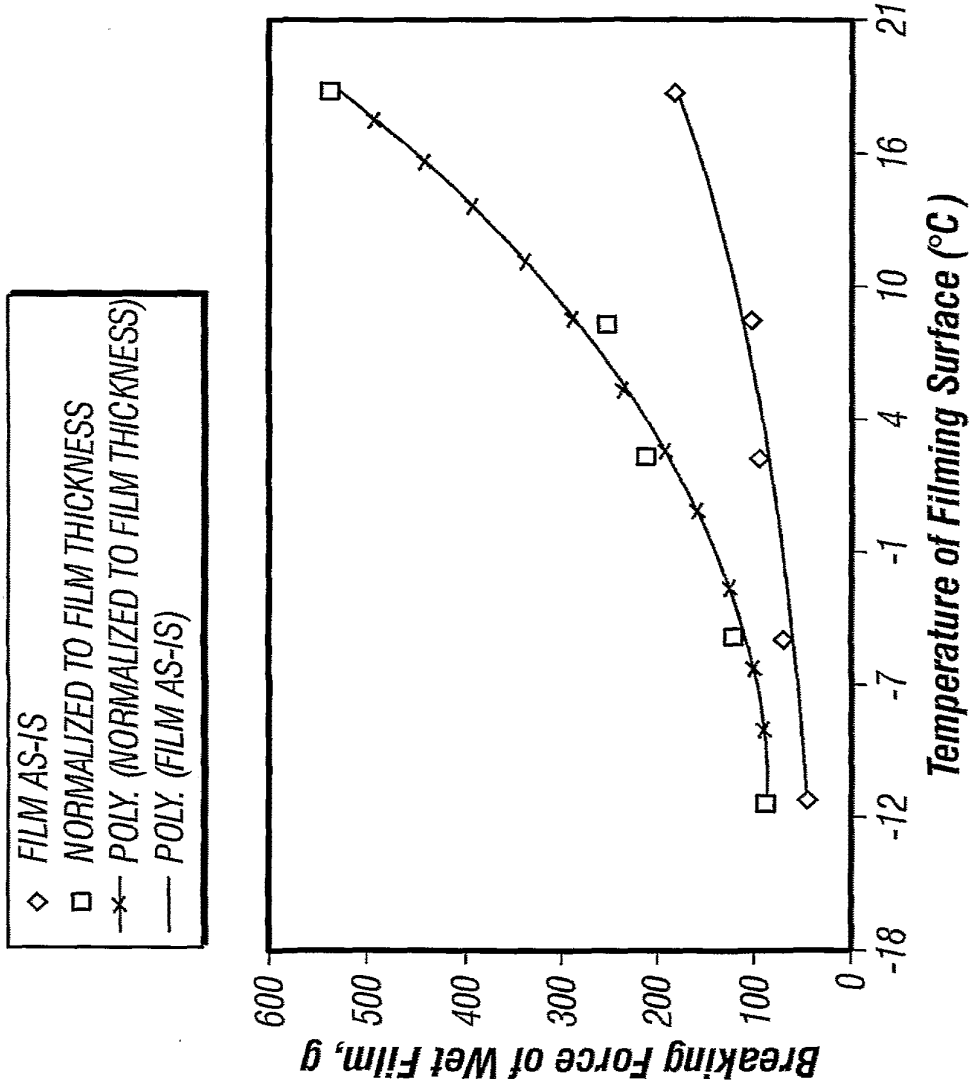

FIG. 1

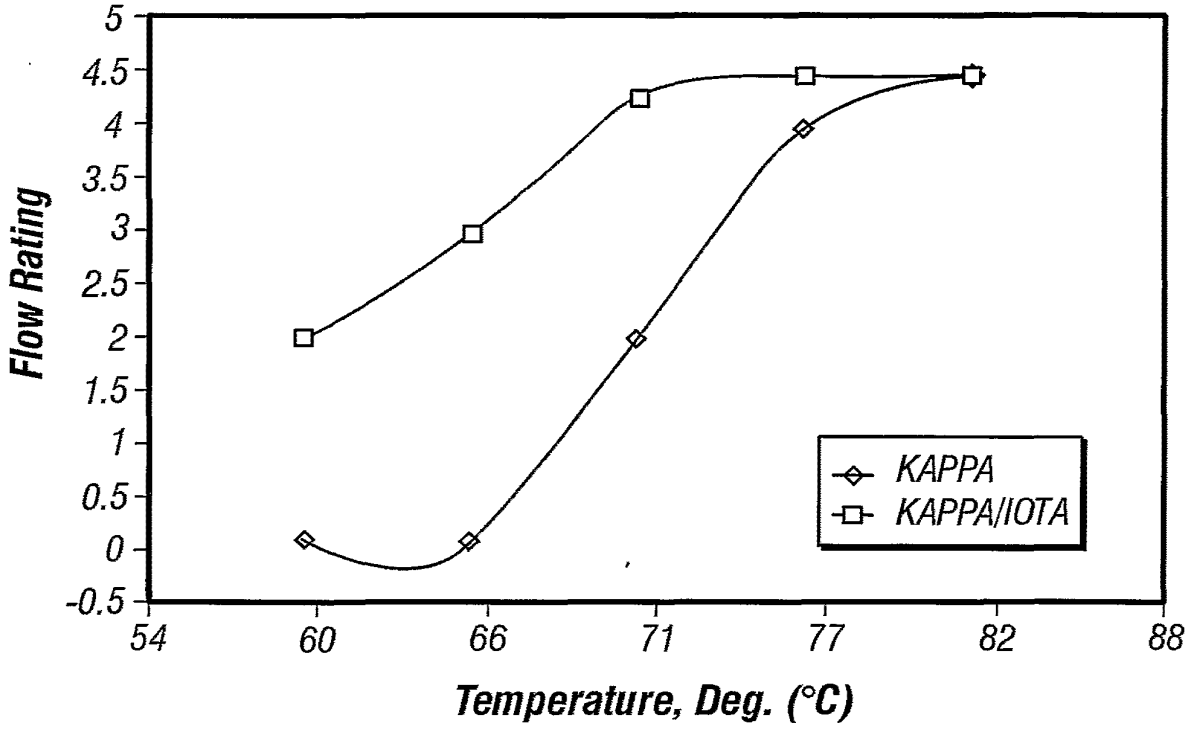

FIG. 2

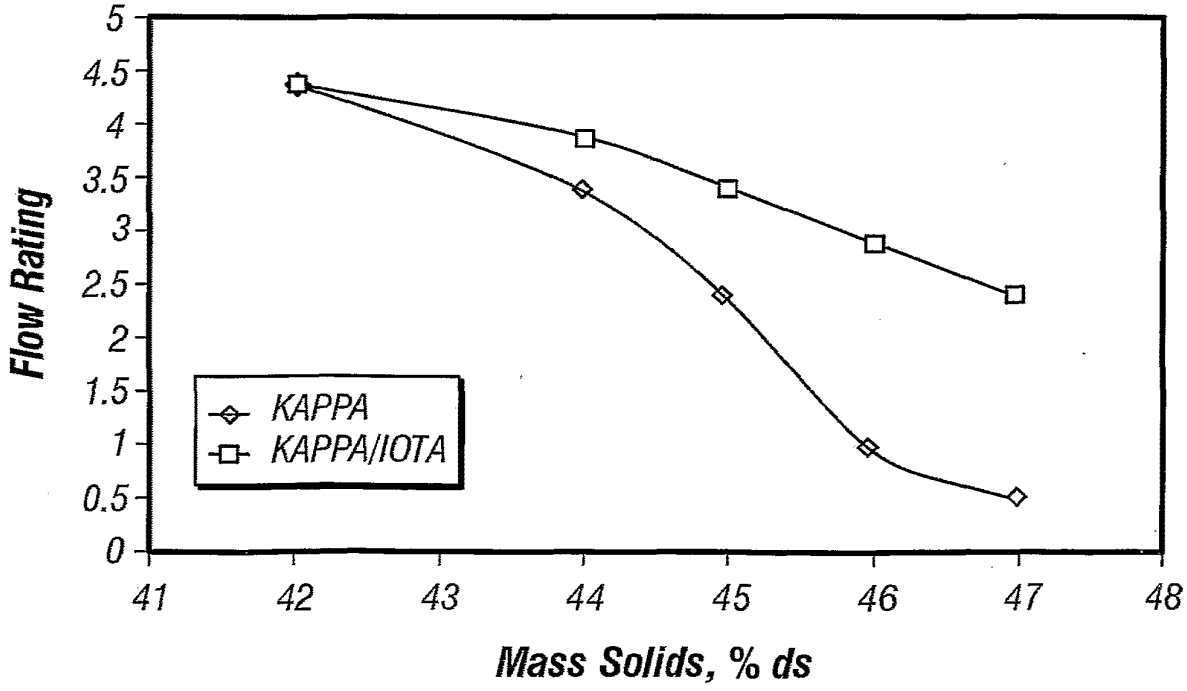

FIG. 3

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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, 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, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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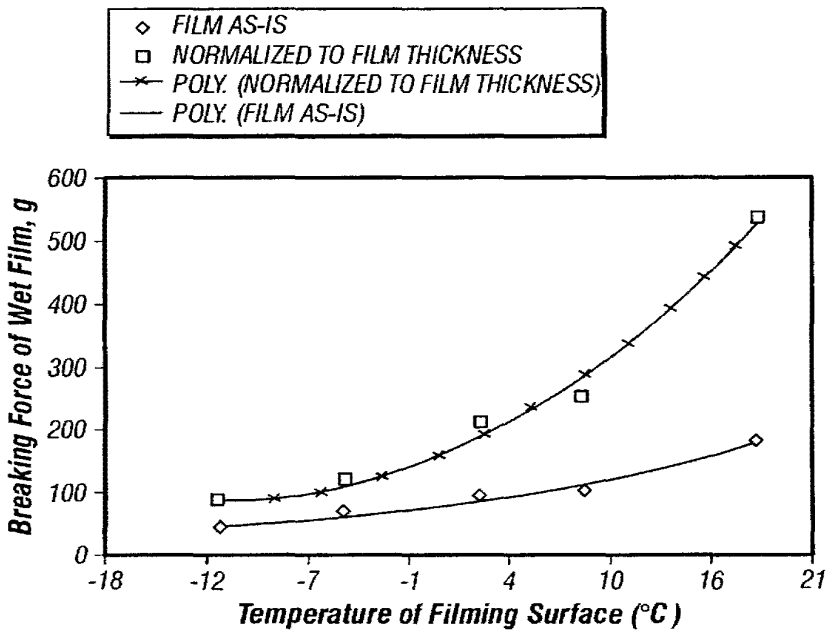
(88) Date of publication of the international search report:
30 May 2002

[Continued on next page]

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



(57) Abstract: Film-forming compositions are disclosed that can comprise, on a dry solid basis, 25 to 75 percent by weight of certain starch derivatives having a DE less than about 1.25 to 75 % plasticizer, and 0.1 to 15 % hydrocolloid gum. The starch derivatives can be chemically modified starches which range in molecular weight from 100,000 to 2,000,000. These starch-based systems can completely replace gelatin in edible film-forming applications such as soft and hard gel capsules.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Inter tional Application No
PCT/US 01/14888

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C08L3/00 C08J5/18 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C08L C08J 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

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Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 2 783 832 A (WARNER LAMBERT COMPANY) 31 March 2000 (2000-03-31) page 2, paragraph 4 -page 3, paragraph 7	1-28
X	WO 00 10538 A (BANNER PHARMACAPS INC) 2 March 2000 (2000-03-02) page 5, line 29 -page 6, line 1 page 7, line 1 -page 9, line 11	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Lensen, H

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INTERNATIONAL SEARCH REPORT

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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.
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Information on patent family members

International Application No
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60/832,725	21 July 2006 (21.07.2006)	US
60/839,504	23 August 2006 (23.08.2006)	US

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(74) Agents: **HANLEY, Elizabeth, A.** et al.; Lahive & Cockfield, Llp, One Post Office Square, Boston, MA 02109-2127 (US).

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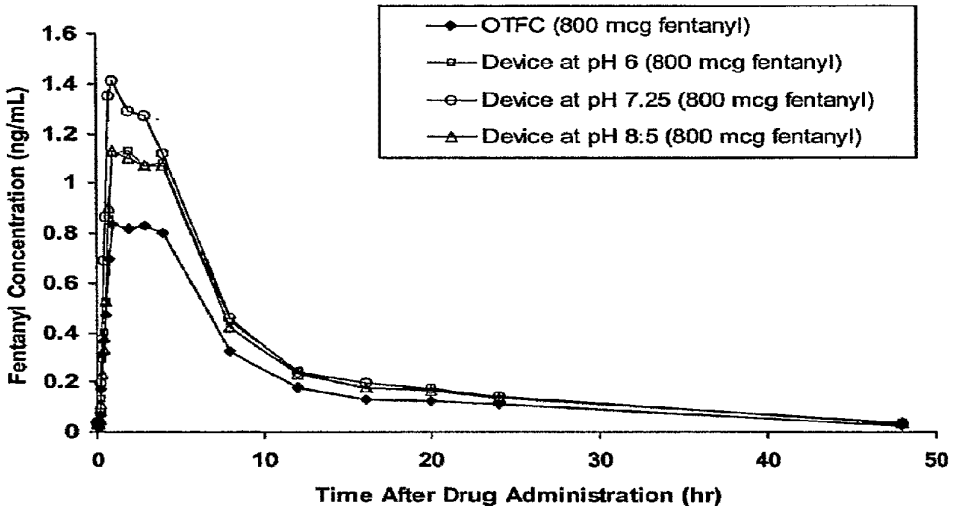
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL,

[Continued on next page]

(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC



(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

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PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/832,725, filed July 21, 2006, U.S. Provisional Application No. 60/832,726, filed July 21, 2006, and U.S. Provisional Application No. 60/839,504, filed August 23, 2006. The entire contents of these applications are incorporated herein by this reference. This application is also related to U.S. Serial No. 11/639,408, filed December 13, 2006, and PCT/US2006/47686, also filed December 13, 2006, both of which claim priority to US Provisional Application No. 60/750,191, filed December 13, 2005, and 60/764,618, filed February 2, 2006. The entire contents of these applications are also incorporated herein by this reference.

BACKGROUND

[0002] US Patent No. 6,264,981 (Zhang *et al.*) describes delivery devices, *e.g.*, tablets of compressed powders that include a solid solution micro-environment formed within the drug formulation. The micro-environment includes a solid pharmaceutical agent in solid solution with a dissolution agent that that facilitates rapid dissolution of the drug in the saliva. The micro-environment provides a physical barrier for preventing the pharmaceutical agent from being contacted by other chemicals in the formulation. The micro-environment may also create a pH segregation in the solid formulation. The pH of the micro-environment is chosen to retain the drug in an ionized form for stability purposes. The rest of the formulation can include buffers so that, upon dissolution in the oral cavity, the pH is controlled in the saliva such that absorption of the drug is controlled.

[0003] US Publication 2004/0253307 also describes solid dosage forms that include buffers that upon dissolution of the solid dosage form maintains the pharmaceutical agent at a desired pH to control absorption, *i.e.*, to overcome the influence of conditions in the surrounding environment, such as the rate of saliva secretion, pH of the saliva and other factors.

BRIEF SUMMARY OF THE INVENTION

[0004] The present invention provides transmucosal devices for enhanced uptake of a medicament and methods of making and using the same. In some embodiments, the devices generally include a mucoadhesive polymeric diffusion environment that facilitates not only the absorption of the medicament across the mucosal membrane to which it is applied, but additionally, the permeability and/or motility of the medicament through the mucoadhesive polymeric diffusion environment to the mucosa.

[0005] Accordingly, in one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

[0006] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

[0007] In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject. The mucoadhesive device generally includes a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

[0008] In another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In yet another embodiment, the present invention is directed to transmucosal delivery devices that

deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more. In still another embodiment, the present invention is directed to devices comprising about 800 μg of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a C_{max} of about 1.10 ng/mL or more; a T_{first} of about 0.20 hours or less; and an AUC_{0-24} of about 10.00 hr·ng/mL or more. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8, *e.g.*, about 7.25. In one embodiment, the device comprises about 800 μg of fentanyl. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa. In another embodiment, the fentanyl is fentanyl citrate.

[0009] In one embodiment, more than 30% of the fentanyl, *e.g.*, more than 55% of the fentanyl, in the device becomes systemically available via mucosal absorption.

[0010] In one embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of buprenorphine to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

[0011] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes. In some embodiments, chronic pain is alleviated in the subject. In other embodiments, acute pain is alleviated in the subject. In other embodiments, the pain is breakthrough cancer pain.

[0012] In yet another embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject. The mucoadhesive device generally includes buprenorphine disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface. In one embodiment, the pH is between about 4.0 and about 7.5, *e.g.*, about 6.0 or about 7.25. In another embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

[0013] In one embodiment of the methods and devices of the present invention, the device comprises a pH buffering agent. In one embodiment of the methods and devices of the present invention, the device is adapted for buccal administration or sublingual administration.

[0014] In one embodiment of the methods and devices of the present invention, the device is a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the medicament is formulated as a mucoadhesive film formed to delineate different dosages. In one embodiment of the methods and devices of the present invention, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

[0015] In one embodiment of the methods and devices of the present invention, the device further comprises an opioid antagonist. In one embodiment of the methods and devices of the present invention, the device further comprises naloxone.

[0016] In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. In one embodiment of the methods and devices of the present invention, the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

[0017] In one embodiment of the methods and devices of the present invention, there is substantially no irritation at the site of transmucosal administration. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes.

[0018] In one embodiment of the methods and devices of the present invention, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures

thereof. In one embodiment, the polymeric diffusion environment comprises a buffer system, *e.g.*, citric acid, sodium benzoate or mixtures thereof. In some embodiments, the device has a thickness such that it exhibits minimal mouth feel. In some embodiments, the device has a thickness of about 0.25 mm.

[0019] In some embodiments, the present invention provides a flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject. The mucoadhesive device includes a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer. The device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] The foregoing and other aspects, embodiments, objects, features and advantages of the invention can be more fully understood from the following description in conjunction with the accompanying figures.

[0021] *Figures 1 and 2* are graphs comparing fentanyl citrate uptake in humans over 2 days post-administration, and 1 hour post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery device (Actiq ® Oral Transmucosal Fentanyl Citrate) as described in Examples 1 and 2.

[0022] *Figure 3* is a graph comparing buprenorphine uptake in humans over 16 hours post-administration, respectively, for exemplary embodiments of the present invention and a commercially available delivery devices as described in Examples 3 and 4.

[0023] *Figures 4A-C* are schematic representations of exemplary embodiments of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0024] The present invention is based, at least in part, on the discovery that transmucosal uptake of medicaments can be enhanced by employing a novel polymeric diffusion environment. Such a polymeric diffusion environment is advantageous, *e.g.*, because the absolute bioavailability of the medicament contained therein is enhanced, while also providing a rapid onset. Additionally, less medicament is needed in the device to deliver a therapeutic effect versus devices of the prior art. This renders the device less abusable, an important consideration when the medicament is a controlled substance, such as an opioid. The polymeric diffusion environment described in more detail herein, provides an enhanced delivery profile and more efficient delivery of the medicament. Additional advantages of a polymeric diffusion environment are also described herein.

[0025] In order to more clearly and concisely describe the subject matter of the claims, the following definitions are intended to provide guidance as to the meaning of terms used herein.

[0026] As used herein, the articles "a" and "an" mean "one or more" or "at least one," unless otherwise indicated. That is, reference to any element of the present invention by the indefinite article "a" or "an" does not exclude the possibility that more than one of the element is present.

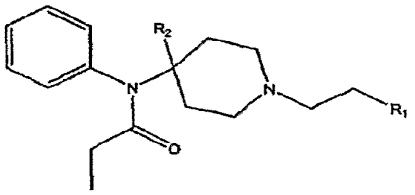
[0027] As used herein, the term "acute pain" refers to pain characterized by a short duration, e.g., three to six months. Acute pain is typically associated with tissue damage, and manifests in ways that can be easily described and observed. It can, for example, cause sweating or increased heart rate. Acute pain can also increase over time, and/or occur intermittently.

[0028] As used herein, the term "chronic pain" refers to pain which persists beyond the usual recovery period for an injury or illness. Chronic pain can be constant or intermittent. Common causes of chronic pain include, but are not limited to, arthritis, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), repetitive stress injuries, shingles, headaches, fibromyalgia, and diabetic neuropathy.

[0029] As used herein, the term "breakthrough pain" refers to pain characterized by frequent and intense flares of moderate to severe pain which occur over chronic pain, even when a subject is regularly taking pain medication. Characteristics of breakthrough pain generally include: a short time to peak severity (*e.g.*, three to five minutes);

excruciating severity; relatively short duration of pain (*e.g.*, 15 to 30 minutes); and frequent occurrence (*e.g.*, one to five episodes a day). Breakthrough pain can occur unexpectedly with no obvious precipitating event, or it can be event precipitated. The occurrence of breakthrough pain is predictable about 50% to 60% of the time. Although commonly found in patients with cancer, breakthrough pain also occurs in patients with lower back pain, neck and shoulder pain, moderate to severe osteoarthritis, and patients with severe migraine.

[0030] As used herein, unless indicated otherwise, the term "fentanyl", includes any pharmaceutically acceptable form of fentanyl, including, but not limited to, salts, esters, and prodrugs thereof. The term "fentanyl" includes fentanyl citrate. As used herein, the term "fentanyl derivative" refers to compounds having similar structure and function to fentanyl. In some embodiments, fentanyl derivatives include those of the following formula:

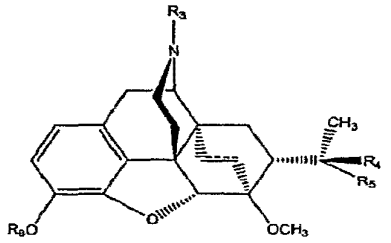


or pharmaceutically acceptable salts or esters thereof, wherein

R_1 is selected from an aryl group, a heteroaryl group or a –COO-C_{1-4} alkyl group; and R_2 is selected from –H, a -C_{1-4} alkyl-O-C_{1-4} alkyl group or a –COO-C_{1-4} alkyl group.

Fentanyl derivatives include, but are not limited to, alfentanil, sufentanil, remifentanil and carfentanil.

[0031] As used herein, unless indicated otherwise, the term "buprenorphine", includes any pharmaceutically acceptable form of buprenorphine, including, but not limited to, salts, esters, and prodrugs thereof. As used herein, the term "buprenorphine derivative" refers to compounds having similar structure and function to buprenorphine. In some embodiments, fentanyl derivatives include those of the following formula:



or pharmaceutically acceptable salts or esters thereof, wherein

 is a double or single bond; R_3 is selected from a -C_{1-4} alkyl group or a cycloalkyl-substituted-C_{1-4} alkyl group; R_4 is selected from a -C_{1-4} alkyl; R_5 is –OH, or taken together, R_4 and R_5 form a =O group; and R_6 is selected from –H or a -C_{1-4} alkyl group.

Buprenorphine derivatives include, but are not limited to, etorphine and diprenorphine.

[0032] As used herein, "polymeric diffusion environment" refers to an environment capable of allowing flux of a medicament to a mucosal surface upon creation of a gradient by adhesion of the polymeric diffusion environment to a mucosal surface. The flux of a transported medicament is proportionally related to the diffusivity of the environment which can be manipulated by, *e.g.*, the pH, taking into account the ionic nature of the medicament and/or the ionic nature polymer or polymers included in the environment and.

[0033] As used herein, "barrier environment" refers to an environment in the form of, *e.g.*, a layer or coating, capable of slowing or stopping flux of a medicament in its direction. In some embodiments, the barrier environment stops flux of a medicament, except in the direction of the mucosa. In some embodiments, the barrier significantly slows flux of a medicament, *e.g.*, enough so that little or no medicament is washed away by saliva.

[0034] As used herein, the term "unidirectional gradient" refers to a gradient which allows for the flux of a medicament (*e.g.*, fentanyl or buprenorphine) through the device, *e.g.*, through a polymeric diffusion environment, in substantially one direction, *e.g.*, to the mucosa of a subject. For example, the polymeric diffusion environment may be a mucoadhesive polymeric diffusion environment in the form of a layer or film disposed adjacent to a backing layer or film. Upon mucoadministration, a gradient is created between the mucoadhesive polymeric diffusion environment and the mucosa, and the medicament flows from the mucoadhesive polymeric diffusion environment, substantially in one direction towards the mucosa. In some embodiments, some flux of the medicament is not entirely unidirectional across the gradient; however, there is typically not free flux of the medicament in all directions. Such unidirectional flux is described in more detail herein, *e.g.*, in relation to Figure 4.

[0035] As used herein, "treating" or "treatment" of a subject includes the administration of a drug to a subject with the purpose of preventing, curing, healing, alleviating, relieving, altering, remedying, ameliorating, improving, stabilizing or affecting a disease or disorder, or a symptom of a disease or disorder (e.g., to alleviate pain).

[0036] The term "subject" refers to living organisms such as humans, dogs, cats, and other mammals. Administration of the medicaments included in the devices of the present invention can be carried out at dosages and for periods of time effective for treatment of a subject. In some embodiments, the subject is a human. In some embodiments, the pharmacokinetic profiles of the devices of the present invention are similar for male and female subjects. An "effective amount" of a drug necessary to achieve a therapeutic effect may vary according to factors such as the age, sex, and weight of the subject. Dosage regimens can be adjusted to provide the optimum therapeutic response. For example, several divided doses may be administered daily or the dose may be proportionally reduced as indicated by the exigencies of the therapeutic situation.

[0037] The term "transmucosal," as used herein, refers to any route of administration via a mucosal membrane. Examples include, but are not limited to, buccal, sublingual, nasal, vaginal, and rectal. In one embodiment, the administration is buccal. In one embodiment, the administration is sublingual. As used herein, the term "direct transmucosal" refers to mucosal administration via the oral mucosa, *e.g.*, buccal and/or sublingual.

[0038] As used herein, the term "water erodible" or "at least partially water erodible" refers to a substance that exhibits a water erodibility ranging from negligible to completely water erodible. The substance may readily dissolve in water or may only partially dissolve in water with difficulty over a long period of time. Furthermore, the substance may exhibit a differing erodibility in body fluids compared with water because of the more complex nature of body fluids. For example, a substance that is negligibly erodible in water may show an erodibility in body fluids that is slight to moderate. However, in other instances, the erodibility in water and body fluid may be approximately the same.

[0039] The present invention provides transmucosal delivery devices that uniformly and predictably deliver a medicament to a subject. The present invention also

provides methods of delivery of a medicament to a subject employing devices in accordance with the present invention. Accordingly, in one embodiment, the present invention is directed to mucoadhesive delivery devices suitable for direct transmucosal administration of an effective amount of a medicament, *e.g.*, fentanyl or fentanyl derivative or buprenorphine to a subject. The mucoadhesive device generally includes a medicament disposed in a polymeric diffusion environment; and a having a barrier such that a unidirectional gradient is created upon application to a mucosal surface, wherein the device is capable of delivering in a unidirectional manner the medicament to the subject. The present invention also provides methods of delivery of a medicament to a subject employing the devices in accordance with the present invention.

[0040] In another embodiment, the present invention is directed to methods for enhancing direct transmucosal delivery of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, to a subject. The method generally includes administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: a medicament disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, wherein an effective amount of the medicament is delivered to the subject.

[0041] In another embodiment, the present invention is directed to methods for treating pain in a subject. The method generally includes transmucosally administering to a subject a therapeutically effective amount of a medicament, *e.g.*, fentanyl, fentanyl derivatives and/or buprenorphine, disposed in a mucoadhesive polymeric diffusion environment having a thickness such that the effective amount of the medicament is delivered in less than about 30 minutes and such that pain is treated. In some embodiments, the medicament is delivered in less than about 25 minutes. In some embodiments, the medicament is delivered in less than about 20 minutes.

[0042] In some embodiments of the above methods and devices, an effective amount is delivered transmucosally. In other embodiments, an effective amount is delivered transmucosally and by gastrointestinal absorption. In still other embodiments, an effective amount is delivered transmucosally, and delivery though the gastrointestinal absorption augments and/or maintains treatment, *e.g.*, pain relief for a desired period of time, *e.g.*, at least 1, 1.5, 2, 2.5, 3, 3.5, or 4 or more hours.

[0043] In yet another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more. The combination of a rapid onset with a delayed maximum concentration is particularly advantageous when treating pain, *e.g.*, relief for breakthrough cancer pain (BTP) in opioid tolerant patients with cancer, because immediate relief is provided to alleviate a flare of moderate to severe pain but persistence is also provided to alleviate subsequent flares. Conventional delivery systems may address either the immediate relief or subsequent flare-ups, but the devices of this embodiment are advantageous because they address both.

Table 1: Selected Pharmacokinetic properties of transmucosal devices.

	T_{first}	T_{max}	Total Bioavailability
BEMA pH 7.25	0.15 hours	1.61 hours	70%
Actiq®	0.23 hours	2.28 hours	47%
Fentora®	0.25 hours*	0.50 hours	65%

* - reported as onset of main relief, first time point measured.

[0044] The devices of the present invention may have a number of additional or alternative desirable properties, as described in more detail herein. Accordingly, in another embodiment, the present invention is directed to transmucosal delivery devices that deliver a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%. In still another embodiment, the present invention is directed to devices comprising about 800 μg of fentanyl, which exhibit upon transmucosal administration to a subject at least one *in vivo* plasma profile as follows: a C_{max} of about 1.10 ng/mL or more; a T_{first} of about 0.20 hours or less; and an AUC_{0-24} of about 10.00 hr·ng/mL or more.

[0045] The pain can be any pain known in the art, caused by any disease, disorder, condition and/or circumstance. In some embodiments, chronic pain is alleviated in the subject using the methods of the present invention. In other embodiments, acute pain is alleviated in the subject using the methods of the present invention. Chronic pain can arise from many sources including, cancer, Reflex Sympathetic Dystrophy Syndrome (RSDS), and migraine. Acute pain is typically directly related to tissue damage, and lasts for a relatively short amount of time, *e.g.*, three to six months. In other embodiments, the pain is breakthrough cancer pain. In some embodiments, the methods and devices of the present invention can be used to

alleviate breakthrough pain in a subject. For example, the devices of the present invention can be used to treat breakthrough pain in a subject already on chronic opioid therapy. In some embodiments, the devices and methods of the present invention provide rapid analgesia and/or avoid the first pass metabolism of fentanyl, thereby resulting in more rapid breakthrough pain relief than other treatments, *e.g.*, oral medications.

[0046] In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 60% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 70% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 80% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 90% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 100% decrease in pain over about 30 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 25 minutes. In one embodiment of the methods and devices of the present invention, the subject experienced about a 50% decrease in pain over about 20 minutes.

[0047] Without wishing to be bound by any particular theory, it is believed that delivery of the medicament is particularly effective because the mucoadhesive polymeric diffusion environment (*e.g.*, the pH and the ionic nature of the polymers) is such that the medicament (*e.g.*, a weakly basic drug such as fentanyl or buprenorphine) can rapidly move through the mucoadhesive polymeric diffusion environment to the mucosa, while also allowing efficient absorption by the mucosa. For example, in some embodiments, the pH is low enough to allow movement of the medicament, while high enough for absorption.

[0048] In some embodiments, the mucoadhesive polymeric diffusion environement is a layer with a buffered pH such that a desired pH is maintained at the mucosal administration site. Accordingly, the effect of any variation in pH encountered

in a subject or between subjects (*e.g.*, due to foods or beverages recently consumed), including any effect on uptake, is reduced or eliminated.

[0049] Accordingly, one advantage of the present invention is that variability in the properties of the device (*e.g.*, due to changes in the pH of the ingredients) between devices, and from lot to lot is reduced or eliminated. Without wishing to be bound by any particular theory, it is believed that the polymeric diffusion environment of the present invention reduces variation, *e.g.*, by maintaining a buffered pH. Yet another advantage is pH variability at the administration site (e.g., due to what food or drink or other medications was recently consumed) is reduced or eliminated, such that, *e.g.*, the variability of the devices is reduced or eliminated.

[0050] A medicament for use in the present invention includes any medicament capable of being administered transmucosally. The medicament can be suitable for local delivery to a particular mucosal membrane or region, such as the buccal and nasal cavities, throat, vagina, alimentary canal or the peritoneum. Alternatively, the medicament can be suitable for systemic delivery via such mucosal membranes.

[0051] In one embodiment, the medicament can be an opioid. Opioids suitable for use in the present invention include, *e.g.*, alfentanil, allylprodine, alphaprodine, apomorphine, anileridine, apocodeine, benzylmorphine, bezitramide, buprenorphine, butorphanol, clonitazene, codeine, cyclorphan, cyprenorphine, desomorphine, dextromoramide, dextropropoxyphene, dezocine, diampromide, diamorphone, dihydrocodeine, dihydromorphine, dimenoxadol, eptazocine, ethylmorphine, etonitazene, etorphine, fentanyl, fencamfamine, fenethylline, hydrocodone, hydromorphone, hydroxymethylmorphinan, hydroxypethidine, isomethadone, levomethadone, levophenacylmorphan, levorphanol, lofentanil, mazindol, meperidine, metazocine, methadone, methylmorphine, modafinil, morphine, nalbuphene, necomorphine, normethadone, normorphine, opium, oxycodone, oxymorphone, pholcodine, profadol remifentanil, sufentanil, tramadol, corresponding derivatives, physiologically acceptable compounds, salts and bases. In some embodiments, the medicament is fentanyl, *e.g.*, fentanyl citrate. In some embodiments, the medicament is buprenorphine.

[0052] The amount of medicament, *e.g.* fentanyl or buprenorphine, to be incorporated into the device of the present invention depends on the desired treatment dosage to be administered, *e.g.*, the fentanyl or fentanyl derivative can be present in

about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight or the buprenorphine can be present in about 0.001% to about 50% by weight of the device of the present invention, and in some embodiments between about 0.005 and about 35% by weight. In one embodiment, the device comprises about 3.5% to about 4.5% fentanyl or fentanyl derivative by weight. In one embodiment, the device comprises about 3.5% to about 4.5% buprenorphine by weight. In another embodiment, the device comprises about 800 μg of a fentanyl such as fentanyl citrate. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of a fentanyl such as fentanyl citrate or fentanyl derivative. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention. In another embodiment, the device comprises about 800 μg of buprenorphine. In another embodiment the device comprises about 100, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, or 2000 μg of buprenorphine. In another embodiment the device comprises about 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700, 900, 1000, 1200, 1500, 1600 or 2000 μg of any of the medicaments described herein.

[0053] One approach to reaching an effective dose is through titration with multiple dosage units such that patients start with a single 200 mcg unit and progressively increase the number of units applied until reaching an effective dose or 800 mcg (4 units) dose as the multiple discs once an effective dose has been identified. Accordingly, in some embodiments, the methods of the present invention also include a titration phase to identify a dose that relieves pain and produces minimal toxicity, because the dose of opioid, *e.g.*, fentanyl, required for control of breakthrough pain episodes is often not easily predicted. The linear relationship between surface area of the devices of the present invention and pharmacokinetic profile may be exploited in the dose titration process through the application of single or multiple discs to identify an appropriate dose, and then substitution of a single disc containing the same amount of medicament.

[0054] In one embodiment, the devices of the present invention are capable of delivering a greater amount of fentanyl systemically to the subject than conventional devices. According to the label for Actiq ® Oral Transmucosal Fentanyl Citrate, approximately 25% of the fentanyl in the ACTIQ product is absorbed via the buccal

mucosa, and of the remaining 75% that is swallowed, another 25% of the total fentanyl becomes available via absorption in the GI tract for a total of 50% total bioavailability. According to Fentora Fentanyl Buccal tablet literature, approximately 48% of the fentanyl in FENTORA product is absorbed via the buccal mucosa, and of the remainig 52%, another 17% of the total fentanyl becomes available via absorption in the GI tract for a total of 65% total bioavailability. Accordingly, in some embodiments, more than about 30% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable via absorption by the mucosa. In some embodiments, more than about 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75% or 80% becomes systemically available via mucosal absorption. In some embodiments, more than about 55%, 60%, 65% or 70% of the fentanyl disposed in the devices of the present invention becomes systemically available or bioavailable by any route, mucosal and/or GI tract. In some embodiments, more than about 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% becomes systemically available.

[0055] Accordingly, another advantage of the devices and methods of the present invention is that because the devices of the present invention more efficiently deliver the medicament, *e.g.*, fentanyl or buprenorphine, than do conventional devices, less medicament can be included than must be included in conventional devices to deliver the same amount of medicament. Accordingly, in some embodiments, the devices of the present invention are not irritating to the mucosal surface on which it attaches. In some embodiments, the devices of the present invention cause little or no constipation, even when the devices include an opioid antagonist such as naloxone. In yet another embodiment, the present invention is directed to transmucosal delivery devices which include a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is not significant or eliminated.

[0056] Another advantage is the devices of the present invention are less subject to abuse than conventional devices because less medicament, *e.g.*, fentanyl or buprenorphine, is required in the device, *i.e.*, there is less medicament to be extracted by an abuser for injection into the bloodstream.

[0057] In some embodiments, the devices of the present invention have a dose response that is substantially directly proportional to the amount of medicament present

in the device. For example, if the C_{max} is 10 ng/mL for a 500 dose, then it is expected in some embodiments that a 1000 μg dose will provide a C_{max} of approximately 20 ng/mL. Without wishing to be bound by any particular theory, it is believed that this is advantageous in determining a proper dose in a subject.

[0058] In some embodiments, the devices of the present invention further comprise an opioid antagonist in any of various forms, e.g., as salts, bases, derivatives, or other corresponding physiologically acceptable forms. Opioid antagonists for use with the present invention include, but are not limited to, naloxone, naltrexone, nalmefene, nalide, nalmexone, nalorphine, naluphine, cyclazocine, levallorphan and physiologically acceptable salts and solvates thereof, or combinations thereof. In one embodiment, the device further comprises naloxone.

[0059] In some embodiments, the properties of the polymeric diffusion environment are effected by its pH. In one embodiment, *e.g.*, when the medicament is fentanyl, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 6.5 and about 8. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and about 7.5, or between about 7.25 and 7.5. In other embodiments, the pH is about 6.5, 7.0, 7.5, 8.0 or 8.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

[0060] In one embodiment, *e.g.*, when the medicament is buprenorphine, the pH of the mucoadhesive polymeric diffusion environment in the devices of the present invention is between about 4.0 and about 7.5. In another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 6.0. In one embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 5.5 to about 6.5, or between about 6.0 and 6.5. In yet another embodiment, the pH of the mucoadhesive polymeric diffusion environment is about 7.25. In another embodiment, the pH is between about 7.0 and 7.5, or between about 7.25 and 7.5. In other embodiments, the pH of the device may be about 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, or 7.5, or any incremental value thereof. It is to be understood that all values and ranges between these values and ranges are meant to be encompassed by the present invention.

[0061] The pH of the mucoadhesive polymeric diffusion environment can be adjusted and/or maintained by methods including, but not limited to, the use of buffering

agents, or by adjusting the composition of the device of the present invention. For example, adjustment of the components of the device of the present invention that influence pH, e.g., the amount of anti-oxidant, such as citric acid, contained in the device will adjust the pH of the device.

[0062] In some embodiments, the properties of the polymeric diffusion environment are effected by its buffering capacity. In some embodiments, buffering agents are included in the mucoadhesive mucoadhesive polymeric diffusion environment. Buffering agents suitable for use with the present invention include, for example, phosphates, such as sodium phosphate; phosphates monobasic, such as sodium dihydrogen phosphate and potassium dihydrogen phosphate; phosphates dibasic, such as disodium hydrogen phosphate and dipotassium hydrogen phosphate; citrates, such as sodium citrate (anhydrous or dehydrate); bicarbonates, such as sodium bicarbonate and potassium bicarbonate may be used. In one embodiment, a single buffering agent, *e.g.*, a dibasic buffering agent is used. In another embodiment, a combination of buffering agents is employed, *e.g.*, a combination of a tri-basic buffering agent and a monobasic buffering agent.

[0063] In one embodiment, the mucoadhesive polymeric diffusion environment of the device will have a buffered environment, *i.e.*, a stabilized pH, for the transmucosal administration of a medicament. The buffered environment of the device allows for the optimal administration of the medicament to a subject. For example, the buffered environment can provide a desired pH at the mucosa when in use, regardless of the circumstances of the mucosa prior to administration.

[0064] Accordingly, in various embodiments, the devices include a mucoadhesive polymeric diffusion environment having a buffered environment that reduces or eliminates pH variability at the site of administration due to, for example, medications, foods and/or beverages consumed by the subject prior to or during administration. Thus, pH variation encountered at the site of administration in a subject from one administration to the next may have minimal or no effect on the absorption of the medicament. Further, pH variation at the administration site between different patients will have little or no effect on the absorption of the medicament. Thus, the buffered environment allows for reduced inter- and intra- subject variability during transmucosal administration of the medicament. In another embodiment, the present invention is directed to methods for enhancing uptake of a medicament that include administering to

a subject a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration. In yet another embodiment, the present invention is directed to methods of delivering a therapeutically effective amount of a medicament to a subject that include administering a device including a medicament disposed in a mucoadhesive polymeric diffusion environment having a buffered environment for the transmucosal administration.

[0065] The devices of the present invention can include any combination or sub-combination of ingredients, layers and/or compositions of, *e.g.*, the devices described in US Patent No. 6,159,498, US Patent No. 5,800,832, US Patent No. 6,585,997, US Patent No. 6,200,604, US Patent No. 6,759,059 and/or PCT Publication No. WO 05/06321. The entire contents of these patent and publications are incorporated herein by reference in their entireties.

[0066] In some embodiments, the properties of the polymeric diffusion environment are effected by the ionic nature of the polymers employed in the environment. In one embodiment, the mucoadhesive polymeric diffusion environment is water-erodible and can be made from a bioadhesive polymer(s) and optionally, a first film-forming water-erodible polymer(s). In one embodiment, the polymeric diffusion environment comprises at least one ionic polymer system, *e.g.*, polyacrylic acid (optionally crosslinked), sodium carboxymethylcellulose and mixtures thereof.

[0067] In some embodiments, the mucoadhesive polymeric diffusion environment can include at least one pharmacologically acceptable polymer capable of bioadhesion (the "bioadhesive polymer") and can optionally include at least one first film-forming water-erodible polymer (the "film-forming polymer"). Alternatively, the mucoadhesive polymeric diffusion environment can be formed of a single polymer that acts as both the bioadhesive polymer and the first film-forming polymer. Additionally or alternatively, the water-erodible mucoadhesive polymeric diffusion environment can include other first film-forming water-erodible polymer(s) and water-erodible plasticizer(s), such as glycerin and/or polyethylene glycol (PEG).

[0068] In some embodiments, the bioadhesive polymer of the water-erodible mucoadhesive polymeric diffusion environment can include any water erodible substituted cellulosic polymer or substituted olefinic polymer wherein the substituents may be ionic or hydrogen bonding, such as carboxylic acid groups, hydroxyl alkyl

groups, amine groups and amide groups. For hydroxyl containing cellulosic polymers, a combination of alkyl and hydroxyalkyl groups will be preferred for provision of the bioadhesive character and the ratio of these two groups will have an effect upon water swellability and disperability. Examples include polyacrylic acid (PAA), which can optionally be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), moderately to highly substituted hydroxypropylmethyl cellulose (HPMC), polyvinylpyrrolidone (PVP, which can optionally be partially crosslinked), moderately to highly substituted hydroxyethylmethyl cellulose (HEMC) or combinations thereof. In one embodiment, HEMC can be used as the bioadhesive polymer and the first film forming polymer as described above for a mucoadhesive polymeric diffusion environment formed of one polymer. These bioadhesive polymers are preferred because they have good and instantaneous mucoadhesive properties in a dry, system state.

[0069] The first film-forming water-erodible polymer(s) of the mucoadhesive polymeric diffusion environment can be hydroxyalkyl cellulose derivatives and hydroxyalkyl alkyl cellulose derivatives preferably having a ratio of hydroxyalkyl to alkyl groups that effectively promotes hydrogen bonding. Such first film-forming water-erodible polymer(s) can include hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), or a combination thereof. Preferably, the degree of substitution of these cellulosic polymers will range from low to slightly above moderate.

[0070] Similar film-forming water-erodible polymer(s) can also be used. The film-forming water-erodible polymer(s) can optionally be crosslinked and/or plasticized in order to alter its dissolution kinetics.

[0071] In some embodiments, the mucoadhesive polymeric diffusion environment, *e.g.*, a bioerodable mucoadhesive polymeric diffusion environment, is generally comprised of water-erodible polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyacrylic acid (PAA) which may or may not be partially crosslinked, sodium carboxymethyl cellulose (NaCMC), and polyvinylpyrrolidone (PVP), or combinations thereof. Other mucoadhesive water-erodible polymers may also be used in the present invention. The term "polyacrylic acid" includes both uncrosslinked and partially crosslinked forms, *e.g.*, polycarbophil.

[0072] In some embodiments, the mucoadhesive polymeric diffusion environment is a mucoadhesive layer, e.g, a bioerodable mucoadhesive layer. In some embodiments, the devices of the present invention include a bioerodable mucoadhesive layer which comprises a mucoadhesive polymeric diffusion environment.

[0073] In some embodiments, the properties of the polymeric diffusion environment are effected by the barrier environment. The barrier environment is disposed such that the flux of medicament is substantially unidirectional. For example, in an exemplary layered device of the present invention, having a layer comprising a medicament dispersed in a polymeric diffusion environment and a co-terminus barrier layer (see, *e.g.*, Figure 4B), upon application to the mucosa, some medicament may move to and even cross the boundary not limited by the mucosa or barrier layer. In another exemplary layered device of the present invention, a barrier layer does not completely circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4C). A majority of the medicament in both of these cases, however, flows towards the mucosa. In another exemplary layered device of the present invention, having a barrier layer which circumscribes the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device (see, *e.g.*, Figure 4A), upon application to the mucosa, substantially all of the medicament typically flows towards the mucosa.

[0074] The barrier environment can be, *e.g.*, a backing layer. A backing layer can be included as an additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The layers can be coterminous, or, *e.g.*, the barrier layer may circumscribe the portion of the mucoadhesive polymeric diffusion environment that will not be in direct contact with the mucosa upon application of the device. In one embodiment, the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment. The device of the present invention can also comprise a third layer or coating. A backing layer can be also included in the devices of the present invention as a layer disposed adjacent to a layer which is, in turn, disposed adjacent to the mucoadhesive polymeric diffusion environment (i.e., a three layer device).

[0075] In one embodiment, the device further comprises at least one additional layer that facilitates unidirectional delivery of the medicament to the mucosa. In one

embodiment, the device of the present invention further comprises at least one additional layer disposed adjacent to the mucoadhesive polymeric diffusion environment. Such layer can include additional medicament or different medicaments, and/or can be present to further reduce the amount of medicament (originally in the mucoadhesive polymeric diffusion environment) that is washed away in the saliva.

[0076] Specialty polymers and non-polymeric materials may also optionally be employed to impart lubrication, additional dissolution protection, drug delivery rate control, and other desired characteristics to the device. These third layer or coating materials can also include a component that acts to adjust the kinetics of the erodability of the device.

[0077] The backing layer is a non-adhesive water-erodible layer that may include at least one water-erodible, film-forming polymer. In some embodiments, the backing layer will at least partially or substantially erode or dissolve before the substantial erosion of the mucoadhesive polymeric diffusion environment.

[0078] The barrier environment and/or backing layer can be employed in various embodiments to promote unidirectional delivery of the medicament (*e.g.*, fentanyl) to the mucosa and/or to protect the mucoadhesive polymeric diffusion environment against significant erosion prior to delivery of the active to the mucosa. In some embodiments, dissolution or erosion of the water-erodible non-adhesive backing layer primarily controls the residence time of the device of the present invention after application to the mucosa. In some embodiments, dissolution or erosion of the barrier environment and/or backing layer primarily controls the directionality of medicament flow from the device of the present invention after application to the mucosa.

[0079] The barrier environment and/or backing layer (*e.g.*, a water-erodible non-adhesive backing layer) can further include at least one water erodible, film-forming polymer. The polymer or polymers can include polyethers and polyalcohols as well as hydrogen bonding cellulosic polymers having either hydroxyalkyl group substitution or hydroxyalkyl group and alkyl group substitution preferably with a moderate to high ratio of hydroxyalkyl to alkyl group. Examples include, but are not limited to, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC), hydroxyethylmethyl cellulose (HEMC), polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), ethylene oxide-propylene oxide co polymers, and combinations thereof. The water-erodible non-adhesive backing layer

component can optionally be crosslinked. In one embodiment, the water erodible non-adhesive backing layer includes hydroxyethyl cellulose and hydroxypropyl cellulose. The water-erodible non-adhesive backing layer can function as a slippery surface, to avoid sticking to mucous membrane surfaces.

[0080] In some embodiments, the barrier environment and/or backing layer, *e.g.*, a bioerodible non-adhesive backing layer, is generally comprised of water-erodible, film-forming pharmaceutically acceptable polymers which include, but are not limited to, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, polyvinylalcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or combinations thereof. The backing layer may comprise other water-erodible, film-forming polymers.

[0081] The devices of the present invention can include ingredients that are employed to, at least in part, provide a desired residence time. In some embodiments, this is a result of the selection of the appropriate backing layer formulation, providing a slower rate of erosion of the backing layer. Thus, the non-adhesive backing layer is further modified to render controlled erodibility which can be accomplished by coating the backing layer film with a more hydrophobic polymer selected from a group of FDA approved Eudragit™ polymers, ethyl cellulose, cellulose acetate phthalate, and hydroxyl propyl methyl cellulose phthalate, that are approved for use in other pharmaceutical dosage forms. Other hydrophobic polymers may be used, alone or in combination with other hydrophobic or hydrophilic polymers, provided that the layer derived from these polymers or combination of polymers erodes in a moist environment. Dissolution characteristics may be adjusted to modify the residence time and the release profile of a drug when included in the backing layer.

[0082] In some embodiments, any of the layers in the devices of the present invention may also contain a plasticizing agent, such as propylene glycol, polyethylene glycol, or glycerin in a small amount, 0 to 15% by weight, in order to improve the "flexibility" of this layer in the mouth and to adjust the erosion rate of the device. In addition, humectants such as hyaluronic acid, glycolic acid, and other alpha hydroxyl acids can also be added to improve the "softness" and "feel" of the device. Finally, colors and opacifiers may be added to help distinguish the resulting non-adhesive backing layer from the mucoadhesive polymeric diffusion environment. Some opacifers include titanium dioxide, zinc oxide, zirconium silicate, etc.

[0083] Combinations of different polymers or similar polymers with definite molecular weight characteristics can be used in order to achieve preferred film forming capabilities, mechanical properties, and kinetics of dissolution. For example, polylactide, polyglycolide, lactide-glycolide copolymers, poly-e-caprolactone, polyorthoesters, polyanhydrides, ethyl cellulose, vinyl acetate, cellulose, acetate, polyisobutylene, or combinations thereof can be used.

[0084] The device can also optionally include a pharmaceutically acceptable dissolution-rate-modifying agent, a pharmaceutically acceptable disintegration aid (*e.g.*, polyethylene glycol, dextran, polycarbophil, carboxymethyl cellulose, or poloxamers), a pharmaceutically acceptable plasticizer, a pharmaceutically acceptable coloring agent (e.g., FD&C Blue #1), a pharmaceutically acceptable opacifier (e.g., titanium dioxide), pharmaceutically acceptable anti-oxidant (e.g., tocopherol acetate), a pharmaceutically acceptable system forming enhancer (*e.g.*, polyvinyl alcohol or polyvinyl pyrrolidone), a pharmaceutically acceptable preservative, flavorants (e.g., saccharin and peppermint), neutralizing agents (e.g., sodium hydroxide), buffering agents (*e.g.*, monobasic, or tribasic sodium phosphate), or combinations thereof. Preferably, these components are individually present at no more than about 1% of the final weight of the device, but the amount may vary depending on the other components of the device.

[0085] The device can optionally include one or more plasticizers, to soften, increase the toughness, increase the flexibility, improve the molding properties, and/or otherwise modify the properties of the device. Plasticizers for use in the present invention can include, *e.g.*, those plasticizers having a relatively low volatility such as glycerin, propylene glycol, sorbitol, ethylene glycol, diethylene glycol, triethylene glycol, propylene glycol, polypropylene glycol, dipropylene glycol, butylene glycol, diglycerol, polyethylene glycol (*e.g.*, low molecular weight PEG's), oleyl alcohol, cetyl alcohol, cetostearyl alcohol, and other pharmaceutical-grade alcohols and diols having boiling points above about 100°C at standard atmospheric pressure. Additional plasticizers include, *e.g.*, polysorbate 80, triethyl titrate, acetyl triethyl titrate, and tributyl titrate. Additional suitable plasticizers include, *e.g.*, diethyl phthalate, butyl phthalyl butyl glycolate, glycerin triacetin, and tributyrin. Additional suitable plasticizers include, *e.g.*, pharmaceutical agent grade hydrocarbons such as mineral oil (*e.g.*, light mineral oil) and petrolatum. Further suitable plasticizers include, e.g., triglycerides such as medium-chain triglyceride, soybean oil, safflower oil, peanut oil,

and other pharmaceutical agent grade triglycerides, PEGylated triglycerides such as Labrifil®, Labrasol® and PEG-4 beeswax, lanolin, polyethylene oxide (PEO) and other polyethylene glycols, hydrophobic esters such as ethyl oleate, isopropyl myristate, isopropyl palmitate, cetyl ester wax, glyceryl monolaurate, and glyceryl monostearate.

[0086] One or more disintegration aids can optionally be employed to increase the disintegration rate and shorten the residence time of the device of the present invention. Disintegration aids useful in the present invention include, *e.g.*, hydrophilic compounds such as water, methanol, ethanol, or low alkyl alcohols such as isopropyl alcohol, acetone, methyl ethyl acetone, alone or in combination. Specific disintegration aids include those having less volatility such as glycerin, propylene glycol, and polyethylene glycol.

[0087] One or more dissolution-rate-modifying agents can optionally be employed to decrease the disintegration rate and lengthen the residence time of the device of the present invention. Dissolution-rate modifying agents useful in the present invention include, *e.g.*, hydrophobic compounds such as heptane, and dichloroethane, polyalkyl esters of di and tricarboxylic acids such as succinic and citric acid esterified with C6 to C20 alcohols, aromatic esters such as benzyl benzoate, triacetin, propylene carbonate and other hydrophobic compounds that have similar properties. These compounds can be used alone or in combination in the device of the invention.

[0088] The devices of the present invention can include various forms. For example, the device can be a disc or film. In one embodiment, the device comprises a mucoadhesive disc. In one embodiment of the methods and devices of the present invention, the device is a layered, flexible device. The thickness of the device of the present invention, in its form as a solid film or disc, may vary, depending on the thickness of each of the layers. Typically, the bilayer thickness ranges from about 0.01 mm to about 1 mm, and more specifically, from about 0.05 mm to about 0.5 mm. The thickness of each layer can vary from about 10% to about 90% of the overall thickness of the device, and specifically can vary from about 30% to about 60% of the overall thickness of the device. Thus, the preferred thickness of each layer can vary from about 0.005 mm to about 1.0 mm, and more specifically from about 0.01 mm to about 0.5 mm.

[0089] In one embodiment, the mucoadhesive polymeric diffusion environment of the device of the present invention has a thickness of about 0.03 mm to about 0.07 mm. In one embodiment, the mucoadhesive polymeric diffusion environment of the

device of the present invention has a thickness of about 0.04 mm to about 0.06 mm. In yet another embodiment, the mucoadhesive polymeric diffusion environment of the present invention has a thickness of about 0.05mm. The thickness of the mucoadhesive polymeric diffusion environment is designed to be thick enough so that it can be easily manufactured, yet thin enough to allow for maximum permeability of the medicament through the layer, and maximum absorption of the medicament into the mucosal layer.

[0090] In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.050 mm to about 0.350 mm. In one embodiment, the backing layer of the device of the present invention has a thickness of about 0.100 mm to about 0.300 mm. In yet another embodiment, the backing layer of the present invention has a thickness of about 0.200 mm. The thickness of the backing layer is designed to be thick enough so that it allows for substantially unidirectional delivery of the medicament (towards the mucosa), yet thin enough to dissolve so that it does not have to be manually removed by the subject.

[0091] In these embodiments, there is relatively minimal mouth feel and little discomfort because of the thinness and flexibility of the devices as compared to conventional tablet or lozenge devices. This is especially advantageous for patients who have inflammation of the mucosa and/or who may otherwise not be able to comfortably use conventional devices. The devices of the present invention are small and flexible enough so that they can adhere to a non-inflamed area of the mucosa and still be effective, *i.e.*, the mucosa does not need to be swabbed with the device of the present invention.

[0092] In various embodiments, the devices of the present invention can be in any form or shape such as a sheet or disc, circular or square in profile or cross-section, etc., provided the form allows for the delivery of the active to the subject. In some embodiments, the devices of the present invention can be scored, perforated or otherwise marked to delineate certain dosages. For example, a device may be a square sheet, perforated into quarters, where each quarter comprises a 200 μg dose. Accordingly, a subject can use the entire device for an 800 μg dose, or detach any portion thereof for a 200 μg, 400 μg or 600 μg dose.

[0093] The devices of the present invention can be adapted for any mucosal administration. In some embodiments of the methods and devices of the present

invention, the device is adapted for buccal administration and/or sublingual administration.

[0094] Yet another advantage of the devices of the present invention is the ease with which they are administered. With conventional devices, the user must hold the device in place, or rub the device over the mucosa for the duration of administration, which may last from twenty to thirty minutes or more. The devices of the present invention adhere to the mucosal surface in less than about five seconds, and naturally erode in about twenty to thirty minutes, without any need to hold the device in place.

[0095] Without wishing to be bound by any particular theory, it is also believed that the devices of the present invention are substantially easier to use than devices of the prior art. When devices of the prior art are used, they are often subject to much variability, *e.g.*, due to variation in mouth size, diligence of the subject in correctly administering the device and amount of saliva produced in the subject's mouth. Accordingly, in some embodiments, the present invention provides a variable-free method for treating pain in a subject. The term "variable-free" as used herein, refers to the fact that the devices of the present invention provide substantially similar pharmacokinetic profile in all subjects, regardless of mouth size and saliva production.

[0096] Without wishing to be bound by any particular theory, it is also believed that the presence of a backing layer also imparts a resistance to the devices of the present invention. Accordingly, in some embodiments, the devices of the present invention are resistant to the consumption of food or beverage. That is, the consumption of food or beverage while using the devices of the present invention does not substantially interfere with the effectiveness of the device. In some embodiments, the performance of the devices of the present invention, *e.g.*, peak fentanyl concentrations and/or overall exposure to the medicament is unaffected by the consumption of foods and/or hot beverages.

[0097] In various embodiments, the devices can have any combination of the layers, ingredients or compositions described herein including but not limited to those described above.

EXEMPLIFICATION

Example 1: Preparation of Devices in Accordance with the Present Invention

[0098] Transmucosal devices were configured in the form of a disc, rectangular in shape with round corners, pink on one side and white on the other side. The drug is

present in the pink layer, which is the mucoadhesive polymeric diffusion environment, and this side is to be placed in contact with the buccal mucosa (inside the cheek). The drug is delivered into the mucosa as the disc erodes in the mouth. The white side is the non-adhesive, backing layer which provides a controlled erosion of the disc, and minimizes the oral uptake of the drug induced by constant swallowing, thus minimizing or preventing first pass metabolism. The mucoadhesive polymeric diffusion environment and backing layer are bonded together and do not delaminate during or after application.

[0099] The backing layer was prepared by adding water (about 77% total formulation, by weight) to a mixing vessel followed by sequential addition of sodium benzoate(about 0.1% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), citric acid (about 0.1% total formulation, by weight) and vitamin E acetate (about 0.01% total formulation, by weight), and sodium saccharin(about 0.1% total formulation, by weight). Subsequently, a mixture of the polymers hydroxypropyl cellulose (Klucel EF, about 14% total formulation, by weight) and hydroxyethyl cellulose (Natrosol 250L, about 7% total formulation, by weight) was added and stirred at a temperature between about 120 and 130°F, until evenly dispersed. Upon cooling to room temperature, titanium dioxide (about 0.6% total formulation, by weight) and peppermint oil (about 0.2% total formulation, by weight) were then added to the vessel and stirred. The prepared mixture was stored in an air-sealed vessel until it was ready for use in the coating operation.

[0100] The mucoadhesive polymeric diffusion environment was prepared by adding water (about 89% total formulation, by weight) to a mixing vessel followed by sequential addition of propylene glycol (about 0.5% total formulation, by weight), sodium benzoate (about 0.06% total formulation, by weight), methylparaben (about 0.1% total formulation, by weight) and propylparaben (about 0.03% total formulation, by weight), vitamin E acetate (about 0.01% total formulation, by weight) and citric acid (about 0.06% total formulation, by weight), red iron oxide (about 0.01% total formulation, by weight), and monobasic sodium phosphate (about 0.04% total formulation, by weight). After the components were dissolved, 800 μg fentanyl citrate (about 0.9% total formulation, by weight) was added, and the vessel was heated to 120 to 130°F. After dissolution, the polymer mixture [hydroxypropyl cellulose (Klucel EF,

about 0.6% total formulation, by weight), hydroxyethyl cellulose (Natrosol 250L, about 1.9% total formulation, by weight), polycarbophil (Noveon AA1(about 0.6% total formulation, by weight), and carboxy methyl cellulose (Aqualon 7LF, about 5.124% total formulation, by weight)] was added to the vessel, and stirred until dispersed. Subsequently, heat was removed from the mixing vessel. As the last addition step, tribasic sodium phosphate and sodium hydroxide were added to adjust the blend to a desired pH. For example, about 0.6% total formulation, by weight of sodium hydroxide and about 0.4% total formulation, by weight of tribasic sodium phosphate can be added to the formulation. Batches were made having pHs of about 6, 7.25, and 8.5. The blend was mixed under vacuum for a few hours. Each prepared mixture was stored in an air-sealed vessel until its use in the coating operation.

[0101] The layers were cast in series onto a St. Gobain polyester liner. First, the backing layer was cast using a knife-on-a-blade coating method. The backing layer was then cured in a continuous oven at about 65 to 95°C and dried. After two coating and drying iterations, an approximately 8 mil (203 to 213 micrometers) thick backing layer is obtained. Subsequently, the mucoadhesive polymeric diffusion environment was cast onto the backing layer, cured in an oven at about 65 to 95 °C and dried. The devices were then die-cut by kiss-cut method and removed from the casting surface.

Example 2: Study of Fentanyl Citrate Uptake in Humans for Delivery Devices of the Present Invention and a Commercially Available Delivery Device

[0102] The effect of system pH on the uptake of fentanyl citrate in three exemplary delivery devices of the present invention was evaluated, and compared to that observed in Actiq® Oral Transmucosal Fentanyl Citrate product (Cephalon, Inc., Salt Lake City, UT), referred to herein as "OTFC". A randomized, open-label, single-dose, four-period, Latin-square crossover study was conducted in 12 healthy volunteers. An Ethical Review Board approved the study and all subjects gave informed consent before participating. Bioanalytical work using a validated liquid chromatography/mass spectrometry/mass spectrometry (LC/MS/MS) method was performed by CEDRA Clinical Research, LLC (Austin, TX).

[0103] Twelve (9 male, 3 female) healthy volunteers ranging in age from 21 to 44 years were recruited for the instant study. Subjects tested were free from any significant clinical abnormalities on the basis of medical history and physical examination, electrocardiogram, and screening laboratories. Subjects weighed between about 50 kg

and 100 kg and were within 15% of their ideal body weight based on Metropolitan Life tables for height and weight. Subjects were instructed to not consume alcohol, caffeine, xanthine, or foods/beverages containing grapefruit for 48 hours prior to the first dose of study medication and for the entire duration of the study. Subjects were also instructed not to use tobacco or nicotine containing products for at least 30 days prior to the first dose of medication. No subject had participated in any investigational drug study for at least 30 days prior to the instant study; had any significant medical condition either at the time of the study or in the past (including glaucoma and seizure disorders); had a positive drug screen; had used any concomitant medication other than oral contraceptives or acetaminophen for at least 72 hours prior to the first dose; or had a history of allergic reaction or intolerance to narcotics. Premenopausal women not using contraception or having a positive urine beta HCG test were excluded. Table 2, below, shows the demographics of the subjects included in this study.

Table 2. Subject Demographics (N=12)

Age, years	
Mean (standard deviation)	32 (7)
Median	31
Range	21-44
Gender, n (%)	
Female	3 (25)
Male	9 (75)
Race, n (%)	
Black	3 (25)
Caucasian	4 (33)
Hispanic	5 (42)
Height (cm)	
Mean (standard deviation)	171.6 (9.3)
Median	172.0
Range	155.0 – 183.5
Weight (kg)	
Mean (standard deviation)	70.5 (9.0)
Median	70.7
Range	52.0 – 86.5

[0104] The study consisted of a screening visit and a 9-day inpatient period during which each subject received single buccal transmucosal doses of each of the four study treatments with 48 hours separating the doses. The four study treatments, each including 800 μg of fentanyl citrate, were: the OTFC and devices prepared as described

in Example 1 and buffered at a pH of about 6 ("device at pH 6"), a pH of about 7.25 ("device at pH 7.25"), and a pH of about 8.5 ("device at pH 8.5").

[0105] Subject eligibility was determined at the screening visit, up to 21 days prior to entering the study facility. Subjects arrived at the study facility at 6:00 PM the day prior to dosing (day 0). Predose procedures (physical examination, clinical laboratory tests, electrocardiogram, and substance abuse screen) were performed. After an overnight fast of at least 8 hours, subjects received an oral dose of naltrexone at 6 AM. A standard light breakfast was served approximately 1 hour prior to study drug dosing. A venous catheter was placed in a large forearm or hand vein for blood sampling, and a pulse oximeter and noninvasive blood pressure cuff were attached. Subjects were placed in a semi-recumbent position, which they maintained for 8 hours after each dose.

[0106] Subjects received the first dose of drug at 8 AM on day 1 and subsequent doses at the same time on days 3, 5, and 7. Blood samples (7 mL) were collected in ethylenediaminetetraacetic acid (EDTA) for measurement of plasma fentanyl just prior to dose 1 and 5, 7.5, 10, 15, 20, 25, 30, 45, and 60 minutes, and 2, 3, 4, 8, 12, 16, 20, 24, and 48 hours after each dose. The 48-hour post dose sample was collected just prior to administration of the subsequent dose. A total of 511 mL of blood was collected over the study period for pharmacokinetic analysis. Samples were centrifuged and the plasma portion drawn off and frozen at -20°C or colder.

[0107] Finger pulse oximetry was monitored continuously for 8 hours after each dose and then hourly for an additional four hours. If the subject's oxyhemoglobin saturation persistently decreased to less than 90%, the subject was prompted to inhale deeply several times and was observed for signs of decreased oxyhemoglobin saturation. If the oxyhemoglobin saturation value immediately increased to 90% or above, no further action was taken. If the oxyhemoglobin saturation remained below 90% for more than 1 minute, oxygen was administered to the subject via a nasal cannula. Heart rate, respiratory rate, and blood pressure were measured just prior to the dose, and every 15 minutes for 120 minutes, and at 4, 6, 8, and 12 hours post dose. Throughout the study, subjects were instructed to inform the study personnel of any adverse events.

[0108] Each subject received a single buccal dose of each of the 4 study treatments in an open-label, randomized crossover design. The measured pH on the three devices during the manufacturing process in accordance with Example 1 were 5.95 for the device at pH 6.0, 7.44 for the device at pH 7.25, and 8.46 for the device at pH

8.5. After subjects rinsed their mouths with water, the delivery devices of the present invention were applied to the oral mucosa at a location approximately even with the lower teeth. The devices were held in place for 5 seconds until the device was moistened by saliva and adhered to the mucosa membrane. After application, subjects were instructed to avoid rubbing the device with their tongues, as this would accelerate the dissolution of the device.

[0109] OTFC doses were administered according to the package insert. After each mouth was rinsed with water, the OTFC unit was placed in the mouth between the cheek and lower gum. The OTFC unit was occasionally moved from one side of the mouth to the other. Subjects were instructed to suck, not chew, the OTFC unit over a 15-minute period. To block the respiratory depressive effects of fentanyl, a 50 mg oral dose of naltrexone was administered to each subject at approximately 12 hours and 0.5 hours prior to each dose of study drug and 12 hours after study drug. Naltrexone has been shown not to interfere with fentanyl pharmacokinetics in opioid naïve subjects. Lor M, et al., *Clin Pharmacol Ther*; 77: P76 (2005).

[0110] At the end of the study, EDTA plasma samples were analyzed for plasma fentanyl concentrations using a validated liquid chromatography with tandem mass spectrophotometry (LC/MS/MS) procedure. Samples were analyzed on a SCIEX API 3000 spectrophotometer using pentadeuterated fentanyl as an internal standard. The method was validated for a range of 0.0250 to 5.00 ng/mL based on the analysis of 0.500 mL of EDTA human plasma. Quantitation was performed using a weighted (1/X2) linear least squares regression analysis generated from calibration standards.

[0111] Pharmacokinetic data were analyzed by noncompartmental methods in WinNonlin (Pharsight Corporation). In the pharmacokinetic analysis, concentrations below the limit of quantitation (<0.0250 ng/mL) were treated as zero from time-zero up to the time at which the first quantifiable concentration (C_{first}) was observed. Subsequent to C_{first}, concentrations below this limit were treated as missing. Full precision concentration data were used for all pharmacokinetic and statistical analyses. C_{first} was defined as the first quantifiable concentration above the pre-dose concentration because quantifiable data were observed in the pre-dose samples in some subjects. λ_z was calculated using unweighted linear regression analysis on at least three log-transformed concentrations visually assessed to be on the linear portion of the terminal slope. The $t_{1/2}$ was calculated as the ratio of 0.693 to λ_z. Pharmacokinetic parameters

were summarized by treatment using descriptive statistics. Values of t_{first}, t_{max}, C_{max}, and AUC_{inf} of the three exemplary devices of the present invention were compared to OTFC using an analysis of variance (ANOVA) model and Tukey's multiple comparison test. Statistical analysis was performed using SAS (SAS Institute Inc.). Table 3, below, presents the fentanyl pharmacokinetics for all 4 treatments after a single dose.

Table 3. Pharmacokinetic Parameters of OTFC and Three Formulations of BEMA Fentanyl Citrate

Parameter	OTFC 800 μg (N=12)		Device at pH 6 Fentanyl 800 μg (N=12)		Device at pH 7.25 Fentanyl 800 μg (N=12)		Device at pH 8.5 Fentanyl 800 μg (N=12)	
	Mean (SD)	CV%	Mean (SD)	CV %	Mean (SD)	CV%	Mean (SD)	CV %
t_{first} (hr)	0.23 (0.18)	78.03	0.13 (0.04)	27.99	0.15 (0.08)	54.18	0.21 (0.11)	55.21
C_{first} (ng/mL)	0.07 (0.05)	64.95	0.05 (0.02)	35.25	0.06 (0.02)	41.59	0.06 (0.02)	30.08
t_{max} (hr)	2.28 (1.32)	58.04	2.15 (1.14)	53.23	1.61 (1.04)	64.49	2.21 (1.34)	60.64
C_{max} (ng/mL)[1]	1.03 (0.25)	24.19	1.40 (0.49)	35.12	1.67 (0.75)	45.07	1.39 (0.41)	29.44
AUC_{last} (hr•ng/mL)	9.04 (3.53)	39.01	12.17 (4.28)	35.19	12.98 (5.59)	43.04	11.82 (4.54)	38.37
AUC_{0-24} (hr•ng/mL)	7.75 (2.52)	32.48	10.43 (3.00)	28.74	11.38 (4.30)	37.78	10.18 (3.20)	31.44
AUC_{inf} (hr•ng/mL)	10.30 (3.84)	37.29	13.68 (4.55)	33.24	14.44 (5.39)	37.33	13.11 (4.77)	36.40
% AUC_{extrap}	12.15 (8.31)	68.40	11.53 (6.84)	59.33	11.72 (6.91)	58.96	10.31 (4.49)	43.49
λz (hr^{-1})	0.05 (0.02)	37.83	0.05 (0.02)	31.10	0.05 (0.01)	21.18	0.06 (0.02)	26.98
$t_{1/2}$ (hr)	15.33 (6.85)	44.67	15.12 (5.09)	33.66	14.28 (2.75)	19.23	13.33 (4.14)	31.04
MRT	15.92 (6.17)	38.73	15.73 (4.19)	26.63	14.45 (3.12)	21.61	14.31 (4.45)	31.09

1. Mean differences of BEMA fentanyl formulations and OTFC significantly different by ANOVA, p=0.0304.

[0112] Abbreviations used herein are as follows: C_{first} is the first quantifiable drug concentration in plasma determined directly from individual concentration-time data; t_{first} is the time to the first quantifiable concentration; C_{max} is the maximum drug concentration in plasma determined directly from individual concentration-time data; t_{max} is the time to reach maximum concentration; λ_z is the observed elimination rate constant; $t_{1/2}$ is the observed terminal elimination half-life calculated as $\ln(2)/\lambda_z$; AUC_{0-24} is the area under the concentration-time curve from time zero to 24 hours post-dose; calculated using the linear trapezoidal rule and extrapolated using the elimination rate

constant if quantifiable data were not observed through 24 hours; AUC_{last} is the area under the concentration-time curve from time zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule; AUC_{inf} is the area under the concentration-time curve from time zero extrapolated to infinity, calculated as $AUC_{last} + C_{last} / \lambda_z$; AUC_{extrap} (%) is the percentage of AUC_{inf} based on extrapolation; MRT is the mean residence time, calculated as $AUMC_{inf}/AUC_{inf}$, where $AUMC_{inf}$ is the area under the first moment curve (concentration-time vs. time), calculated using the linear trapezoidal rule form time zero to T_{last} ($AUMC_{last}$) and extrapolated to infinity. It should be noted that, because quantifiable data were observed in the pre-dose samples for some subjects, C_{first} was redefined as the first quantifiable concentration above the pre-dose concentration, which was set to zero in calculating mean fentanyl concentrations.

[0113] Figure 1 illustrates the plasma fentanyl concentration from 0 to 48 hours post-dose for the OTFC dose and the doses provided by the three exemplary devices of the present invention. The device at pH 7.25 provided the highest peak concentrations of fentanyl of the three devices of the present invention used in this study. In general, OTFC provided lower fentanyl concentrations for most time points as compared with the devices of the present invention. The device at pH 6 and the device at pH 8.5 yielded very similar concentration-time profiles, with C_{max} values of 1.40 ng/mL and 1.39 ng/mL, respectively. These values are midway between the maximum plasma fentanyl values of 1.03 ng/mL for OTFC and 1.67 ng/mL for the device at pH 7.25. After approximately 6 hours post-dose, the fentanyl concentration-time profiles for the three devices of the present invention were similar. The differences in fentanyl C_{max} values were statistically significant when comparing all of the devices of the present invention to OTFC ($p=0.0304$), and for pairwise comparisons of the device at pH 7.25 to OTFC ($p<0.05$).

[0114] In general, quantifiable fentanyl concentrations were observed earlier after administration of one of the three exemplary devices of the present invention (mean t_{first} of 8 to 13 minutes) compared with OTFC (mean t_{first} of 14 minutes). The device at pH 7.25 yielded the earliest average t_{max} (1.61 hours) and highest C_{max} (mean 1.67 ng/mL). As shown in Figure 2, fentanyl absorption from a device at pH 7.25 was more rapid over the first hour post dose than from OTFC, with 30-minute mean plasma concentrations of 0.9 ng/mL for the device at pH 7.25 and 0.5 ng/mL for OTFC.

[0115] The delivery devices of the present invention provided overall greater exposure to fentanyl, based on $AUC_{0\,24}$ as compared to OTFC. Fentanyl exposure as measured by AUC_{0-24} values, were similar across groups treated with one of the devices of the present invention, suggesting that comparable amounts of fentanyl enter the systemic circulation from each of the devices. The device at pH 7.25, however, demonstrated approximately 19% greater maximum plasma fentanyl concentration.

[0116] Overall, fentanyl concentrations were observed earlier and increased more rapidly after administration of a device of the present invention compared with OTFC. Mean 30 and 60 minute plasma fentanyl concentrations observed with use of the device at pH 7.25 were 1.8 and 1.7 times higher than with OTFC, respectively. Similarly, the maximum plasma fentanyl concentration was 60% higher using a device of the present invention (mean 1.67 ng/mL) when compared to use of OTFC (mean 1.03 ng/mL). The C_{max} for OTFC identified in this study is nearly identical to the 1.1 ng/mL C_{max} value reported by Lee and co-workers with both a single 800 mcg lozenge as well as two 400 mcg lozenges. Lee, M., et al., *J Pain Symptom Manage* 2003; 26:743-747. Overall, fentanyl exposure for the fentanyl formulations of the present invention were greater than for OTFC. Mean estimates of AUC_{last} and AUC_{inf} were slightly larger, but the same general trends were observed. This indicates that the transmucosal uptake is significantly improved in the devices of the present invention as compared to OTFC.

[0117] Mean $t_{1/2}$ values and MRT values were similar for all treatment groups and the values in both cases followed the same trend. Additionally, because MRT after extravascular administration is dependent on the absorption and elimination rates, the MRT values suggest that fentanyl absorbs faster from a delivery device of the present invention, particularly with the device at pH 7.25 and the device at pH 8.5. This observation is consistent with the t_{max} for the delivery devices of the present invention relative to OTFC.

[0118] Adverse events were similar across treatment groups and confounded by the co-administration of naltrexone with each study treatment. The most frequent adverse events were sedation and dizziness. One subject experienced oral mucosal irritation with OTFC. No subject experienced mucosal irritation with any of the three exemplary devices of the present invention. All reported adverse events were mild or moderate in nature.

[0119] As demonstrated above, the delivery devices of the present invention provide significantly higher plasma fentanyl concentrations than OTFC. The delivery device at pH 7.25 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization. Similar studies have shown that the delivery devices of the present invention provide an absolute bioavailability of about 70.5% and buccal absorption was about 51% (estimated by subtracting the AUC_{inf} following an oral dose of fentanyl from the AUC_{inf} following BEMA fentanyl applied to the buccal mucosa, dividing by the single disc BEMA Fentanyl AUC_{inf}, and multiplying by 100).

Example 3: Preparation of Devices in Accordance with the Present Invention

[0120] Devices containing buprenorphine were also produced using the same method as described in Example 1, except that buprenorphine was added to the mucoadhesive polymeric diffusion environment, rather than fentanyl citrate.

Example 4: Study of Buprenorphine Uptake in Humans for Delivery Devices of the Present Invention

[0121] A study similar to that described in Example 2 was also performed with buprenorphine in exemplary devices of the present invention (at pH 6 and 7.25), suboxone sublingual and buprenex intramuscular. Results from this study are summarized in the graph in Figure 3. As demonstrated in Table 4, the delivery devices of the present invention at pH 6 appeared to provide enhanced uptake believed to be attributable to a favorable balance between drug solubility and ionization.

Table 4: Pharmacokinetic data for buprenorphine

pH	6	7.25
t_{first} (hr)	0.75	0.75
C_{first} (ng/mL)	0.0521	0.0845
t_{max} (hr)	3	3
C_{max} (ng/mL)[1]	1.05	0.86

EQUIVALENTS

[0122] Numerous modifications and alternative embodiments of the present invention will be apparent to those skilled in the art in view of the foregoing description. Accordingly, this description is to be construed as illustrative only and is for the purpose

of teaching those skilled in the art the best mode for carrying out the present invention. Details of the structure may vary substantially without departing from the spirit of the invention, and exclusive use of all modifications that come within the scope of the appended claims is reserved. It is intended that the present invention be limited only to the extent required by the appended claims and the applicable rules of law.

[0123] All literature and similar material cited in this application, including, patents, patent applications, articles, books, treatises, dissertations and web pages, regardless of the format of such literature and similar materials, are expressly incorporated by reference in their entirety. In the event that one or more of the incorporated literature and similar materials differs from or contradicts this application, including defined terms, term usage, described techniques, or the like, this application controls.

[0124] The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described in any way.

[0125] While the present inventions have been described in conjunction with various embodiments and examples, it is not intended that the present teachings be limited to such embodiments or examples. On the contrary, the present inventions encompass various alternatives, modifications, and equivalents, as will be appreciated by those of skill in the art.

[0126] The claims should not be read as limited to the described order or elements unless stated to that effect. It should be understood that various changes in form and detail may be made without departing from the scope of the appended claims. Therefore, all embodiments that come within the scope and spirit of the following claims and equivalents thereto are claimed.

Claims:

1. A method for enhancing direct transmucosal delivery of a fentanyl or fentanyl derivative to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of a subject, the device comprising: a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface and the fentanyl or fentanyl derivative is delivered to the subject.

2. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of a fentanyl or fentanyl derivative disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the fentanyl or fentanyl derivative is delivered in less than about 30 minutes.

3. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

4. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

5. The method or device of any of the preceding claims, wherein the pain is breakthrough cancer pain.

6. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl or fentanyl derivative to a subject, the mucoadhesive device comprising: a fentanyl or fentanyl derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is upon application to a mucosal surface.

7. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative with at least 50% direct buccal absorption and an absolute bioavailability of at least about 70%.

8. A transmucosal delivery device that delivers a fentanyl or fentanyl derivative directly to the mucosa to achieve onset of pain relief (T_{first}) of about 0.20 hours or less and time to peak plasma concentration (T_{max}) of about 1.6 hours or more.

9. A device comprising about 800 μg of fentanyl, which exhibits upon transmucosal administration to a subject at least one *in vivo* plasma profile selected from the group consisting of:

a C_{max} of about 1.10 ng/mL or more;

a T_{first} of about 0.20 hours or less; and

an AUC_{0-24} of about 10.00 hr·ng/mL or more.

10. A transmucosal delivery device comprising a fentanyl or fentanyl derivative that delivers the fentanyl or fentanyl derivative in an amount effective to treat pain, wherein oral irritation, oral ulceration and/or constipation associated with the delivery of the fentanyl or fentanyl derivative is insignificant or eliminated.

11. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is between about 6.5 and about 8.

12. The method or device of any of the preceding claims, wherein the pH of the mucoadhesive polymeric diffusion environment is about 7.25.

13. The method or device of any of the preceding claims, wherein the device comprises about 800 μg of fentanyl.

14. The method or device of any of the preceding claims, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the fentanyl or fentanyl derivative to the mucosa.

15. The method or device of any of the preceding claims, wherein the fentanyl is fentanyl citrate.

16. The method or device of any of the preceding claims, wherein more than 30% of the fentanyl in the device becomes systemically available via mucosal absorption.

17. The method or device of any of the preceding claims, wherein more than 55% of the fentanyl in the device becomes systemically available.

18. A method for enhancing direct transmucosal delivery of buprenorphine to a subject, said method comprising:

administering a bioerodable drug delivery device to an oral mucosal surface of the subject, the device comprising: buprenorphine disposed in a mucoadhesive polymeric diffusion environment; and a barrier environment disposed relative to the

polymeric diffusion environment such that a unidirectional gradient is created upon application to the mucosal surface, and the buprenorphine is delivered to the subject.

19. A method for treating pain in a subject comprising transmucosally administering to a subject a therapeutically effective amount of buprenorphine disposed in a mucoadhesive polymeric diffusion environment such that the effective amount of the buprenorphine is delivered in less than about 30 minutes.

20. The method of any of the preceding claims wherein chronic pain is alleviated in the subject.

21. The method of any of the preceding claims wherein acute pain is alleviated in the subject.

22. A mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of buprenorphine to a subject, the mucoadhesive device comprising: buprenorphine derivative disposed in a polymeric diffusion environment; and a barrier environment disposed relative to the polymeric diffusion environment such that a unidirectional gradient is created upon application to a mucosal surface.

23. The method or device of any of claims 18-22, wherein the pH is between about 4.0 and about 7.5.

24. The method or device of any of claims 18-23, wherein the pH is about 6.0.

25. The method or device of any of claims 18-24, wherein the pH is about 7.25.

26. The method or device of any of claims 18-25, wherein the device further comprises at least one additional layer that facilitates unidirectional delivery of the buprenorphine to the mucosa.

27. The method or device of any of the preceding claims, wherein the device comprises a pH buffering agent.

28. The method or device of any of the preceding claims, wherein the device is adapted for buccal administration.

29. The method or device of any of the preceding claims, wherein the device is adapted for sublingual administration.

30. The method or device of any of the preceding claims, wherein the device is a mucoadhesive disc.

31. The method or device of any of the preceding claims, wherein the medicament is formulated as a mucoadhesive film formed to delineate different dosages.

32. The method or device of any of the preceding claims, wherein the device comprises a backing layer disposed adjacent to the mucoadhesive polymeric diffusion environment.

33. The method or device of any of the preceding claims, wherein the device further comprises an opioid antagonist.

34. The method or device of any of the preceding claims, wherein the device further comprises naloxone.

35. The method or device of any of the preceding claims, wherein the device is a layered, flexible device.

36. The method or device of any of the preceding claims, wherein the mucoadhesive polymeric diffusion environment has a buffered environment for the transmucosal administration.

37. The method or device of any of the preceding claims, wherein there is substantially no irritation at the site of transmucosal administration.

38. The method or device of any of the preceding claims, wherein there is about a 50% decrease in pain over about 30 minutes.

39. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises at least one ionic polymer system.

40. The method or device of claim 39, wherein the ionic polymer system is selected from the group consisting of POLYCARBOPHIL, sodium carboxymethylcellulose and mixtures thereof.

41. The method or device of any of the preceding claims, wherein the polymeric diffusion environment comprises a buffer system.

42. The method or device of claim 41, wherein the buffer system comprises citric acid, sodium benzoate or mixtures thereof.

43. The method or device of any of the preceding claims, wherein the device has a thickness such that it exhibits minimal mouth feel.

44. The method or device of any of the preceding claims, wherein the device has a thickness of about 0.25 mm.

45. A flexible, bioerodable mucoadhesive delivery device suitable for direct transmucosal administration of an effective amount of a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative to a subject, the mucoadhesive device comprising:

a mucoadhesive layer comprising a fentanyl, fentanyl derivative, buprenorphine or buprenorphine derivative disposed in a polymeric diffusion environment, wherein the polymeric diffusion environment has a pH of about 7.25 for the fentanyl or fentanyl derivative or a pH of about 6 for the buprenorphine or buprenorphine derivative; and

a backing layer comprising a barrier environment which is disposed adjacent to and coterminous with the mucoadhesive layer,

wherein the device has no or minimal mouth feel and is able to transmucosally deliver the effective amount of the , fentanyl derivative, buprenorphine or buprenorphine derivative in less than about 30 minutes; and

wherein a unidirectional gradient is created upon application of the device to a mucosal surface.

Figure 1. Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC

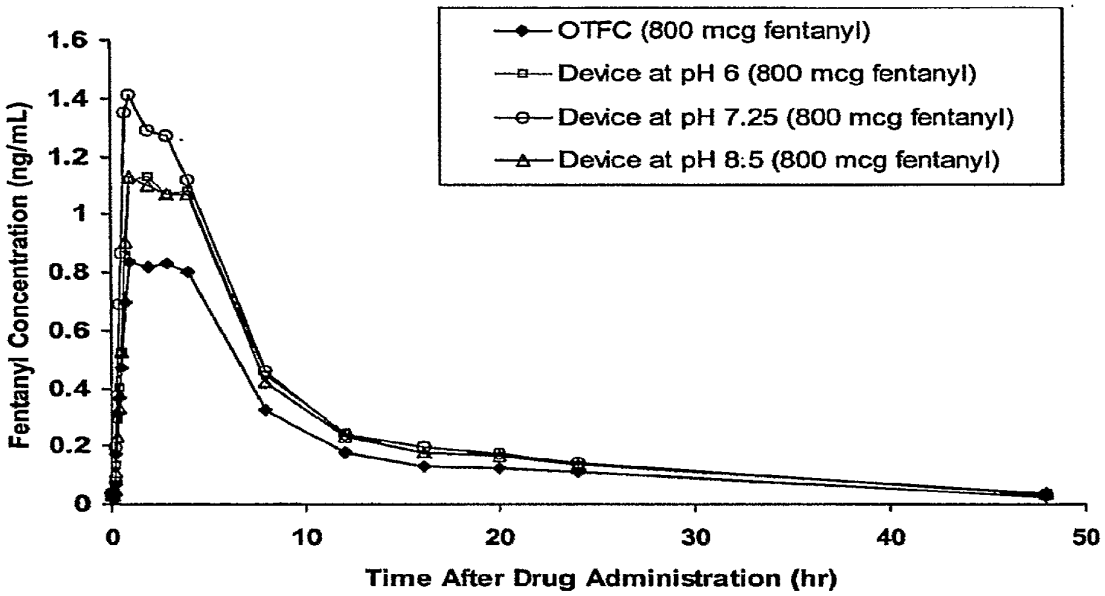


Figure 2. Mean (SD) Fentanyl Concentration Over Time Comparing an Exemplary Device According To The Present Invention and OTFC

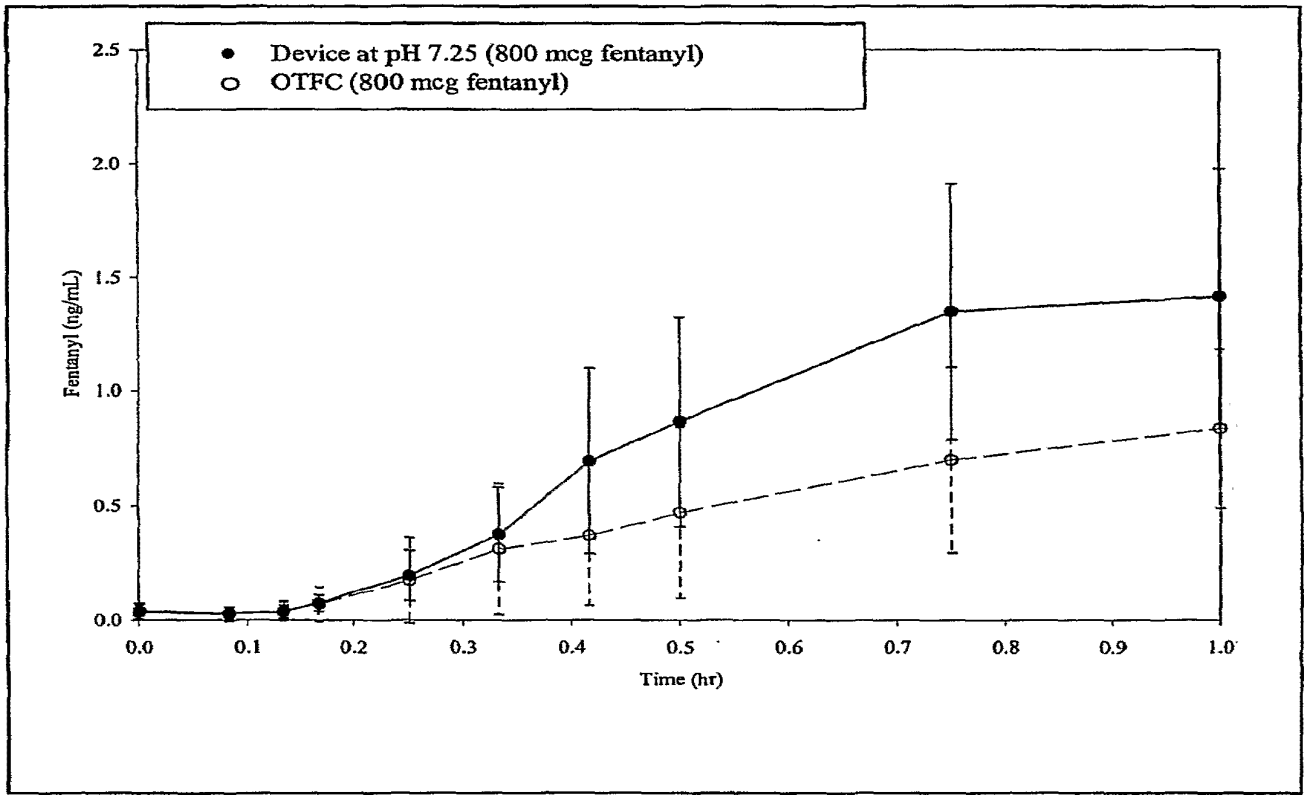


Figure 3. Mean (SD) Buprenorphine Concentration Over Time Comparing an Exemplary Device According To The Present Invention and Conventional Buprenorphine Delivery

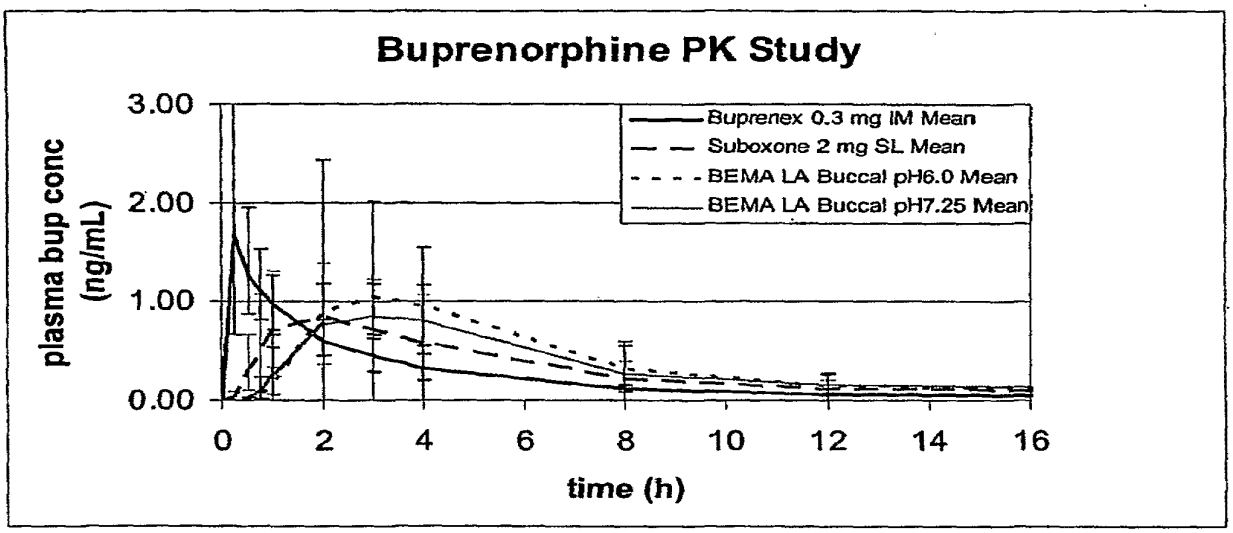


Figure 4: Exemplary Embodiments of the Present Invention

Figure 4A

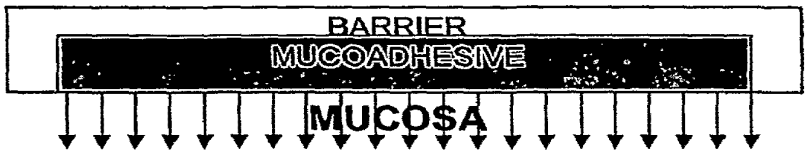


Figure 4B

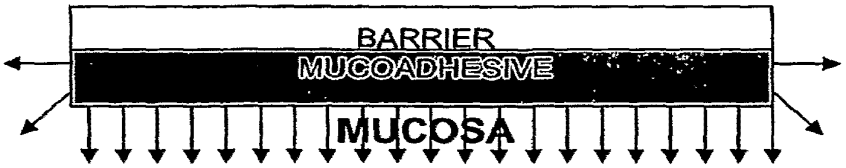
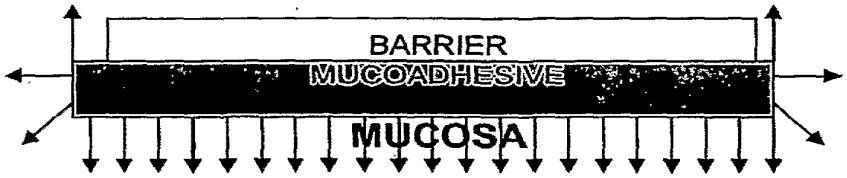


Figure 4C



(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(74) Agents: **HANLEY, Elizabeth, A.** et al.; Lahive & Cockfield, Llp, One Post Office Square, Boston, MA 02109-2127 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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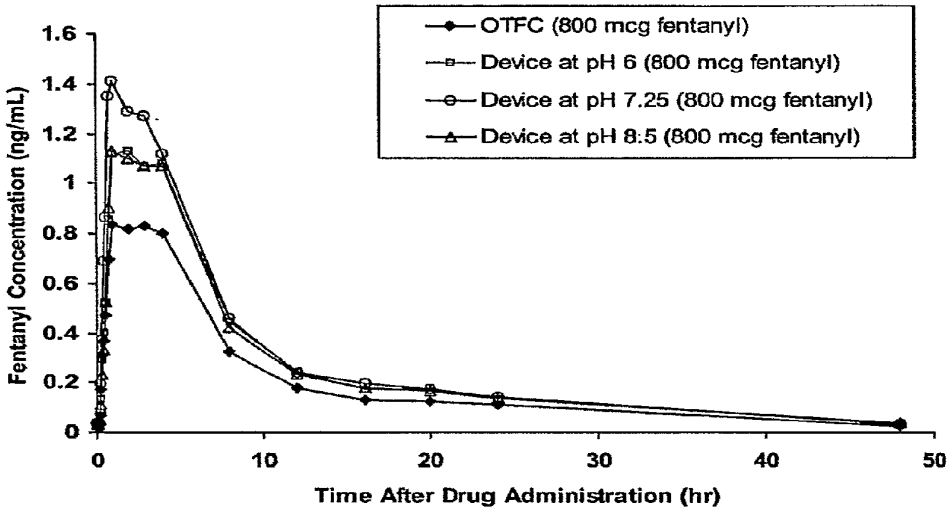
[Continued on next page]

(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

Mean Fentanyl Concentration-Time Plots For Three Exemplary Devices of the Invention and OTFC



(57) Abstract: The present invention provides methods for enhancing transmucosal uptake of a medicament, e.g., fentanyl or buprenorphine, to a subject and related devices. The method includes administering to a subject a transmucosal drug delivery device comprising the medicament. Also provided are devices suitable for transmucosal administration of a medicament to a subject and methods of their administration and use. The devices include a medicament disposed in a mucoadhesive polymeric diffusion environment and a barrier environment.

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PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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INV. A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
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)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 1 642 579 A (TEIKOKU SEIYAKU KK [JP]) 5 April 2006 (2006-04-05) claims; examples	1-8,10, 14-17, 20,21, 28, 30-32, 35,37, 38,43
X	WO 01/43728 A (LOHMANN THERAPIE SYST LTS [DE]; ASMUSSEN BODO [DE]; KRUMME MARKUS [DE]) 21 June 2001 (2001-06-21) page 7, line 9 - page 11, line 29; claims	1,3-6, 10,14, 20,21, 28-35, 37,43

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 March 2008	17/03/2008

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Couckuyt, Philippe

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2007/016634

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/58447 A (EURO CELTIQUE SA [LU]; OSHLACK BENJAMIN [US]; CURTIS WRIGHT [US]) 16 August 2001 (2001-08-16) example 11	18-22, 30, 32-35, 37,43
Y	example 11	11,12, 23-25, 27,36, 41,42,45
X	WO 01/30288 A (ANESTA CORP [US]) 3 May 2001 (2001-05-03) claims 1,2,4,22; table 1	1-8,10, 14, 16-22, 26-28, 30,32, 35-38, 41,43
Y	claims 1,2,4,22; table 1	11,12, 23-25, 27,36, 41,42,45
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P,X	WO 2007/070632 A (BIODELIVERY SCIENCES INTERNATI [US]; FINN ANDREW [US]; VASISHT NIRAJ [ ) 21 June 2007 (2007-06-21) cited in the application claims; examples	1-4,6, 10,14, 18, 20-22, 26,28, 30,32, 35,37,43

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Information on patent family members

International application No
PCT/US2007/016634

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International application No
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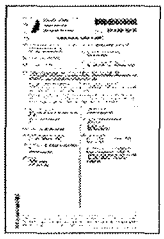
The Delphion Integrated View

Title: **EP0949925B1: FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME**[German][French]

Derwent Title: Flat administration form containing buprenorphine which disintegrates in aqueous media, for application and release in oral cavity, for analgesia or (opiate or cocaine) addiction treatment [Derwent Record]



High Resolution

Low Resolution

5 pages

Country: **EP** European Patent Office (EPO)

Kind: **B1** PATENT SPECIFICATION (See also: EP0949925A2)

Inventor: **CREMER, Karsten;**
LUESSEN, Henrik;

Assignee: **LTS LOHMANN Therapie-Systeme AG**
Corporate Tree data: LTS Lohmann Therapie Systeme (LTSLOHMANN);
News, Profiles, Stocks and More about this company

Published / Filed: **2004-01-07** / 1997-11-14

Application Number: **EP1997000952767**

IPC Code: Advanced: **A61K 9/00**; **A61K 9/20**; **A61K 9/70**; **A61K 31/485**;
Core: more...
IPC-7: **A61K 9/70**; A61K 31/485;

Priority Number: 1996-12-16 **DE1996019652188**

Abstract: [From equivalent EP0949925A2] The invention concerns a solid medicament preparation which can decompose in aqueous media and has a flat-, foil-, paper- or wafer-type presentation for the application and release of active substances in the buccal cavity. The invention is characterized in that it contains buprenorphine, an active substance which is pharmacologically comparable thereto, or a therapeutically suitable salt of buprenorphine or of the pharmacologically comparable active substance. [French]

Attorney, Agent or Firm: **Flaccus, Rolf-Dieter, Dr.** ;

INPADOC Legal Status: Show legal status actions **Get Now:** Family Legal Status Report

Designated Country: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE SI

Family: Show 21 known family members

First Claim: Show all claims

1. Buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine, morphine, dihydromorphine derivatives, substances from the methadone or fentanyl groups as such or as a therapeutically suitable salt, **characterized by** a wafer-shaped administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose, the said

administration form having a non-muco-adhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.
[German] [French]

Description
Expand description

Vorliegende Erfindung betrifft eine Arneizubereitung zur Applikation von Buprenorphin oder pharmakologisch vergleichbaren Wirkstoffen im Bereich der Mundhöhle bzw. der Mundschleimhaut. Sie betrifft insbesondere eine Zubereitung, die flach und als folien-, papier- oder oblatenartige Darreichungsform ausgestaltet ist.

Other Abstract Info:

None

(19) Europäisches Patentamt
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Office européen des brevets

(11) EP 0 949 925 B1

(12) **EUROPÄISCHE PATENTSCHRIFT**

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07.01.2004 Patentblatt 2004/02

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(22) Anmeldetag: **14.11.1997**

(51) Int Cl.[7]: **A61K 31/485**, A61K 9/70

(86) Internationale Anmeldenummer:
PCT/EP1997/006369

(87) Internationale Veröffentlichungsnummer:
WO 1998/026780 (25.06.1998 Gazette 1998/25)

(54) **FLACHE ARZNEIZUBEREITUNG ZUR APPLIKATION UND FREISETZUNG VON BUPRENORPHIN ODER EINER PHARMAKOLOGISCH VERGLEICHBAREN SUBSTANZ IN DER MUNDHÖHLE UND VERFAHREN ZU IHRER HERSTELLUNG**

FLAT MEDICAMENT PREPARATION FOR THE APPLICATION AND RELEASE OF BUPRENORPHINE OR A PHARMACOLOGICALLY COMPARABLE SUBSTANCE IN THE BUCCAL CAVITY, AND METHOD OF PRODUCING THE SAME

PREPARATION MEDICAMENTEUSE PLATE POUR ADMINISTRER OU LIBERER, DANS LA CAVITE BUCCALE, DE LA BUPRENORPHINE OU UNE SUBSTANCE COMPARABLE SUR LE PLAN PHARMACOLOGIQUE ET PROCEDE PERMETTANT DE LA PREPARER

(84) Benannte Vertragsstaaten:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE
Benannte Erstreckungsstaaten:
SI

(30) Priorität: **16.12.1996 DE 19652188**

(43) Veröffentlichungstag der Anmeldung:
20.10.1999 Patentblatt 1999/42

(73) Patentinhaber: **LTS LOHMANN Therapie-Systeme AG**
56626 Andernach (DE)

(72) Erfinder:
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- **LUESSEN, Henrik**
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(74) Vertreter: **Flaccus, Rolf-Dieter, Dr.**
Patentanwalt
Bussardweg 10
50389 Wesseling (DE)

(56) Entgegenhaltungen:
EP-A- 0 219 762 **FR-A- 2 514 642**
US-A- 4 673 679

- **J.P. CASSIDY ET AL.: "controlled buccal delivery of buprenorphine" JOURNAL OF CONTROLLED RELEASE, Bd. 25, Nr. 1/2, 27.Mai 1993, AMSTERDAM (NL), Seiten 21-29, XP000361365**

EP 0 949 925 B1

Printed by Jouve, 75001 PARIS (FR)

Beschreibung

[0001] Vorliegende Erfindung betrifft eine Arneizubereitung zur Applikation von Buprenorphin oder pharmakologisch vergleichbaren Wirkstoffen im Bereich der Mundhöhle bzw. der Mundschleimhaut. Sie betrifft insbesondere eine Zubereitung, die flach und als folien-, papier- oder oblatenartige Darreichungsform ausgestaltet ist.

[0002] Flache Wirkstoffträger wurden bereits für verschiedene Zwecke entwickelt und hergestellt. Als grundlegend für diese Darreichungsform kann die DE-OS 27 46 414 angesehen werden, die ein folienartiges Band aus Wirkstoff, Bindemittel und weiteren Hilfsstoffen beschreibt, bei dem aufgrund homogenen Dicke, Dichte und Breite ein direkter Zusammenhang zwischen einer Längeneinheit des Bandes und der darin enthaltenen Wirkstoffdosis besteht. Die Vorteile der kontinuierlichen Dosierbarkeit wurden auch von anderen Anmeldern erkannt und in speziellen Einzelvarianten beschrieben. So beschreibt DE-PS 36 30 603 ein flächiges Trägermaterial z.B. in Form eines Trennpapieres mit einer wirkstoffhaltigen Beschichtung, wobei letztere nach Vorzerteilung in Dosiereinheiten vom Trägermaterial dosisweise abziehbar ist.

[0003] Die Praktikabilität des flachen Formates im allgemeinen sowie die Vorteile bei der Herstellung der Darreichungsform und bei der Dosierung unter ihrer Anwendung wurden im Stand der Technik erkannt. Darüber hinaus lassen sich weitere Vorteile solcher Darreichungsformen ableiten, wie etwa die Bedruckbarkeit einer relativ großen Fläche auf der Arzneiform im Verhältnis zu ihrem Gewicht, womit die Einnahmesicherheit erhöht werden kann, wie auch die Möglichkeit der diskreten Einnahme, ohne daß Flüssigkeit zur Verfügung steht.

[0004] Trotz dieser klaren Vorteile haben sich solche Darreichungsformen bisher kaum durchgesetzt. Offensichtlich reicht für viele Hersteller von Pharmazeutika der Nutzen gegenüber konventionellen Darreichungsformen nicht aus, um Produkte dieser Art mit den gebräuchlichen Wirkstoffen zu entwickeln und deren arzneimittelrechtliche Zulassung zu betreiben. Darüber hinaus können vorhandene Produktionsmaschinen und existierendes Knowhow für diese neuartigen Produkte nicht genutzt werden; ein hoher Investitionsbedari: würde entstehen. Trotz der oben beschriebenen Vorteile von flächen- film- oder papierartigen Darreichungsformen ist der therapeutische und/oder wirtschaftliche Nutzen bei der Verabreichung von gängigen, auch peroral applizierbaren Wirkstoffen im Vergleich zu konventionellen Tabletten anscheinend nicht so groß, daß er die Kosten der Umstellung auf diese Darreichungsformen rechtfertigen würde.

[0005] Zu den Wirkstoffen, dies sich nur wenig für eine perorale Verabreichung eignen, zählt das in der Schmerztherapie seit Jahren erfolgreich eingesetzte Opiat Buprenorphin. Nach peroraler Applikation ist es kaum bioverfügbar, d. h. erscheint nur in einem sehr geringen Ausmaß von wenigen Prozent der eingenommenen Dosis im Blutkreislauf (McQuay & Moore, in: Buprenorphine, Hrsg. Cowan & Lewis, New York 1995). Der Grund für die mangelnde Bioverfügbarkeit liegt vermutlich im weitgehenden Abbau der Substanz während der ersten Leberpassage nach der gastrointestinalen Resorption ("First-pass Effekt"). Eine Möglichkeit, den First-pass-Effekt bei der oralen Verabreichung zu umgehen, besteht darin, den Wirkstoff bereits an der Mundschleimhaut zur Resorption zu bringen. Wirkstoff, welcher hier ins Blut übertritt, muß nicht als erstes das Pfortadersystem und damit in konzentrierter Form die den Wirkstoff metabolisierende Leber passieren, um in den zentralen Körperkreislauf zu gelangen. Voraussetzung für eine buccale oder sublinguale Applikation ist jedoch die ausreichende Permeabilität der oralen Mucosa für den Wirkstoff unter Berücksichtigung der notwendigen Dosis. Die Permeabilität wiederum hängt in hohem Maße von den physikochemischen Eigenschaften des Wirkstoffs ab. Da Buprenorphin in sehr geringen Dosen wirksam ist und außerdem die erforderlichen physikochemischen Charakteristika besitzt, ist die buccale oder sublinguale Applikation sehr attraktiv.

[0006] In der Zeitschrift "Journal of Controlled Release", Bd. 25, Nr. 1/2, 1993, werden nicht zerfallsfähige polymere Systeme zur buccalen Anwendung von Buprenorphin beschrieben, die mit einer für den Wirkstoff nicht permeablen Schicht abgedeckt wurden, so daß eine gerichtete Freisetzung des Wirkstoffs möglich und der Verlust von Wirkstoff durch Schlucken vermindert wurde. Die wirkstoffundurchlässige Schicht wurde dabei mit Hilfe eines randständig aufgebrachten Klebers in der Mundhöhle in Position gehalten und das System wurde nach mehreren Stunden wieder aus der Mundhöhle entfernt.

[0007] Die US Patentschrift US 4 673 679 offenbart eine pharmazeutische Zubereitung zur buccalen und sublingualen Verabreichung von Opiaten und Opiatantagonisten in Form von im wässrigen Medium der Mundhöhle zerfallsfähigen Pflastern. Die zur buccalen Anwendung offenbarten Pflaster enthalten u. a. den mukoadhäsiven Hilfsstoff Carbopol 934P sowie ersterifizierte Derivate von Nalbuphin als "prodrugs".

[0008] Tatsächlich befinden sich - zumindest in Deutschland - neben den injektabilen Darreichungsformen keine peroralen, sondern nur sog. Sublingualtabletten mit Buprenorphin im Handel (Temgesic® sublingual). Diese Tabletten würdigen zwar - wenn auch vorwiegend durch die Einnahmevorschrift, denn nur diese, nicht die Tablette an sich, legt die sublinguale Gabe nahe - die Tatsache, daß eine sublinguale Applikation des Wirkstoffes der peroralen vorzuziehen ist; sie bieten jedoch ein für den Anwendungszweck mit erhetblichen Nachteilen behaftetes Vehikel. Hierzu gehört zunächst die nicht unbeträchtliche Zerfallzeit, die bei gepreßten Tabletten selbst unter günstigen Voraussetzungen mindestens einige Minuten beträgt, bei den im Handel er-

hältlichen Buprenorphin-Tabletten in der Regel etwa 5 bis 10 Minuten. Für Patienten mit starken, akuten Schmerzen bedeutet diese Zerfallzeit eine unerwünschte Verzögerung des Wirkstoffeintritts, bei einer Substitutions- oder Entwöhnungstherapie dagegen eine zeitliche Belastung des medizinischen Personals, welches die bestimmungsgemäße Verwendung der Tabletten überwachen und eine mißbräuchliche Wiederentnahme der unzerfallenen Tabletten aus dem Mund verhindern muß. Weitere Nachteile der Tablette sind das Fremdkörpergefühl im Mund während der Zerfallzeit, aber auch die große Variabilität beim Ausmaß der sublingualen Absorption, die dadurch verursacht wird, daß der Wirkstoff beim oder nach dem Zerfall der Tablette überwiegend keinen direkten Kontakt zur Mundschleimhaut hat, sondern in den Speichel freigesetzt wird; der Speichel kann sich aber mehr und weniger zufällig über eine sehr variable Zeit in der Mundhöhle befinden, bevor er geschluckt wird.

[0009] Aufgabe der vorliegenden Erfindung ist daher die Schaffung von Arzneizubereitungen auf der Basis von und mit den allgemeinen Vorteilen von flachen, film- oder papierartigen Wirkstoffträgern, welche durch die Kombination mit einem speziellen Wirkstoff noch zusätzliche therapeutische und/oder wirtschaftliche Vorteile gegenüber Arzneizubereitungen desselben Wirkstoffes auf der Basis konventioneller Darreichungsformen wie etwa Tabletten aufweist. Darüber hinaus ist es ebenso die Aufgabe der Erfindung, eine Applikationsform für Buprenorphin bereitzustellen, die den Wirkstoff in der Mundhöhle freisetzt, ohne die im Stand der Technik beschriebenen Nachteile zu besitzen.

[0010] Die Aufgabe wird entsprechend den Merkmalen des Anspruchs 1 dadurch gelöst, dass eine im wässrigen Medium der Mundhöhle zerfallsfähige oblatenförmige Arzneizubereitung mit einer mukoadhäsiven, als Wirkstoff Buprenorphin oder eine therapeutisch vergleichbare Wirksubstanz enthaltende Schicht auf der Basis von wasserlöslichen filmbildenden Polymeren bereitgestellt wird, die eine der mucoadhäsiven Fläche entgegengesetzte nicht-mucoadhäsive Außenschicht mit geringerer Permeabilität für den Wirkstoff aufweist.

[0011] Eine Arzneizubereitung nach Anspruch 1 ist, wie im folgenden dargelegt werden soll, einer konventionellen Darreichungsform zur Verabreichung von Buprenorphin sowohl unter wirtschaftlichen als auch unter therapeutischen Gesichtspunkten weit überlegen und eignet sich insbesondere einerseits zur Analgesie bei starken Schmerzzuständen, andererseits zur Therapie der Opiat oder Cocainabhängigkeit im Sinne einer Substitutionstherapie oder eines Entwöhnungsprogrammes.

[0012] Die Arzneizubereitung nach Anspruch 1 kann bei der Applikation direkt mit der Mundschleimhaut in Kontakt gebracht werden. Durch die flächige Ausgestaltung befindet sich sofort nach der Applikation etwa die Hälfte der ohnehin großen Oberfläche der Darreichungsform unmittelbar auf der Mucosa. Das freigesetzte Buprenorphin findet also für den Eintritt in den Körper zwei besonders günstige Faktoren vor, nämlich eine kurze Diffusionsstrecke und eine große Diffusionsfläche. Hierdurch wird der Anteil an Buprenorphin herabgesetzt, der verschluckt wird, was bei vielen anderen Wirkstoffen nicht sonderlich problematisch wäre. Bei Buprenorphin jedoch ist das Verschlucken von Wirkstoff möglichst zu vermeiden oder herabzusetzen, da verschlucktes Buprenorphin aus den dargelegten Gründen unwirksam bleibt. Bereits bei der einfachsten erfindungsgemäßen Ausgestaltung und mit einer Zerfallzeit von wenigen Minuten nach Applikation oder nach dem Einbringen in wässrige Medien wird sich daher die Überlegenheit eines buprehorphinhaltigen Films gegenüber einer buprenorphinhaltigen Tablette zeigen.

[0013] Ein verbesserter Kontakt der erfindungsgemäßen Arzneizubereitung mit der Mundschleimhaut läßt sich durch die Auswahl der Hilfsstoffe herbeiführen. Von bestimmten pharmazeutisch gebräuchlichen, oral applizierbaren Hilfsstoffen ist bekannt, daß sie schleimhauthaftende Eigenschaften besitzen. Beispiele für solche mucoadhäsiven Substanzen sind Polyacrylsäure, Carboxymethylcellulose, Traganth, Alginsäure, Gelatine, Hydroxymethylcellulose,Methylcellulose und Gummi Arabicum. Darüber hinaus ist von verschiedenen nicht mucoadhäsiven Stoffen bekannt, daß sie in bestimmten Mischungsverhältnissen ebenfalls mucoadhäsive Eigenschaften ausbilden. Ein Beispiel für ein solches Gemisch ist Glycerinmonooleat/ Wasser im Verhältnis 84: 16 (Engström et. aL., Pharm. Tech. Eur. 7 [1995], Nr. 2, S. 14-17).

[0014] Durch den zwei oder mehrschichtigen Aufbau der Darreichungsform der erfindungsgemäßen Arzneizubereitung kann vermieden werden, daß die Zubereitung verschiedene Schleimhautpartien miteinander verklebt, was zu erheblichen Missempfindungen führen würde. Außerdem kann bei einem solchen Aufbau, bei dem die nicht mukoadhäsive Schicht eine relativ geringere Permeabilität gegenüber dem Wirkstoff als die mukoadhäsive Schicht besitzt, vermieden werden, dass durch die Freisetzung in den Speichel der Mundhöhle statt zur Schleimhaut Wirkstoffverluste eintreten.

[0015] Erfindungsgemäße Arzneizuberoitungen sind auch solche, die neben dem Wirkstoff Buprenorphin oder einem diesem pharmakologisch vergleichbaren Wirkstoff noch einen oder mehrere weitere Wirkstoffe enthalten. Eine solche Zubereitung kann in mehrfacher Hinsicht vorteilhaft sein. Zum einen ist es eine anerkannte Methode zur Behandlung mehrerer gleichzeitig auftretender Symptome oder Zustände, eine fixe Wirkstoffkombination in einem Medikament zu verabreichen. Hierzu lassen sich beliebige, therapeutisch sinnvolle Wirkstoffe in die erfindungsgemäße Zubereitung einarbeiten. Zum anderen ist die erfindungsgemäße Kombination eines Opiatwirkstoffes mit einer anderen Substanz, welche die spezifischen Risiken einer Opiatverabreichung reduzieren kann, besonders sinnvoll und vorteilhaft. So lassen sich beispielsweise - gegebe-

nenfalls partielle- Opiatantagonisten wie etwa Nalbuphin, Naloxon oder Naltrexon mit dem Opiatwirkstoff kombinieren, was zur Folge hat, daß die Sucht- bzw. Gewöhnungsgefahr durch die wiederholte Verabreichung der Zubereitung dadurch verringert wird, daß sich die Dosis nicht steigern läßt, ohne gleichzeitig eine Steigerung des antagonistischen Effektes in Kauf zu nehmen. Von der Wahl eines geeigneten Antagonisten sowie des Dosisverhältnisses in der Zubereitung wird der Erfolg dieser Strategie abhängen.

[0016] Wenn auch Buprenorphin - gegebenenfalls in Form eines seiner therapeutisch akzeptablen Salze - der am meisten bevorzugte Wirkstoff ist, betrifft die Erfindung auch solche Wirkstoffe, die dem Buprenorphin pharmakologisch ähnlich oder vergleichbar sind, da die beschriebenen Vorteile der Erfindung, wenn auch in unterschiedlichem Ausmaße, auch hier zum Tragen kommen können. Insbesondere sind weitere geeignete Wirkstoffe, die hier auch als "pharmakologisch ähnlich oder vergleichbar " bezeichnet sind, solche, die den Opiaten oder Opioiden zuzurechnen sind, da viele von ihnen nicht nur pharmakodynamisch, sondern auch pharmakokinetische Ähnlichkeiten mit Buprenorphin aufweisen, also eine relativ niedrige Dosis, eine gute Membrangängigkeit und einen hohen First-Pass-Effekt. Insbesondere bevorzugt sind Morphin- oder Dihydromorphinderivate sowie Substanzen aus der Methadon und aus der Fentanylgruppe.

[0017] Um einer mißbräuchlichen oder nicht bestimmungsgemäßen Anwendung keinen Vorschub zu leisten, wird die erfindungsgemäße Arzneizubereitung in der Regel dosisweise vorzerteilt und voneinander separiert in einer geeigneten Verpackung vorliegen, so daß zur Entnahme einer Dosiseinheit jeweils nur diese entnehmbar gemacht wird, wie etwa im Falle einer Blisterpackung, in welcher jede Dosiseinheit in einem Tiefziehnapf einzeln eingesiegelt ist. Im Rahmen von Programmen zur Behandlung der Opiatoder Cocainabhängigkeit kann es jedoch auch sinnvoll sein, z. B. den betreuenden Ärzten die Zubereitung in Form von Verpakkungseinheiton anzubieten, in denen sie als unzerteiltes blatt- oder bandförmiges Material vorliegt, von welchem sich die Dosiseinheiten zum Zwecke der Applikation abteilen lassen. Dies erleichtert eine Massenapplikation und gibt den verabreichenden Ärzten die Möglichkeit, unterschiedliche Dosiseinheiten je nach Dosisbedarf aus ein und demselben Material abzuteilen.

[0018] Da von der erfindungsgemäßen Arzneizubereitung ein gegenüber bekannten Zubereitungen erhöhtes Ausmaß der Bioverfügbarkeit zu erwarten ist, muß die Dosierung gegebenenfalls angepaßt werden. Im Falle des Buprenorphins wird die analgetische Einzeldosis bei 0,1 bis 1 mg liegen, in der Suchttherapie bzw. Substitutionstherapie jedoch möglicherweise deutlich höher.

Die Herstellung der Arzneizubereitung erfolgt erfindungsgemäß in mehreren Schritten. Zur Herstellung des bahnförmigen Ausgangsmaterials, aus dem zuletzt entweder die Einzeldosen oder aber ganze Verpakkungseinheiten durch Schneiden oder Stanzen abgeteilt werden, sind zwei grundlegende Verfahrensvarianten geeignet. Die erste Gruppe von Verfahren umfaßt jene, bei denen mit wässrigen bzw. lösemittelhaltigen Flüssigkeiten teilweise höherer Viskoität ein Band oder eine Prozessfolie gleichmäßig beschichtet und anschließend einem Trocknungsprozeß unterworfen wird. Hierzu wird zunächst die Beschichtungsmasse hergestellt, wozu mindestens ein wasserlösliches, zur Filmbildung befähigtes Polymer, der oder die Wirkstoffe und eine geeignete, verdampfbare Flüssigkeit innig gemischt werden müssen. Bedarfweise können weitere Hilfsstoffe wie zerfallmodifizierende Polymere, Weichmacher, Füllstoffe, texturvermittelnde Substanzen, Pigmente, Farbstoffe, Geschmackkorrigenzien, Löslichkeitsvermittler, Substanzen zur Einstellung des pH-Wertes, Glättungsmittel, Mattierungsmittel, Zerfallbeschleuniger etc. eingearbeitet werden. Alternativ läßt sich das bahnförmige Ausgangsmaterial durch thermoplastische Formung, d. h. ohne Zuhilfenahme von Flüssigkeiten herstellen. Hierzu gehören alle Hot-Melt-Beschichtungs- und alle Extrusionsverfahren. Eine Voraussetzung ist in diesem Fall, daß das zur Filmbildung befähigte Polymer oder Polymergemisch thermoplastisch formbar ist. Die erforderlichen Zutaten werden gemischt und unter Einwirkung von Druck und/oder Wärme durch Extrudieren, Blasen oder durch Beschichten von Bändern oder Folien geformt und nach dem Erstarren der weiteren Verarbeitung zugeführt. Für die Herstellung von erfindungsgemäßen Zubereitungen mit mehrschichtigem Aufbau eignen sich entsprechend modifizierte Verfahren, wobei es unerheblich ist, ob mehrere bahnförmige Materialien gleichzeitig oder nacheinander hergestellt und zusammengefügt werden.

Patentansprüche

1. Buccale Arzneizubereitung zur Bekämpfung starker Schmerzzustände oder Suchttherapie mit Buprenorphin, Morphin-, Dihydromorphin-Derivaten, Substanzen aus der Methadon- oder Fentanylgruppe oder als therapeutisch geeignetes Salz als Wirkstoff, **gekennzeichnet durch** eine im wäßrigen Medium der Mundhöhle zerfallfähige oblatenförmige Darreichungsform mit einer mucoadhäsiven, wirkstoffhaltigen Schicht auf der Basis von wasserlöslichen, filmbildenden Polymeren für die rasche Wirkstoffübertragung **durch** kurze Diffusionswege bei einer der wirksamen Dosis angemessenen großen Fläche, wobei die Darreichungsform eine der mucoadhäsiven Fläche entgegengesetzte nicht-mucoadhäsive Außenschicht mit geringerer Permeabilität für den Wirkstoff aufweist.

2. Arzneizubereitung nach Anspruch 1, **gekennzeichnet durch** einen zwei oder mehrschichtigen

Aufbau mit einer mucoadhäsiven wirkstoffhlatigen Schicht auf der Basis von wasserlöslichen, filmbildenden Polymeren für die rasche Wirkstoffaufnahme **durch** kurze Diffusionswege.

3. Arzneizubereitung nach Anspruch 1 oder 2, **gekennzeichnet durch** einen Einzeldosen-Buprenorphingehalt von 0,1-1 mg.

4. Arzneizubereitung nach einem der vorangehenden Ansprüche, **dadurch gekennzeichnet, daß** sie durch den Zusatz eines haftungsvermittelnden Hilfsstoffes oder Hilfsstoffgemisches mit bio- bzw. mucoadhäsiven Eigenschaften ausgerüstet ist.

5. Arzneizubereitung nach Anspruch 4, **dadurch gekennzeichnet, daß** als weiterer Wirkstoff ein Opiatantagonist oder partieller Opiatantagonist vorhanden ist.

Claims

1. Buccal pharmaceutical preparation for treating acute conditions of pain or for addiction therapy, comprising as active substance buprenorphine, morphine, dihydromorphine derivatives, substances from the methadone or fentanyl groups as such or as a therapeutically suitable salt, **characterized by** a wafer-shaped administration form, disintegratable in the aqueous medium of the oral cavity, which has a mucoadhesive, active substance-containing layer based on water-soluble, film-forming polymers, for rapid active substance transfer through short diffusion paths, while having a large surface appropriate to the effective dose, the said administration form having a non-muco-adhesive outer layer, opposed to the mucoadhesive surface, which outer layer has a lower permeability to the active substance.

2. Pharmaceutical preparation according to claim 1, **characterized by** a two- or multi-layered structure having a mucoadhesive active substance-containing layer based on water-soluble, film-forming polymers for rapid active substance uptake through short diffusion paths.

3. Pharmaceutical preparation according to claim 1 or 2, **characterized by** a single-dose buprenorphine content of 0.1-1 mg.

4. Pharmaceutical preparation according to any one of the preceding claims, **characterized in that** it is equipped with bioadhesive or mucoadhesive properties by the addition of an adhesion-promoting auxiliary substance or auxiliary substance mixture.

5. Pharmaceutical preparation according to claim 4, **characterized in that** as a further active substance an opiate or a partial opiate antagonist is present.

Revendications

1. Préparation médicamenteuse destinée à être libérée dans la cavité buccale et à soulager des douleurs intenses ou à traiter une toxicomanie, qui comprend, en tant que principe actif, de la buprénorphine, des dérivés de la morphine et de la dihydromorphine, des substances du groupe de la méthadone ou du fentanyle, ou leurs sels thérapeutiquement appropriés, **caractérisée par** une forme galénique de type cachet apte à se désintégrer dans le milieu aqueux de la cavité buccale, qui porte une couche mucoadhésive contenant le principe actif, à base de polymères filmogènes hydrosolubles, permettant un transfert rapide du principe actif par un court trajet de diffusion, avec une surface dont les dimensions sont ajustées en fonction de la dose efficace, la forme galénique présentant une couche extérieure non-mucoadhésive, opposée à la surface mucoadhésive et moins perméable au principe actif.

2. Préparation médicamenteuse selon la revendication 1, **caractérisée par** une structure bicouche ou multicouche qui comprend une couche mucoadhésive contenant le principe actif, à base de polymères filmogènes hydrosolubles, permettant un transfert rapide du principe actif par un court trajet de diffusion.

3. Préparation médicamenteuse selon la revendication 1 ou 2, **caractérisée par** une teneur en buprénorphine correspondant à une dose individuelle de 0,1-1 mg.

4. Préparation médicamenteuse selon l'une quelconque des revendications précédentes, **caractérisée en ce que**, par suite de l'addition d'un adjuvant ou d'un mélange d'adjuvants favorisant l'adhérence, elle présente des propriétés bio- et/ou mucoadhésives.

5. Préparation médicamenteuse selon la revendication 4, **caractérisée en ce que** comme principe actif supplémentaire, elle contient un antagoniste des opiacés ou un antagoniste partiel des opiacés.

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(54) Buprenorphine- wafer for drug substitution therapy

(57) The present invention relates to oral pharmaceutical dosage forms comprising buprenorphine with the dosage form releasing buprenorphine instantly upon oral, preferably sublingual, application of the dosage form. The present invention also relates to the use of such dosage forms for treating pain in a human or animal or for drug substitution therapy in drug-dependent human subjects.

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Description

[0001] The present invention relates to oral pharmaceutical dosage forms comprising buprenorphine with the dosage form releasing buprenorphine instantly upon oral, preferably sublingual, application of the dosage form. The present invention also relates to the use of such dosage forms for treating pain in a human or animal or for drug substitution therapy in drug-dependent human subjects.

Background of the Invention

[0002] Chronic pain, which may be due to idiopathic reasons, cancer or other diseases such as rheumatism and arthritis, is typically treated with strong opioids.

[0003] Over the last decades prejudices in the medical community as to the use of strong opioids for treating chronic pain in patients has significantly decreased. Many of these prejudices were due to some of the characteristics being inherent to opioids.

[0004] While opioids have always been known to be useful in pain treatment, they also display an addictive potential in view of their euphorigenic activity. Thus, if opioids are taken by healthy human subjects with a drug seeking behaviour they may lead to psychological as well as physical dependence.

[0005] These usually undesired characteristics of opioids can however become important in certain scenarios such as drug substitution therapies for drug addicts. One of the fundamental problems of illicit drug abuse by drug addicts ("junkies") who are dependent on the constant intake of illegal drugs such as heroin is the drug-related criminal activities resorted to by such addicts in order to raise enough money to fund their addiction. The constant pressures upon addicts to procure money for buying drugs and the concomitant criminal activities have been increasingly recognised as a major factor that counteracts efficient and long-lasting withdrawal and abstinence from drugs.

[0006] Therefore, programmes have been developed, particularly in the United States and western European countries, in which drug addicts are allowed to take prescription drugs under close supervision of medical practitioners instead of illegal drugs such as street heroin.

[0007] The aim of drug substitution theory is thus to first enable addicts to lead a regular life by administering legal drugs to prevent withdrawal symptoms, but because of their legal character and prescription by medical practitioners do not lead to the aforementioned described drug-related criminal activities. In a second and / or alternate step in the treatment of drug addiction may be to slowly make the drug addict less dependent on the drug by gradually reducing the dose of the substitution drug or to bridge the time until a therapy place in a withdrawal programme is available.

[0008] The standard drug used in drug substitution therapy programmes has for a long time been methadone. However, in recent years the potential of other opioids as substitution drugs in substitution therapy has been recognised. A particularly suitable drug for that purpose is the opioid buprenorphine, which is a mixed opioid agonist/antagonist.

[0009] Nowadays, buprenorphine preparations are administered in drug substitution programmes in the form of a tablet for sublingual administration. One of the reasons that the tablets are formulated for sublingual administration is that this the preferred route of administration for buprenorphine. Furthermore, if a patient swallows such tablets they will not provide euphorigenic activity.

[0010] One example of sublingual tablets for drug substitution therapy is the preparation Subutex® (being marketed in Germany by Essex Pharma).

[0011] Nevertheless, drug addicts sometimes still try to divert these sublingual buprenorphine tablets by removing them from the mouth when the supervising healthcare professional's attention is directed to other activities. Later the tablets may be sold or the active agent buprenorphine isolated/extracted to apply it parenterally.

[0012] Another buprenorphine preparation aimed at preventing this potential possibility of abuse has recently gained administrative approval in the United States (Suboxone®). The Suboxone® preparation comprises buprenorphine hydrochloride and the opioid antagonist naloxone hydrochloride dihydrate. The presence of naloxone is intended to prevent parenteral abuse of buprenorphine as parenteral co-administration of buprenorphine and naloxone in e.g. an opioid-dependent addict will lead to serious withdrawal symptoms.

[0013] However, there remains a need for other diversion and / or abuse-resistant dosage forms of buprenorphine, which can be used in drug substitution therapy as described above. Additionally, it would be desirable to have a buprenorphine preparation available which is diversion and / or abuse-resistant in cases where the preparation is used for drug substitution therapy and which could also provide efficient analgesia in cases where the preparation is administered to alleviate pain in a patient.

Object and Summary of the Invention

[0014] It is an object of the present invention to provide an oral pharmaceutical dosage form of the active agent buprenorphine that is less prone to diversion and / or abuse in drug substitution therapy. It is another object of the present invention to provide an oral dosage form of the active agent buprenorphine that can be used for drug substitution therapy and/or pain treatment.

[0015] In one embodiment the present invention relates to an oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof with a dosage form releasing buprenorphine or said pharmaceutically acceptable salt thereof instantly upon or oral, preferably sublingual, application of the dosage form. It is, however, understood that the invention and its various embodiments which are set out below,

can be extended to any opioid or analgesic whose preferred route of administration is oral, prefereably sublingual, as is the case for buprenorphine.

[0016] An instant release of buprenorphine or a pharmaceutically acceptable salt thereof upon oral, preferably sublingual, application means that substantially all of the buprenorphine or said pharmaceutically acceptable salt thereof will be released within less than three minutes, preferably within less than two minutes or less than one minute. Even more preferably, substantially all of the buprenorphine or said pharmaceutically acceptable salt thereof will be released within less than thirty seconds, twenty seconds, ten seconds or even within less than five seconds after oral, preferably sublingual, application of the dosage form. In one of the preferred embodiments these oral dosage forms will comprise between approximately 0.1 mg and approximately 16 mg buprenorphine or the equivalent amounts of a pharmaceutically acceptable salt thereof.

[0017] In a further preferred embodiment these oral pharmaceutical dosage forms will achieve an average C_{max} of between 1.5 ng/ml and approximately 2.25 ng/ml in the case of a dose of 0.4 mg buprenorphine hydrochloride being administered. In the case of a dose of 8 mg buprenorphine HC1 being administered, the C_{max} will typically be between approximately 2.5 and 3.5 ng/ml and if a dose of 16 mg buprenorphine hydrochloride is administered the C_{max} will preferably be between 5.5 to 6.5 ng/ml.

[0018] Yet another preferred embodiment of the invention relates to oral pharmaceutical dosage forms which may provide for the above-mentioned characteristics and/or an average Tmax of from approximately 45 to approximately 90 minutes.

[0019] In a particularly preferred embodiment the dosage forms will additionally comprise an opioid antagonist, preferably naloxone or a pharmaceutically acceptable salt thereof.

[0020] In yet a further preferred embodiment, the pharmaceutical dosage form will comprise buprenorphine and the opioid antagonist, which preferably is naloxone, in a weight ratio of from approximately 1:1 to approximately 10:1.

[0021] One embodiment of the present invention also relates to oral pharmaceutical dosage forms, which may have some or all of the aforementioned characteristics and wherein the dosage form has a film-like or wafer-like shape.

[0022] Another embodiment relates to a method of manufacturing the afore-mentioned described dosage forms.

[0023] Embodiments of the present invention also relate to the use of the afore-described oral, preferably sublingual, pharmaceutical dosage forms in the manufacture of a medicament for treating pain in a human or animal and/or for drug substitution therapy in drug-dependent human subjects.

[0024] One aspect of the invention also relates to a method of drug substitution therapy in drug-dependent human subjects wherein the aforementioned oral pharmaceutical dosage forms are administered to a drug-dependent subject in need thereof.

Detailed description of the invention

[0025] From the prior art, sublingual tablets are known under the trade names Subutex® or Suboxone® both of which comprise the active agent buprenorphine hydrochloride for drug substitution therapy.

[0026] The suitability of particularly buprenorphine for drug substitution therapy had been recognised early on in view of buprenorphine's very long elimination half-life (reported as approximately 20 to 37 hours), which allows a reduced frequency of administration. As a consequence drug addicts who participate in drug substitution therapy have to report less frequently to the medical agency or healthcare professional supervising the substitution programme.

[0027] Furthermore, the sublingual absorption of buprenorphine has the advantage that an abuse by swallowing tablets of buprenorphine is less likely to occur. The tablets that are currently on the market in the form of Subutex® and Suboxone® preparations are both for sublingual administration and typically disintegrate over a time period of five to ten minutes. However, within that time period the drug addict may be able to divert the tablet before subsequently either selling the tablets on the street or isolating the active agents therefrom.

[0028] In order to reduce of eliminate these problems, the present invention provides oral pharmaceutical dosage forms which comprise the active agent buprenorphine and which release buprenorphine instantly after oral, preferably sublingual, administration of the drug.

[0029] It is understood that if reference is made in the context of this invention to the term "buprenorphine" this refers to the free base as well as to any pharmaceutically acceptable salt thereof such as the hydrochloride, sulfate, bisulfate, tartrate, nitrate, citrate, bitartrate, phosphate, malate, maleate, hydrobromide, hydroiodide, fumarate, succinate salts and the like.

[0030] A particularly preferred pharmaceutically acceptable salt of buprenorphine is buprenorphine hydrochloride.

[0031] The provision of a pharmaceutical dosage form comprising buprenorphine or a pharmaceutically acceptable salt thereof in e.g. film-like or wafer-like shapes which allows for instant release of the active agent upon oral, preferably sublingual, administration of the dosage form should prevent the type of abuse resulting from illicit diversion of the tablets by drug addicts participating in drug substitution therapy programmes.

[0032] In the context of the present invention instant release means that substantially the whole amount of the buprenorphine or the respective pharmaceutically acceptable salt thereof will be released in less than five minutes. Preferably, substantially all of the buprenor-

phine or its pharmaceutically acceptable salt thereof will be released within less than four, within less than three, within less than two and more preferably within less than one minute.

[0033] In a particularly preferred embodiment, instant release refers to the situation that substantially all of the buprenorphine or the respective pharmaceutically acceptable salt thereof will be released within less than thirty seconds, within less than twenty seconds, or within less than ten seconds. In an even more preferred embodiment, the term "instant release" means that substantially all of the buprenorphine will be released from the dosage form within less than five seconds or within less than three seconds.

[0034] The term "substantially all" means that approximately 95% of the drug will have been released.

[0035] The term "approximately" in the context of the present invention describes a deviation from the indicated value of 10% and preferably of 5%.

[0036] Such efficient release of the drug is hard to achieve with a sublingual tablet which generally requires a greater amount of time to melt or to disintegrate.

[0037] Fast-dissolving or rapidly disintegrating dosage forms for other pharmaceutically active compounds are known which disintegrate within seconds upon contact with the mucosal saliva of the mouth and particularly the sublingual mucosa.

[0038] These pharmaceutical dosage forms and formulation principles are well known to the person skilled in the art and will be described in more detail below.

[0039] As regards the dosage amount, the pharmaceutical compositions in accordance with the present invention will typically comprise between approximately 0.1 mg and approximately 16 mg of buprenorphine or a pharmaceutically acceptable salt thereof such as buprenorphine hydrochloride. Preferred dosage amounts will be in the range of between approximately 0.4 mg and approximately 12 mg or between approximately 2 mg and approximately 8 mg buprenorphine or a pharmaceutically acceptable salt thereof.

[0040] The oral pharmaceutical dosage forms in accordance with the invention may have the further characteristic of providing a C_{max} of approximately 1.5 to 2.5 ng/ml in the case of a dose of 4 mg buprenorphine hydrochloride being administered. A preferred C_{max} in the case of a dose of 4 mg of buprenorphine hydrochloride being administered may be approximately between 1.7 ng/ml to 2 ng/ml.

[0041] In the case of a dose of 8 mg buprenorphine hydrochloride being administered, the C_{max} may be approximately between 2.5 and 3.5 ng/ml. In a preferred embodiment the C_{max} may be approximately between 2.75 ng/ml and 3.25 ng/ml in the case of a dose of 8 mg buprenorphine hydrochloride being administered.

[0042] In case of a dose of 16 mg buprenorphine hydrochloride being administered, the C_{max} may preferably be in the range of approximately 5 to 7 ng/ml. In a preferred embodiment the C_{max} may be between 5.5 and 6.5 ng/ml if 16 mg of buprenorphine hydrochloride are administered.

[0043] The AUC_{0-48} (i.e. the Area under the Curve for 48 hours after administration) may in the case of administration of 4 mg of buprenorphine hydrochloride be in the range of approximately 10 to 15 hours x ng/ml. In a preferred embodiment the AUC_{0-48} may be approximately 12 to 13 hours x ng/ml. In the case of 8 mg buprenorphine hydrochloride being administered the AUC_{0-48} may be approximately in the range of 15 to 25 hours x ng/ml. In a preferred embodiment the AUC_{0-48} in this case may be between approximately 20 to 22 hours x ng/ml. In the case of 16 mg buprenorphine hydrochloride being administered, the AUC_{0-48} may be in the range of 25 to 40 hours x ng/ml. In a preferred embodiment the AUC_{0-48} in this case may be in the range of approximately 30 to 35 hours x ng/ml.

[0044] The average T_{max} values for such preparations will preferably be from approximately 45 to approximately 90 minutes.

[0045] It is understood that the aforementioned pharmacokinetic parameters C_{max} and AUC_{0-48} are average values that are obtained by measuring the blood plasma levels in a group of eight to approximately twenty-four patients. These patients will be selected according to inclusion and exclusion criteria, as they are common for drug substitution programmes. It is understood that such patients typically will be of average weight and Caucasian origin.

[0046] The pharmaceutical dosage form in accordance with the invention will be administered such that the maximal dosage per day is 32 mg of buprenorphine. Once a patient is enrolled in substitution therapy, the initial dosage will be typically between 2 mg to 4 mg of buprenorphine. The formulations may be administered once a day, every two days, preferably every three days or even less fequently.

[0047] In a preferred embodiment, the oral dosage forms of the invention will additionally comprise an opioid antagonist. Such antagonists may be selected from the group comprising naltrexone, naloxone, nalmefene, nalorphine, nalbuphine, naloxoneazinen, methylnaltrexone, ketylcyclazocine, norbinaltorphimine, naltrindol, 6-β-naloxol and 6-β-naltrexol or the pharmaceutically acceptable salts thereof.

[0048] Especially preferred antagonists comprise naltrexone, nalmefene and naloxone. Specifically preferred as an antagonist is naloxone and its hydrochloride salt.

[0049] It is understood, that if in the context of the present invention reference is made to an opioid antagonist, this also not only refers to the free base but also to pharmaceutically acceptable salts thereof such as those mentioned for buprenorphine.

[0050] A particularly preferred antagonist is naloxone. Of the naloxone salts, naloxone hydrochloride dihydrate may be particularly preferable in combination with buprenorphine hydrochloride.

[0051] The pharmaceutical dosage forms in accord-

ance with the invention will comprise buprenorphine and the antagonist, which preferably is naloxone, in a weight ratio of from 1:1 to 10:1. A weight ratio of from 2:1 to 8:1 may be preferred, with a weight ratio of 4:1 being particularly preferred.

[0052] Thus, if an oral dosage form in accordance with the present invention for example comprises 2 mg buprenorphine hydrochloride it will comprise approximately 0.5 mg naloxone. If the dosage form comprises 0.4 mg buprenorphine hydrochloride, it will comprise 0.1 mg naloxone and if the dosage form comprises 8 mg buprenorphine hydrochloride it will comprise e.g. 2 mg naloxone hydrochloride.

[0053] A particularly preferred embodiment thus relates to an oral dosage form comprising buprenorphine, preferably buprenorphine hydrochloride, and naloxone, preferably naloxone hydrochloride, wherein the dosage form releases said active agents within less than one minute, preferably within less than thirty seconds and more preferably within less than ten seconds after sublingual application of the dosage form. In addition, the dosage forms may provide the preferred values of the aforementioned pharmacokinetic parameters C_{max}, and AUC_{0-48}.

[0054] Thus, the person skilled in the art will have to ensure that indeed an oral dosage form is used which is able to allow for incorporation of sufficient amounts of buprenorphine and preferably also of naloxone and which at the same time disintegrates rapidly enough to release the active agents instantly.

[0055] In one embodiment one may use non-gelatin film materials, e.g. films of modified cellulose materials as dosage forms. In this case, buprenorphine and optionally opioid antagonists such as naloxone are incorporated into the film matrix and films thus prepared may be administered orally.

[0056] In accordance with this aspect of the invention, the active ingredients may be dissolved in a hydrophilic, organic system to form a homogenous solution or dispersion. The solution or dispersion can then be applied to one or more surfaces of a non-gelatin polymeric film, e.g. a dry cellulose ether film, resulting in the active ingredient(s) and/or liquid carrier phase being transported through the surface of the "dry" film resulting in a new film composition.

[0057] The film substrate may remain completely intact or relatively physically unchanged immediately following the incorporation process. It can, however, be converted to any size or shape of unit dosage form. Alternatively, the film substrate may liquefy or dissolve partly or fully during the incorporation process, but nevertheless finally forming a single discrete film, after curing. Films according to this aspect of the invention are typically made up of one or more soluble polymer or polymers which will otherwise degrade at the intended site of release after administration in the mouth, e.g. sublingual administration, in order to provide the instant release of the active agents. Suitable cellulose ether film bases include e.g. hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), hydroxyethylmethylcellulose (HEMC), hydroxyethylcellulose (HEC), methylcellulose (MC), carboxymethylcellulose (CMC) and salts and derivates of all of the aforesaid materials. A particularly suitable cellulose ether for forming the film is HPMC.

[0058] Optional ingredients may be added including colorants, emulsifiers, humectants, and antiblocking agents.

[0059] Once one has a film being based on a cellulose ether available, in a next step the active ingredient(s) will be applied in the form of a liquid to the film. Appropriate means of liquid application onto the film substrate include extrusion, roller application, pouring, spraying, brush painting or whipping. Further details of the preparation of such films can be taken e.g. from WO 2005/079750 A2 which is incorporated by reference herewith.

[0060] Another possible technology in order to provide the afore-described pharmaceutical dosage forms of buprenorphine and preferably naloxone is described in WO 03/030883. In this latter embodiment of the present invention, a thin film drug delivery composition includes (i) a flowable water-soluble film-forming matrix and (ii) the active agent(s) uniformly stationed therein. Optionally a taste-masking agent may be coated or intimately associate with the active agent(s) to provide taste masking of the active agent(s). The flowable water-soluble film-forming matrix together with the active agent(s) is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

[0061] The matrix may be a cellulosic material, a gum, a protein, a starch, a glucan and combinations thereof. For example one may use the already aforementioned methylcellulose, HMC, HEC, HC, HPC, HPMC, HMPC, gum Arabic, xanthan gum etc. The films are prepared according to standard technology and the active agents are displaced thereon and therein as described in WO 03/030883.

[0062] Yet another interesting technology relates to immediate release drug delivery forms as described in WO 99/17744, which is also incorporated by reference herein as far as it describes fast releasing oral dosage forms. The person skilled in the art will understand that the processes and dosage forms in WO 99/17744 may be used to obtain the aforementioned described pharmaceutical dosage forms of buprenorphine and preferably also naloxone.

[0063] One may of course also use fast disintegrating tablets that disintegrate upon contacting the saliva, e.g. under the tongue, following oral administration. Such fast-disintegrating tablets are described e.g. in WO 99/44580 and are well known to the person skilled in the art.

[0064] A particularly interesting technology for fast-releasing dosage forms that may be used for the purpose of the present invention to provide an oral dosage form of buprenorphine and preferably an opioid antagonist such as naloxone can be taken from WO 96/26720.

[0065] Therein it is described how the active agent selegiline is formulated into a rapidly releasing dosage form that can be used e.g. for sublingual administration. WO 96/26720 describes in detail a "fast-dispersing dosage form" with the term encompassing all types of dosage forms being described in US patent 5,120,549, US 5,079,018, WO 93/12769, US 5,298,261 and WO 91/04757.

[0066] As for WO 96/26720 in the case of the active agent selegiline, the present invention contemplates particularly using fast-dispersing dosage forms as described in UK patent number 1548022, that is, a solid fast-dispersing dosage form comprising a network of the active ingredient(s) and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

[0067] It is preferred that such a composition in accordance with the invention disintegrates within one to ten seconds, and particularly within two to eight seconds of being placed in the oral cavity and particularly sublingually.

[0068] The composition will preferably contain in addition to the active ingredient, matrix forming agents and secondary components.

[0069] Matrix forming agents suitable for use in this aspect of the present invention include materials derived from animal or vegetable proteins, such as gelatins, dextrins and soy, wheat and psyllium seed proteins, gums such as acacia, guar, agar, and xanthan, polysaccharides, alginates, carboxymethylcelluloses, carrageenans, dextrans, pectins, synthetic polymers such as polyvinylpyrrolidone, and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

[0070] Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

[0071] One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension.

[0072] Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame and thaumatin. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

[0073] Such fast-dispersing dosage forms containing buprenorphine and preferably an opioid antagonist such as naloxone may be similarly obtained as described in GB 1548022B or WO 96/26720, in particular Example 1 of the latter, which are incorporated herein in their entirety.

[0074] A particularly preferred embodiment of the present invention relates to dosage forms, which are produced along the lines described in WO 03/070227 A1.

[0075] This prior art reference describes taste-masked, film-type or wafer-type medicinal preparations. It is to be understood that the dosage forms in accordance with the present invention may preferably be such film-type or wafer-type medicinal preparations with the taste-masking being only an optional feature.

[0076] Flat active agent carriers that have a film-type or wafer-type structure provide for various advantages. As a consequence of the low thickness in comparison to the surface area, there is only a short diffusion pathway if such a dosage form is applied e.g. to the mucosa of the oral cavity. This typically leads to a very rapid release of the active agents which can then be quickly, efficiently and directly absorbed by the mucosa of the oral cavity and particularly sublingually if the active agent is absorbable at all via that route. Thus, in case of buprenorphine such very flat film-type or wafer-type dosage forms are highly desirable as they will allow for the provision of an instant release of active ingredient, thereby minimising the abuse problems encountered with the formulations of the prior art.

[0077] Flat active agent carriers have been developed for different purposes. One of the basic prior art references in this context is DE 27 46 414 in which active agent, binding agent and additional excipients are processed to yield a dosage form in the form of film-type strand.

[0078] One of the advantages of wafer-type pharmaceutical dosage forms as described in WO 03/070227 A1 is that there is a direct correlation between the amount of the active agent and the length of a certain part of the strand in view of the homogenous thickness, density and width. Thus, one can easily obtain a certain unit dosage by simply cutting the wafer-like dosage form in to appropriately sized pieces.

[0079] Such film-type or wafer-type dosage forms in accordance with the present invention are characterised in that they comprise a matrix which is formed from at least one matrix-forming polymer and in which buprenorphine and preferably an opioid antagonist such as

naloxone are dissolved or homogenously dispersed.

[0080] The rapidly disintegrating matrix of the pharmaceutical dosage forms in accordance with the invention comprises as one of its basic substances water-soluble polymers or mixtures of such polymers. Preferably synthetic or partially synthetic polymers or naturally occurring biopolymers are used which can form films and are water-soluble. Particularly suitable for this purpose are polymers which may be selected from the group comprising cellulose derivatives, polyvinylalcohol, polyacrylates and polyvinylpyrrlidone.

[0081] Within the cellulose derivatives, hydroxypropylmethylcellulose, carboxymethylcellulose, sodium carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, methylcellulose, and hydroxypropylmethylcellulose may be used. One may also use water-soluble polysaccharides being derived from plants or microbes. Preferred polysaccharides include pullulan, trantan, alginate, dextrin and pectins.

[0082] One may also use proteins and preferably gelatin or other gel-forming proteins. One may also use starch and starch derivatives, gelatin, polyvinylpyrrilidone, gum Arabic, pullulan, acrylates, polyethylene oxide with a particular focus on polyox 10, polyox 80, polyox 205, polyox 301, polyox 750 or copolymers of methylvinylether and maleic acid anhydride.

[0083] The person skilled in the art will appreciate that the extent to which buprenorphine and optionally an opioid antagonist such as naloxone are instantly released depends in part on the type of matrix-forming polymer chosen. For example, a dosage form using polyvinylalcohol as matrix-forming polymer may disintegrate faster than a dosage form using HPMC as matrix-forming polymer. The disintegration time may be adjusted by mixing a combination of different polymers in suitable amounts.

[0084] The person skilled in the art also knows disintegrating agents, which can "pull" water into the matrix which then pushes the dosage forms apart. Thus, such disintegrating agents may also be used for adjustment of the disintegration time.

[0085] In order to allow absorption of buprenorphine over the mucosa of the mouth, and particularly sublingually, in one embodiment the dosage forms may additionally use agents that enhance absorption of the active agent, i.e. so-called permeation enhancers.

[0086] Such permeation enhancers may be selected from the group comprising propandiol, dexpanthenol, and oleic acid. The permeation enhancers may also be selected from the group comprising saturated or unsaturated fatty acids, hydrocarbons, linear or branched fatty alcohols, dimethylsulfoxide, propylene glycol, decanol, dodecanol, 2-octyldodecanol, glycerine, ethanol or other alcohols.

[0087] According to a preferred embodiment the film-type or wafer-type oral dosage forms of the present invention in the presence of saliva can disintegrate within e.g. one second to three minutes or within five seconds to one minute or five seconds to thirty seconds.

[0088] The disintegration times of the oral dosage forms in accordance with the invention are measured according to the European pharmacopoeia, 4th edition 2002.

[0089] In the present case where the active agent buprenorphine is administered sublingually, the dosage forms in accordance with the invention may additionally comprise an excipient that mediates adhesion to the respective mucosa. Examples of such muco-adhesive substances are e.g. polyacrylic acid, carboxymethylcellulose, hydroxymethylcellulose, methylcellulose, alginic acid, gelatin and gum Arabic.

[0090] The thickness of the film-type or wafer-type dosage forms in accordance with the invention may typically be between 5 μm and 10 mm, 30 μm and 2 mm, or 0.1 mm and 1 mm. The dosage forms may be round, oval, elliptic, or may have a triangular, quadrangular, or multiangular form. Typically the surface of the pharmaceutical dosage forms in accordance with the invention is flat.

[0091] As stated above, the film-type or wafer-type matrix of the dosage forms of this aspect of the invention comprises at least one matrix-forming polymer. The matrix-forming polymer(s) are an essential component of the matrix.

[0092] The polymer amount within the matrix may be between approximately 3 % by weight and approximately 98% by weight and preferably between 7 and 80 % by weight and even more preferably between 20 and 50% by weight, the weight percentages being based on the total weight of the dosage forms.

[0093] The mucoadhesive properties as well as the disintegrating properties are to a large extent determined by the type of matrix-forming polymer(s), as well as the relative amount of the polymer(s) used in the dosage forms.

[0094] Besides the matrix-forming polymers, buprenorphine and optionally an opioid antagonist, further excipients may be present within the matrix.

[0095] These additional excipients may be filling agents such as SiO_2, colorants and pigments (such as TiO_2) disintegrating agents particularly those which attract water (such Aerosil), emulsifying agents, plasticizers, sweeteners or conserving agents. Additionally, auxiliary excipients such as stabilising agents or antioxidants may be added.

[0096] If a taste-masking effect is to be obtained, the dosage form in accordance with this aspect of the invention may comprise additionally a carbon dioxide-forming agent that upon contact with the saliva develops carbon dioxide. Such carbonates are well known in the prior art from effervescent formulations and include e.g. sodium hydrogen carbonate, sodium carbonate, potassium hydrogen carbonate or potassium carbonate. In order to enhance CO_2 development, one may add acidic components such as e.g. sodium dihydrogen- or disodiumhydrogen phosphate, sodium tatrate, sodium ascorbate etc. One may of course also use citric acid, tartartic acid, adipinic acid, ascorbic acid, acetic acid, lactic acid etc.

[0097] Thus, one preferred embodiment of the invention relates to oral dosage forms of film-type or wafer-type film as described above which comprise buprenophine and optionally an opioid antagonist such as naloxone with the oral dosage form having the above-described characteristics as to the amount of buprenophine and the optional antagonist, the pharmacokinetic parameters C_{max} and AUC_{0-48} and the instant release of the active agents from the dosage form. The person skilled in the art will know how to produce such film-type or wafer-type dosage forms on the basis of the above-mentioned information. This may be achieved by common film-coating technologies, extrusion processes, spray drying etc. More details can be taken from WO 03/070227.

[0098] The person skilled in the art will also know other dosage forms, which allow an instant release of the active agent upon sublingual administration, so that such formulation technology may be applied to buprenorphine and optionally opioid antagonists preferably being naloxone.

[0099] In a further embodiment, the present invention relates to the use of any of the aforementioned described pharmaceutical dosage forms comprising buprenorphine and optionally an opioid antagonist being preferably naloxone for the manufacture of a medicament for drug substitution therapy. The pharmaceutical dosage forms described above may, of course, also be used in the manufacture of a medicament for treating pain. Thus, the dosage forms may be used in opioid naive patients or patients who are not dependent on opioids in order to provide fast pain relief by oral, preferably sublingual, administration of the preparations.

[0100] As far as drug substitution therapy is concerned, the effectiveness of the afore-described amounts and pharmacokinetic parameters of buprenorphine and optionally naloxone are known from the pharmaceutical preparations Subutex® and Suboxone®. Therefore it can be firmly assumed that the same efficacy will be observed in drug substitution therapy with the inventive preparations of the present invention.

[0101] One of the advantages of the preparations in accordance with the present invention is to be seen in the fact that in view of the instant release of buprenorphine, a drug addict will have a diminished chance of illicitly diverting the dosage form given that particularly the film-type and the wafer-type of dosage forms will disintegrate instantly upon contact with the saliva during sublingual administration. If an opioid antagonist such as naloxone is included in the dosage form it is additionally ensured that parenteral abuse of such dosage forms by dissolving the active agents out of the rapidly disintegrating dosage forms will be significantly diminished.

[0102] In yet a further embodiment, the present invention relates to a method of drug substitution therapy in drug addicts by administering a pharmaceutical formulation as described above which instantly releases buprenorphine and optionally an opioid antagonist being preferably naloxone upon oral, preferably sublingual, administration to a patient.

[0103] One embodiment of the present invention also relates to a method of treating pain by administering a pharmaceutical formulation as described above which instantly releases buprenorphine and optionally an opioid antagonist being preferably naloxone upon oral, preferably sublingual, administration to a patient.

[0104] The present invention has been described by reference to some of its preferred embodiments. This description is, however, in no way meant to limit the scope of the invention. Other embodiments that do not depart from the spirit of the invention should be similarly encompassed and addressed by the aforementioned description and the subsequent claims.

Claims

1. Oral pharmaceutical dosage form comprising at least buprenorphine or a pharmaceutically acceptable salt thereof wherein the dosage form releases buprenorphine or said pharmaceutically acceptable salt thereof instantly upon oral, preferably sublingual, application of the dosage form.

2. Oral pharmaceutical dosage form according to claim 1,
wherein the dosage form releases substantially all of buprenorphine or said pharmaceutically acceptable salt within less than 2 minutes, preferably within less than 1 minute and more preferably within less than 30 seconds after oral, preferably sublingual, application of the dosage form.

3. Oral pharmaceutical dosage form according to claim 1 or 2,
wherein the dosage form comprises between approximately 0.1 mg and approximately 12 mg, preferably between approximately 0.4 mg and approximately 10 mg or between approximately 2 mg and approximately 8 mg buprenorphine or the equivalent amounts of a pharmaceutically salt thereof.

4. Oral pharmaceutical dosage form according to any of claims 1 to 3,
wherein the dosage form achieves an average Cmax of between approximately 1.5 ng/ml and approximately 2.25 ng/ml in case that 0.4 mg are administered, an average Cmax of between approximately 2.5 ng/ml and approximately 3.5 ng/ml in case that 8 mg are administered or an average Cmax of between approximately 5.5 ng/ml and approximately 6.5 ng/ml in case that 16 mg are administered.

5. Oral pharmaceutical dosage form according to any of claims 1 to 4,
wherein an average Tmax from approximately 45 to

approximately 90 minutes is obtained after administration.

6. Oral pharmaceutical dosage form according to any of claims 1 to 5,
wherein the dosage form additionally comprises an opioid antagonist, preferably naloxone or a pharmaceutically acceptable salt thereof.

7. Oral pharmaceutical dosage form according to claim 6 wherein the dosage form comprises buprenorphine or a pharmaceutically acceptable salt thereof and naloxone or a pharmaceutically acceptable salt thereof in a weight ratio of between approximately 1:1 and approximately 10:1, preferably in a weight ratio of between approximately 2:1 and approximately 8:1 and more preferably in a weight ratio of approximately 4:1.

8. Oral pharmaceutical dosage form according to any of claims 1 to 7,
wherein the dosage form has a film-like or wafer-like shape of mucoadhesive properties.

9. Use of an oral pharmaceutical dosage form according to any of claims 1 to 8 in the manufacture of a medicament for treating pain.

10. Use of an oral pharmaceutical dosage form according to any of claims 1 to 8 in the manufacture of a medicament for drug substitution therapy.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 06 11 9839

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TECHNICAL FIELDS SEARCHED (IPC)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
Munich	6 February 2007	GIMENEZ MIRALLES, J

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 06 11 9839

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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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(12) UK Patent Application (19) GB (11) 2 447 016 (13) A

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A61K 31/485 (2006.01) ***A61P 29/00*** (2006.01)

(56) Documents Cited:
GB 2356348 A **GB 2150832 A**
WO 2004/014336 A3
Psychopharmacology (1999), 141 (1), 37-46, Mendelson et al, ISSN 0033-3158 - see abstract
Drug and Alcohol Dependence, (2003), 72(1), 75-83, McAleer et al, ISSN No 0376-8716 - see abstract

(58) Field of Search:
INT CL **A61K**
Other: **ONLINE - EPODOC, WPI, CAS ONLINE, BIOSIS, MEDLINE**

(54) Abstract Title: **Buprenorphine/naloxone compositions**

(57) A composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the dermis or mucosa, comprises buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1. The analgesic action of the buprenorphine is potentiated by the low dose of naloxone, which also serves to reduce the likelihood of abuse of the composition by drug addicts.

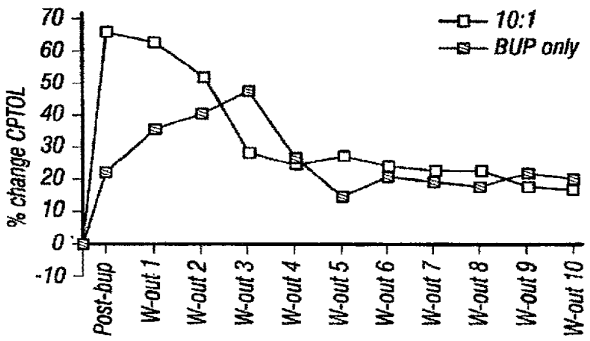

FIG. 3

GB 2 447 016 A

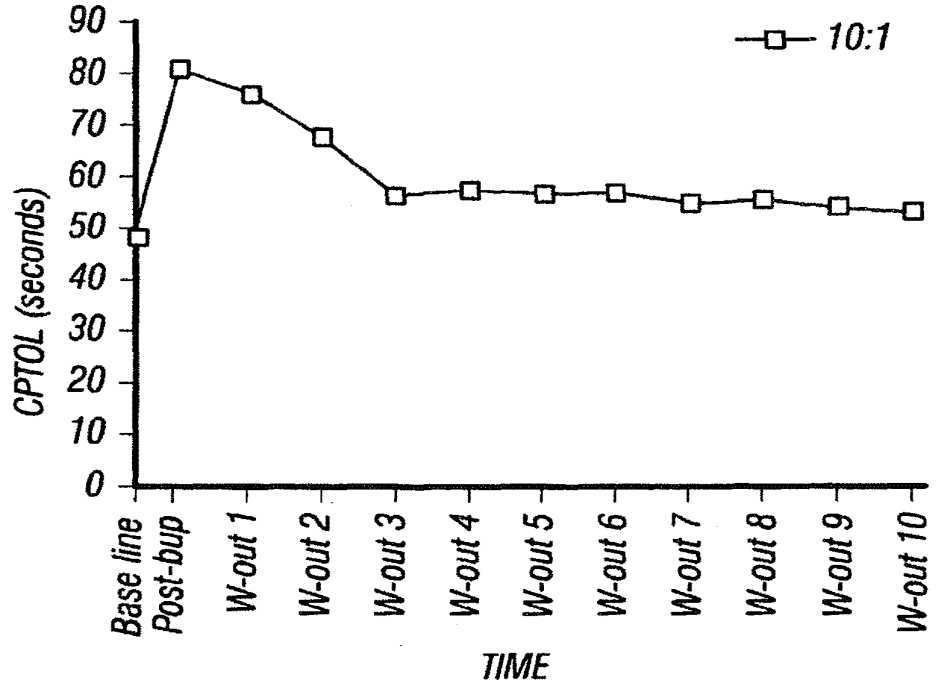

FIG. 1

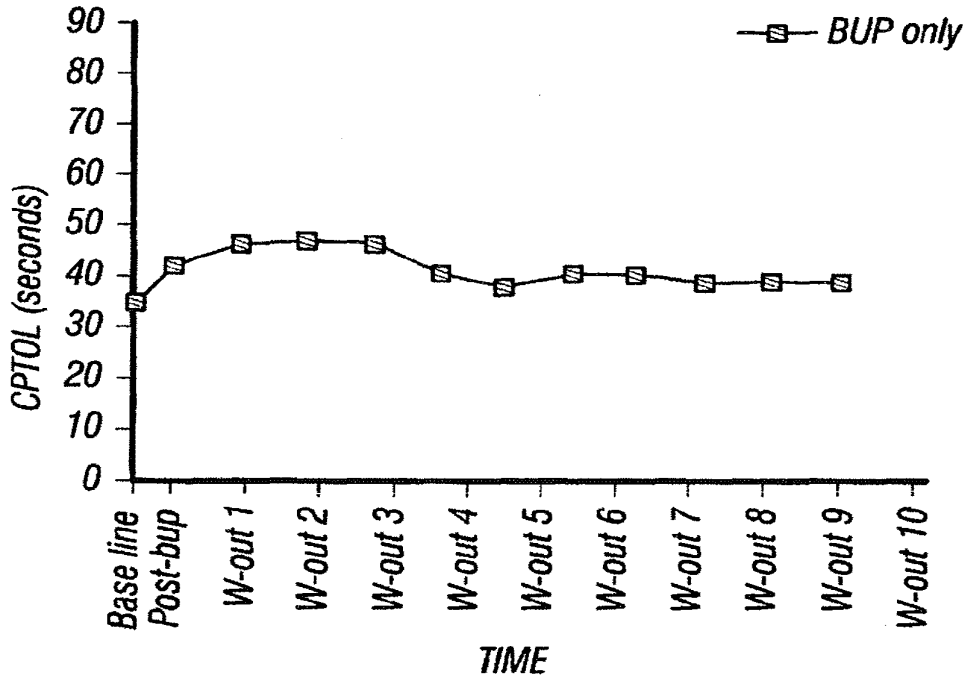

FIG. 2

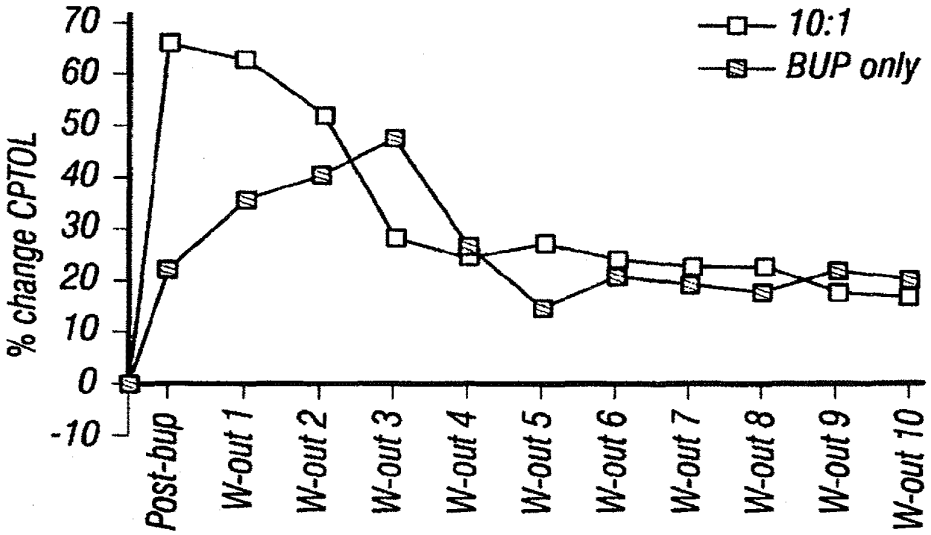

FIG. 3

IMPROVEMENTS IN AND RELATING TO MEDICINAL COMPOSITIONS

The present invention relates to medicinal compositions containing buprenorphine in combination with naloxone; as well as to their use in the manufacture of such compositions and in clinical practice, as analgesics.

Whilst opioids are particularly effective in the management of moderate to severe pain their use is limited by unpleasant and potentially dangerous adverse effects. Such adverse effects can include sedation, respiratory depression, nausea and gastrointestinal problems. Thus efforts have been made to minimise adverse effects.

There are many opioids and some produce more significant adverse effects than others. Accordingly, careful selection of the opioid employed in an analgesic composition may itself reduce the incidence and severity of adverse effects. One particularly suitable opioid is buprenorphine which has been shown to have both agonist (morphine-like) and antagonist properties without producing significant physical dependence.

Buprenorphine (International Non-proprietary Name for N-cyclopropylmethyl-7[alpha]-[1-(S)-hydroxy-1,2,2-trimethyl-propyl]6,14-endoethano-6,7,8,14-tetrahydronororipavine) is a potent opiate partial agonist analgesic lacking the psychotomimetic effects found with other opiate analgesics. However, buprenorphine suffers from side effects typical of opiate agonists such as nausea and vomiting, constipation and respiratory depression in some patients, although there is a ceiling to its effects on

respiratory depression as a direct consequence of its partial agonist properties.

Attempts have also been made to enhance the analgesic effect of opioids while minimising the incidence and severity of adverse effects by combining opioid treatment with other drugs.

One approach is the addition of a non-opioid analgesic to the opioid treatment. The rationale here is that lower levels of opioid should be required to achieve antinociception and thus there should be a reduction of adverse effects.

Another approach is the co-administration of an opioid agonist and low doses of an opioid antagonist.

Given the potent blockade of opioid binding associated with administration of an opioid antagonist it would classically be expected that the use of such an agent would provide no improvement to pain relief and could conceivably increase pain through partial blockage effects of the agonist it is combined with. However it has been found that in some instances antinociception may be potentiated by co-administration of an antagonist.

One such antagonist is naloxone (International Non-proprietary Name for 1-N-allyl-14-hydroxynorhydro morphinone) which is a narcotic antagonist.

In GB 2150832A there is disclosed an analgesic composition in parenteral or sublingual form comprising an active dose of buprenorphine and an amount of naloxone sufficient to

prove aversive to a narcotic addict by parenteral administration but insufficient to compromise the analgesic action of the buprenorphine. The parenteral dosage form may contain buprenorphine and naloxone within the weight ratio of 3:1 to 1:1 and the sublingual form within the ratio 1:2 to 2:1. The testing in GB-A-2150832 was on rats.

In EP 1242087A it is disclosed that parenteral and sub-lingual levels of buprenorphine are potentiated and enhanced by low doses of naloxone. Based on testing on rats, there is stated a suitable ratio by weight of buprenorphine to naloxone of 12.5:1 to 27.5:1, preferably 15:1 to 20:1.

Human studies have now been carried out and have generated new findings for the combined use of buprenorphine, as opioid agonist, and naloxone, as opioid antagonists. These new findings extend our understanding of the therapeutic doses which will give effective analgesia in humans.

According to a first aspect of the present invention there is provided an analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the mucosa or dermis, the composition comprising buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1.

It is believed that the analgesic action of buprenorphine is potentiated by the relatively small amount of naloxone.

It is to be understood that the terms buprenorphine and naloxone as used herein are intended to cover simple related, pharmaceutically acceptable, compounds such as esters, bases and salts, for example acid addition salts. Particularly preferred salts are the hydrochlorides. However the ratios and weights referred to herein refer to buprenorphine and naloxone *per se*, not salts, bases or esters.

The term parenteral is intended to encompass administration of the compositions by any way other than through the alimentary tract.

The term mucosa is intended to encompass any mucous membrane and includes oral mucosa, rectal mucosa, vaginal mucosa and nasal mucosa. The term dermis denotes non-mucosal skin.

Administration may take a few minutes, depending on its nature. Preferably it takes over a period of at least one minute, preferably at least two minutes, preferably at least three minutes. Preferably it take place over a period of up to ten minutes, preferably up to seven minutes, preferably up to five minutes.

Transdermal administration may encompass any mode of administration trough the dermis. Transmucosal administration may encompass any mode of administration trough the mucosa, and sites of administration may include, for example, vaginal and rectal mucosa and, preferably, mucosa of the oral-nasal cavity, for example

nasal, throat, buccal and, sublingual sites. Nasal and sublingual administration is especially preferred.

Preferably the defined ratio of buprenorphine to naloxone is achieved within sixty minutes after administration being completed; that is, preferably at some time within sixty minutes of administration being completed, the defined drug ratio in the plasma is achieved.

The composition may comprise buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is at least X:1 (X to 1) where X is 8.0, preferably 9.0, preferably 9.5, preferably 10.0, preferably 10.5, preferably 11.0.

The composition may comprise buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is no greater than Y:1 (Y to 1) where Y is 12.3, preferably 12.2 preferably 12.0, preferably 11.5.

Surprisingly, it has been found that although the relative amount of naloxone to buprenorphine is higher in the present invention than in EP 1242087B, the antagonist action of naloxone does not "win out" and naloxone in fact potentiates the agonist action of buprenorphine.

The composition may comprise a parental unit dosage form and the ratio of buprenorphine to naloxone within the parenteral composition may be substantially the same as that reaching or delivered to the plasma of a patient upon application. Thus the parenteral dosage form may comprise

buprenorphine and naloxone in the weight ratio 7.5:1 to 12.4:1, with preferred upper and lower limits of the ratio being as stated above for buprenorphine and naloxone in the plasma.

In a human being, as stated in EP 1242087B dosages of about 40 µg of buprenorphine per kilogram of body weight are suitably required to obtain satisfactory pain relief in the absence of potentiation. Thus for typical body weights of 50 to 80 kg, the buprenorphine dosage would be from 2 mg to 3.2 mg of buprenorphine per day. This would conveniently be administered as four unit doses.
The amounts of buprenorphine which are required to be effective in the compositions of the invention are less than the amounts which are required to be effective in the absence of the potentiating effects of naloxone.

Importantly when equal doses of buprenorphine with and without the potentiating effect of naloxone are compared, the magnitude and duration of analgesia achieved by the former compositions (i.e. also containing naloxone), are markedly increased. Therefore the same analgesic performance can be achieved with a lower buprenorphine dose when combined with naloxone. It is proposed that an increased analgesic effect can be achieved and/or reduced concentration of buprenorphine can be used, within or across the therapeutic range.

Suitably, unit doses of the compositions of the present invention (containing naloxone) contain buprenorphine in an amount which is below that required to obtain corresponding pain relief in a unit dose of buprenorphine without naloxone.

Suitably, the compositions of the present invention comprise at least 10 µg of buprenorphine per unit dose, preferably at least 15 µg, preferably at least 20 µg, preferably at least 30 µg, and most preferably at least 40 µg. These values reflect the benefit of the invention in achieving analgesia at low dosages.

Suitably, the compositions of the present invention may contain any amount of buprenorphine, up to the upper end of conventional clinical practice. Suitably, they may contain up to 8 mg buprenorphine per unit dose, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 600 µg, preferably up to 400 µg, preferably up to 200 µg, preferably up to 160 µg, and most preferably up to 100 µg.

Suitably, in accordance with the present invention, a patient is administered at least 0.25 µg of buprenorphine per kg (of body weight) per 24 hours. Preferably the amount is at least 0.5 µg, preferably at least 1 µg, preferably at least 1.5 µg and most preferably at least 2 µg.

Suitably, in accordance with the present invention, a patient is administered up to 640 µg of buprenorphine per kg per 24 hours. Preferably the amount is up to 320 µg, preferably up to 160 µg, preferably up to 80 µg, preferably up to 40 µg, preferably up to 20 µg, preferably up to 16 µg, and preferably up to 12 µg. Most preferably the amount is not greater than 8 µg.

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is at least 40 µg per 24 hours, preferably at least 60 µg, preferably at least 80 µg, preferably at least 120 µg, and most preferably at least 160 µg.

Suitably by use of compositions of the present invention the amount of buprenorphine administered to a patient for the purpose of achieving relief from pain is up to 32 mg, preferably up to 16 mg, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 800 µg, preferably up to 600 µg, and most preferably up to 400 µg.

Suitably, the composition comprises at least 1 µg of naloxone per unit dose, preferably at least 1.5 µg, preferably at least 2 µg, and most preferably at least 4 µg.

Suitably, the composition comprises up to 4 mg of naloxone per unit dose, preferably up to 2 mg, preferably up to 1 mg, preferably up to 500 µg, preferably up to 300 µg, preferably up to 200 µg, preferably up to 100 µg, preferably up to 80 µg, and most preferably up to 50 µg.

Suitably the amount of naloxone administered is at least 0.025 µg naloxone per kg per 24 hours. Preferably the amount is at least 0.05 µg, preferably at least 0.1 µg, preferably at least 0.15 µg, preferably at least 0.2 µg, and most preferably at least 0.4 µg.

Suitably the amount of naloxone administered is up to 320 µg naloxone per kg per 24 hours. Preferably the amount is up to 160 µg, preferably up to 80 µg, preferably up to 40 µg, preferably up to 20 µg, preferably up to 10 µg, preferably up to 8 µg, and preferably up to 6 µg. Preferably the amount is not greater than 4 µg per kg per 24 hours.

Suitably the amount of naloxone administered is at least 5 µg per 24 hours, preferably at least 8 µg, preferably at least 10 µg, preferably at least 15 µg, and most preferably at least 20 µg.

Suitably the amount of naloxone administered is up to 16 mg µg per 24 hours, preferably up to 8 mg, preferably up to 4 mg, preferably up to 2 mg, preferably up to 1 mg, preferably up to 500 µg, preferably up to 400 µg, preferably up to 300 µg, and most preferably up to 200 µg.

References above to the amounts of compounds which may be administered to a patient are with reference to an adult patient.

Whatever the absolute amounts of buprenorphine and naloxone administered, the definition(s) stated herein of the ratio of buprenorphine to naloxone must be satisfied.

It is preferable to formulate the compositions in unit dosage forms i.e. physically discrete units containing the appropriate amounts of buprenorphine and naloxone, together with pharmaceutically acceptable diluents and/or carriers. Such unit dosage forms for parenteral administration are suitably in the form of ampoules. The

unit dosage form for transdermal or transmucosal administration may, for example, be a tablet, film, spray, patch, rub-in composition or lozenge. Administration, which will be further described in the second aspect, may comprise the delivery of a medicament comprising buprenorphine and naloxone, preferably in such a form.

Compositions of the invention may contain a buffer system, for example an organic acid and a salt thereof, such as citric acid and sodium citrate.

Compositions in the form of sublingual dosage forms suitably contain soluble excipients selected from materials such as lactose, mannitol, dextrose, sucrose or mixtures thereof. They suitably also contain granulating and disintegrating agents selected from materials such as starch, binding agents such as povidone or hydroxypropyl-methyl cellulose and lubricating agents such as magnesium stearate.

Compositions intended for parenteral administration may comprise an isotonic solution of buprenorphine and naloxone in sterile water. Conveniently the solution may be made isotonic by use of dextrose and sterilised by autoclaving or by filtration through a membrane filter. The compositions may be administered intramuscularly, intradermally, intraperitonealy, intravenously, intraarterially, subcutaneously or by the epidural route.

The compositions for parenteral administration, or for delivery via the mucosa, such as by sublingual administration, as detailed above, may be prepared by

manufacturing techniques which are well known to those skilled in the art.

According to a second aspect the present invention there is provided a method for the treatment of pain in a human patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is in the range from 7.5:1 to 12.4:1.

Preferred ratios of buprenorphine to naloxone are as defined above with respect to the first aspect.

Suitably, the method comprises delivery via the mucosa. The method may comprise delivery in a sublingual unit dosage form.

Suitably, the method comprises the administration of buprenorphine and an amount of naloxone for the purpose of potentiating the analgesic action of the buprenorphine and in particular to optimising the balance between the analgesic action of the buprenorphine and the anti-abuse presence of the naloxone. It will be appreciated that this balance is extremely important. The medicament must be a potent analgesic for it to fulfil its intended function. At the same time in the present day it is vitally important that opioid medicaments discourage abuse by addicts. It is believed that the present invention is extremely effective in these respects.

Separate administration of buprenorphine and of naloxone is not excluded in the method. Suitably, however, the method comprises administering a composition comprising buprenorphine and naloxone, to a human. Suitably, the method employs a composition according to the first aspect. The definitions given above in relation to the first aspect apply to the second aspect, noting however that the buprenorphine and naloxone may in principle be administered separately in the second aspect.

Suitably, the method comprises administering to the human or animal from 0.25 µg to 20 µg per kilogram of body weight of buprenorphine per day.

The method may comprise administering a dose of buprenorphine which would, if administered alone, produce minimal or no antinociception. The method may comprise administering to the human amounts of buprenorphine and naloxone as stated above in relation to the first aspect of the invention.

The method may comprise any feature as described in relation to the first aspect.

According to a third aspect of the present invention there is provided the use of naloxone and buprenorphine in the manufacture of a medicament for the treatment of pain, wherein the naloxone and buprenorphine are used in an amount such that the medicament is delivered to the patient or reaches, in the plasma of a patient, a ratio by weight of buprenorphine to naloxone in the range of from 7.5:1 to 12.4:1.

Suitably the use comprises the use of buprenorphine and naloxone in the manufacture of a medicament for the treatment of pain, wherein buprenorphine is used for its analgesic effect, but at a lower level than would be needed, for a given analgesic effect against a given pain in a given patient, in the absence of naloxone. Thus the naloxone potentiates the analgesic effect of buprenorphine. Further, it renders the medicament less attractive (and preferably entirely unattractive) to drug addicts.

The use of buprenorphine and naloxone in the manufacture of a medicament according to the third aspect may comprise any feature as described in relation to the first or second aspect.

Suitably, the use of buprenorphine and naloxone in the manufacture of a medicament comprises the manufacture of a medicament comprising a composition according to the first aspect. However the use of buprenorphine and naloxone in the manufacture of a medicament having two dosage units, containing buprenorphine and naloxone respectively, is not excluded.

The present invention will now be illustrated by way of example with reference to the accompanying drawings in which:

Figure 1 is a graph of pain tolerance results for a buprenorphine and naloxone combination;

Figure 2 is a graph of pain tolerance results for buprenorphine alone; and

Figure 3 is a comparative graph.

Methods

Nociceptive testing

The cold pressor (CP) test was used to assess antinociception of buprenorphine and buprenorphine and naloxone combinations. The compound forms were buprenorphine HCl and naloxone HCl dihydrate. The CP test utilised two plastic cylindrical containers, one of which was filled with warm water and the other with a combination of water and crushed ice to achieve a "slushy" consistency. The subject immersed the non-dominant forearm and hand into the warm water for exactly 2 minutes. At 1 minute 45 seconds, a blood pressure cuff on the immersed arm was inflated to a pressure 20 mmHg below the diastolic blood pressure. The blood pressure cuff minimised the role of blood flow in determining the reaction to cold. At exactly 2 minutes, the forearm was transferred from the warm water to the cold water bath. The subject's eyes were covered for the entire procedure to minimise distraction and cues for time. Upon immersion of the limb in the cold water bath, subjects were asked to indicate when they first experienced pain (pain threshold, CPTHR), then asked to leave their arm submerged until they can no longer tolerate the pain (pain tolerance, CPTOL). Pain threshold and tolerance times were recorded in seconds from immersion in cold. An undisclosed cut-off of 180 seconds was imposed, after which time pain tolerance can no longer be accurately assessed due to numbness. Pain

tolerance (CPTOL) is the reported pain response parameter in the current investigations.

For the present tests nociceptive testing was conducted in the same environment, with minimal background noise, audible voices and no clock with audible ticking. Ambient room temperature and lighting was consistent. At no time did the experimenter discuss with the subject his/her performance on the test, or answer any questions related to the average pain tolerance time or any previous results.

Screening

Before testing subjects were screened according to the inclusion and exclusion criteria based upon such factors as previous medical conditions and drug abuse.

Test Procedure

Suitable screened subjects were tested according to the following procedure. Subjects provided a urine sample upon arrival on the day of testing, which was tested for drugs of abuse (opioids, cannabinoids, benzodiazepines and sympathomimetic amines) and, for female subjects, pregnancy. A 22 gauge indwelling venous catheter was inserted into the best available forearm vein on each arm (above the CP immersion line for the non-dominant arm). A male luer lock adaptor injection site was attached to each catheter. One catheter was used for blood sampling throughout the testing day, and the other for infusions. The participant was then connected to a monitor, which was

set to continuously monitor physiological parameters for the duration of the testing session.

On each testing day, subjects received a 30 minute unblinded intravenous infusion of saline, followed by one or more 30 minute drug (or placebo) infusions. The purpose of the initial saline infusion was two-fold: to establish whether any changes in pain or physiological parameters would occur as a response to the infusion process itself, and to ensure that there was no obstruction to venous access via the catheter and the infusion pump was operating correctly.

Infusions were administered using a syringe pump. Drugs and saline were prepared in 30ml BD Plastipak syringes. Infusions were run at a rate of 20ml per hour for 30 minutes. Each syringe was attached to a minimum volume extension set (150cm tubing, female luer lock, male luer lock, 0.5mL/30cm). The male luer lock was attached to a lever lock cannula. The extension set was primed with the drug/saline, and inserted into the injection site. In buprenorphine:antagonist ratio studies, BUP and antagonist were administered simultaneously. For the simultaneous infusion of two drugs (via one cannula), a Y-type catheter extension set with two injection sites was attached to the catheter, and the lever lock cannulas (connected via the minimum volume extension set to each syringe) were inserted in each of the injection sites.

Testing sessions were conducted on numerous occasions during each testing day. Each testing session consisted of the following measures in the order listed: nausea and sedation recorded, blood sample taken, physiological

parameters recorded (pulse, oxygen saturation and blood pressure), nociceptive testing (as detailed above) completed, and respiration recorded (breaths per minute counted for one full minute during warm water component of CP).

Testing sessions were conducted at set intervals throughout each testing day. These were as follows: 1. Prior to the commencement of infusions; 2. Twenty minutes after the commencement of the 30 minute saline infusion; 3. Twenty minutes after the commencement of the 30 minute drug infusion, and hourly following the cessation of the (last) drug infusion. This is referred to as the washout period. The purpose of conducting the testing session 20 minutes after commencing each 30 minute infusion was to allow time for the testing to be completed before starting the subsequent infusion.

Comparison of results

As baseline values were different between conditions, CPTOL data were expressed as percent change from baseline in order to compare the effect associated with different drug combinations. Each participant's response at each time point for each condition was expressed as a percent change from baseline response according to the equation below. Data are expressed as the mean (±SEM) of these values at each post-drug testing session for each condition.

$$\frac{\text{Post-drug latency} - \text{baseline latency}}{\text{baseline latency}} * 100$$

This provides a value for percentage change CPTOL.

Examples

Example 1

Eight healthy Caucasian volunteers (4 male, 4 female) were enrolled in the study. Data from one 37 year old male was excluded from analyses due to an opioid positive urine on the BUP only testing day. The final sample (n=7), then, comprised 3 males and 4 females, with a mean age of 25.14 (±1.02, range 21-37) and mean CPTOL at screening of 43.00 (±6.73, range 29-80). There were no significant differences between males and females in terms of age (p=0.265) or CPTOL at screening (0.764).

Subjects were administered buprenorphine and Naloxone in a ratio of 10:1 by IV infusion with buprenorphine administered at a dose of 0.5 µg/kg body weight. The washout monitoring was performed for a period of 10 hours. The CPTOL results are presented in Figure 1. No adverse effects causing concern were noted.

Example 2 - comparative

As a comparative example the same subjects from Example 1 were administered, on a separate day, buprenorphine and saline (referred to subsequently as "BUP only") by IV infusion. Buprenorphine was again administered at a dose of 0.5 µg/kg body weight and the washout monitoring performed over 10 hours. The CPTOL results are presented in Figure 2.

Comparison of examples

The percentage change for CPTOL from the baseline was calculated for Examples 1 and 2 and the results are presented in Figure 3. It may be seen that in the early hours of the test there was a benefit of the buprenorphine and naloxone combination compared to buprenorphine alone.

Example 3 - parenteral composition

A parenteral formulation having the following composition:

	mg/ml.
Buprenorphine as HCl salt	0.05
Naloxone as HCl salt	0.005
Anhydrous dextrose	50.0
Hydrochloric acid to pH 4.0	
Water for injection to 1.0 ml	

was prepared by dissolving dextrose, buprenorphine hydrochloride and naloxone hydrochloride in that order with stirring, in about 95% batch volume of water for Injection. The acidity of the solution was adjusted to pH 4.0 by the addition of 0.1M hydrochloric acid, and the solution was made up to volume with Water for Injection. The solution was filtered through a membrane filter and transferred to sterilised 2 ml glass ampoules containing 2 ml of the solution. The ampoules were sealed and the product sterilised by autoclaving.

Example 4 - sublingual composition

A sublingual tablet having the following composition:

	mg/tablet
Buprenorphine as HCl salt	0.04
Naloxone as HCl salt	0.006
Mannitol	18.0
Maize starch	9.0
Povidone	1.2
Magnesium stearate	0.45
Lactose	to 60.0

was prepared by screening all the materials with the exception of the magnesium stearate through a 750 µm sieve and blending them together. The mixed powders were then subjected to an aqueous granulation procedure and dried at 50°C. The resulting granules were forced through a 750 µm sieve and blended with magnesium stearate (pre-sieved through a 500 µm sieve). The tablet granules were compressed to yield tablets of 5.56 mm diameter and weight 60 mg.

CLAIMS

1. An analgesic composition, in parenteral unit dosage form or in a unit dosage form suitable for delivery via the mucosa or dermis, the composition comprising buprenorphine and an amount of naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of a patient is in the range of from 7.5:1 to 12.4:1.

2. A composition as claimed in claim 1, wherein said ratio is at least X:1 where X is 8.0 or 9.0 or 9.5 or 10.0 or 10.5 or 11.0.

3. A composition as claimed in claim 1 or 2, wherein said ratio is up to Y:1 where Y is 12.3 or 12.2 or 12.0 or 11.5.

4. A composition as claimed in claim 1 wherein the amount of buprenorphine in the unit dosage form is from 10 µg to 8 mg.

5. A method for the treatment of pain in a human patient, which method comprises the administration to a human patient, by a parenteral or dermal or mucosal route, of buprenorphine and naloxone such that the ratio by weight of buprenorphine to naloxone delivered to or reaching the plasma of the patient is in the range from 7.5:1 to 12.4:1.

6. The use of naloxone and buprenorphine in the manufacture of a medicament for the treatment of pain,

wherein the naloxone and buprenorphine are used in an amount such that the medicament is delivered to the patient or reaches, in the plasma of a patient, a ratio by weight of buprenorphine to naloxone in the range of from 7.5:1 to 12.4:1.

7. A method or use as claimed in claim 5 or 6, wherein the administration of buprenorphine is in the range 0.25 to 640 µg per kg per 24 hours.

8. A composition or method or use, substantially as hereinbefore described in accordance with the present invention.

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Application No: GB0703968.8 **Examiner:** Mr Martin Price

Claims searched: 1-8 **Date of search:** 22 June 2007

Patents Act 1977: Search Report under Section 17

Documents considered to be relevant:

Category	Relevant to claims	Identity of document and passage or figure of particular relevance
Y	1-8	GB 2356348 A Reckitt - the whole document
X	1-8	WO 2004/014336 A3 Gruenenthal - see e.g. claim 6 and page 8 lines 21-22
Y	1-8	GB 2150832 A Reckitt - see e.g. claim 4
X	1-8	Psychopharmacology (1999), 141 (1), 37-46, Mendelson et al, ISSN 0033-3158 - see abstract
Y	1-8	Drug and Alcohol Dependence, (2003), 72(1), 75-83, McAleer et al, ISSN No 0376-8716 - see abstract

Categories:

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.

Field of Search:

Search of GB, EP, WO & US patent documents classified in the following areas of the UKC^{X} :

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The following online and other databases have been used in the preparation of this search report

ONLINE - EPODOC, WPI, CAS ONLINE, BIOSIS, MEDLINE

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(54) Title: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

(57) Abstract: A thin film drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the stationing of the particulate bioeffecting agent therein. The combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness.

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

FIELD OF THE INVENTION

The present invention relates to compositions and methods for the preparation and use of a uniform rapid dissolve dosage form in the form of a film that includes a pharmaceutically active or bioeffecting agent and a taste-masking agent for masking the taste of the pharmaceutically active agent.

BACKGROUND OF RELATED TECHNOLOGY

While active ingredients such as pharmaceutical preparations may be included in a tablet or similar form to provide an accurate and consistent dose, including medicaments in such a form has several disadvantages in both the administration and preparation of the drug. Moreover, in such oral dosage forms, such as tablets or emulsions, pharmaceuticals have been coated to provide control release or taste-masking. Particle sizes of particulate pharmaceuticals are not critical in such dosage forms and generally large particle sizes, i.e., greater than 200 microns have been used.

There have been several attempts to provide an alternate dosage form, such as a film that would include a pharmaceutical active. However, such attempts have not been successful in providing a film that incorporates a drug with sufficient uniformity to provide accurate dosing.

Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not specifically disclosed likely include the use of relatively long drying times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent governmental or agency standards relating to the variation of active in dosage forms. Currently, by law, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

Moreover, the problems of self-aggregation leading to non-uniformity of a film can result in an unpleasant tasting film when the film contains an unpleasant tasting pharmaceutical agent. Agglomerates of unpleasant tasting pharmaceutical agents may not be adequately masked by flavoring agents and sweeteners that are simply mixed into a film because the non-uniformity of the agglomerates may result in segregation of the unpleasant tasting agents from the flavoring agents and sweeteners. Fuchs merely mixes flavors and sweeteners into a film forming mix and fails to address the problem of aggregation or segregation of these materials.

Similarly, WO 00/42,992 also discloses the use of taste-modifying agents in a film dosage form. This international application also merely mixes taste-modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents.

Furthermore, WO 01/70,194 discloses the use of ion exchange resins to for covalently binding pharmaceutical agents thereto. The resins have particle sizes from 20 microns to 200 microns and are described as being taste masking agents. The ion exchange resins are described as being bound with pharmaceutical agents and being mixed into consumerable films having thicknesses from 7 to 11 mils, or 180 microns to 280 microns. Such ion exchange resins, however, have limitations in the binding of pharmaceutical agents to the ion exchange resins, making the process for producing taste-masked comsumerable films complicated and expensive. Moreover, the use of ion exchange resins, which are water insoluble, limits the selection of useful pharmaceutical agents in water soluble films to only certain water soluble pharmaceutical agents that can covalently bond to the ionic resin.

Therefore, there is a need for a rapid dissolve dosage form, presented as a uniform film that addresses and corrects the problems associated with non-uniformity of a drug in film such as agglomeration or separation of particles within the film and the unpleasant tasting effects of the same. Moreover, there is a need for taste-masked, pharmaceutically active agents suitably contained within such a uniform film.

SUMMARY OF THE INVENTION

The present invention seeks to attain low adjuvant content, high taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and uniformity. The present invention also provides for a unique method of producing the inventive compositions such that the compositional components are evenly distributed throughout the film. This process is described in detail in co-pending U.S. Patent Application No. 10/074,272, entitled "Thin Film with Non-Self-Aggregating Uniform Heterogeneity and Drug Delivery Systems Made Therefrom", the subject matter of which is herein incorporated by its entirety.

In one aspect of the present invention, a drug delivery composition includes (i) a flowable water-soluble film forming matrix; (ii) a particulate bioeffecting agent uniformly stationed therein; and (iii) a taste-masking agent coated or intimately associated with the particulate to provide taste-masking of the bioeffecting agent. The combined particulate and taste-masking agent have a particle size of 200 microns or less, and the flowable water-soluble film forming matrix is capable of being dried without loss of uniformity in the

stationing of the particulate bioeffecting agent therein. The importance of such particle sizes has not been recognized in the prior art, especially in prior art dosage forms, such as tablets and emulsions. Moreover, the importance of particle size is heightened in orally ingestible thin films, where uniformity is also of particular importance, and the prior art has failed to recognize such critically important features.

Desirably, the size of the combined particulate and taste-masking agent have a particle size of 150 microns or less, for example 100 microns or less. Moreover, the flowable water-soluble film forming matrix is formable into a dry film of less than about 380 microns in thickness, for example less than about 250 microns in thickness. Desirably, such particle sizes are contained within these dry films. In other words the dry films of the present invention desirably have smooth surfaces free of exposed agents that could impart grittiness or maldistribution of the active. Thus, in one aspect of the invention there is provided a film vehicle which contains a uniform distribution of actives, as defined herein, being suitably free of particles which accumulate on the film surface when dried.

Desirably, taste-masking agent is a thin film coating over portions of the bioeffecting agent. Useful taste-masking agents include polymeric materials. Water-soluble polymers are also useful. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Furthermore, water-soluble polymers may be acrylic polymers, cellulosic polymers, and combinations thereof. Additionally, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof may also be used as taste-masking agents.

The matrix may be a cellulosic material; a gum; a protein; a starch; a glucan; and combinations thereof; such as but not limited to carboxymethyl cellulose; methyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch, including tapioca starch, rice starch, corn starch, potato starch, and wheat starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins, such as, gelatin, zein, gluten, soy protein, soy protein isolate, and whey protein; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

The bioeffecting agent may be present in amounts of up to about 0.1% to about 60% by weight of the total composition. Useful bioeffecting agents include, but are not limited to, antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, anti-pyretics, psychopharmacological drugs and combinations thereof. The delivery vehicle composition may further include an organoleptic agent.

In another aspect of the present invention, a drug delivery vehicle includes (i) a water-soluble film matrix; and (ii) a particulate bioeffecting agent uniformly suspended within the matrix and having associated with it a taste-masking agent. The uniformity is determined by the presence of no more than a 10% by weight of drug variance throughout the matrix. Desirably, the drug variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight. Moreover, the particulates have a particle size of 200 microns or less. Furthermore, the film matrix desirably has a thickness of less than about 380 microns. Useful taste-masking agents include water-soluble polymers. Desirably, the water-soluble polymer has an average molecular weight of equal to or greater than about 40,000. Non-limiting water-soluble polymers include acrylic polymers, cellulosic polymers, and combinations thereof. The taste-masking agents may also include vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof. The drug delivery vehicle of claim may further include an organoleptic agent with the bioeffecting agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent coated or encapsulated with a water-soluble polymer having an average molecular weight of equal to or greater than about 25,000. Water-soluble polymers having an average molecular weight of equal to or greater than about 40,000 are also useful. Useful water-soluble polymers include of acrylic polymers, cellulosic polymers, and combinations thereof. Desirably, the pharmaceutically active particles are embedded within the film. Additionally, the film includes sections of substantially equal size and the particles are distributed in an amount that varies less than about 10% among the sections. Desirably,

the size of the particles are about 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. Moreover, the drug delivery vehicle may further include an organoleptic agent with the water-soluble polymer.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle having a pharmaceutically active agent and a taste-masking agent present in the amount of about 15-80% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 20-60% by weight of the particle. More desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle. The pharmaceutically active particle is desirably embedded within the film, and the film includes sections of substantially equal size where the particles are distributed in an amount that varies less than about 10% among the sections. Useful sizes of the pharmaceutically active particles include particle sizes of 200 microns or less. Desirably, the film has a thickness of less than about 380 microns. The drug delivery vehicle may further include an organoleptic agent with the taste-masking agent.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The active particle has a particle size of less than about 200 microns. Desirably, the thickness of the film is less than about 380 microns.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and a taste-masking agent. The particle desirably has a particle size of less than about 200 microns and the taste-masking agent is present in amounts of about 15-80% by weight of the particle. A particle size of about 150 microns or less is also useful. Desirably, the particle size of the particle is about 100 microns or less. Desirably, the thickness of the film is less than about 380 microns, for example, less than about 250 microns. Furthermore, the taste-masking agent may be present in the amount of about 20-

60% by weight of the particle. Desirably, the taste-masking agent is present in the amount of about 25-35% by weight of the particle.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent and an organoleptic agent. The active particle is taste-masked with a taste-masking agent. Useful organoleptic agents include flavors, sweeteners and combinations thereof.

In another aspect of the present invention, a drug delivery vehicle includes a dry mucoadhering film having a thickness defined by opposed surfaces. The film includes (i) a water-soluble polymer; and (ii) a pharmaceutically active particle comprising a pharmaceutically active agent being taste-masked with a taste-masking composition comprising a water-soluble polymer and at least one of a flavor or a sweetener.

In another aspect of the present invention, a method of preparing a thin film drug delivery vehicle is provided. The method includes the steps of (a) providing a pharmaceutically active agent / taste-masking agent complex; (b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of the complex therein; (c) casting the mixture onto a planar carrier surface to form a thin film on the carrier surface; and (d) controllably drying the thin film to form a distribution variance of the complex having less than about 10% variance throughout any given area of the thin film. The step of providing the pharmaceutically active agent with the taste-masking agent includes a treatment for coating the taste masking agent onto portions of the pharmaceutically active agent. The drying includes applying heat the bottom of the carrier surface. Moreover, the drying may include applying microwave energy to the film. Useful methods for providing the pharmaceutically active agent with the taste-masking agent include fluidized bed coating, spray congealing coating, agglomeration or granulation coating, entrapment coating, coaccervation coating, infusion coating, spin coating, ion exchange coating the taste masking agent onto portions of the pharmaceutically active agent.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

Figure 2 shows a top view of two adjacently coupled packages containing individual unit dosage forms of the present invention, separated by a tearable perforation.

Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

Figure 4 shows a perspective view of a dispenser for dispensing the packaged unit dosage forms, dispenser containing the packaged unit dosage forms in a stacked configuration.

Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

Figure 6 is a schematic view of an apparatus suitable for preparation of a pre-mix, addition of an active, and subsequent formation of the film.

Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a pharmaceutical composition in the form of a film for external or topical administration, including a composition having a uniformly distributed combination of a polymer, a polar solvent, and a taste-masked pharmaceutically active or bioeffecting agent. The composition in its dried film form maintains the uniform distribution of components through the application of controlled bottom drying of the film.

Water-soluble polymers useful in the present invention include cellulosic materials, gums, proteins, starches, and combinations thereof.

As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

Examples of cellulosic materials include, without limitation, carboxymethyl cellulose, methyl cellulose, ethyl cellulose, hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof.

Examples of water-soluble gums include gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

Examples of other polymeric materials which may be incorporated include polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

Useful starches include gelatinized, modified or unmodified starches. The source of the starches may vary and include pullulan, tapioca, rice, corn, potato, wheat and combinations thereof.

Useful water-soluble protein polymers include gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof. Additional water-soluble polymers include dextrin, dextran and combinations thereof, as well as chitin, chitosin and combinations thereof, polydextrose and fructose oligomers.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The edible water-soluble delivery system of the present invention further include glucans, such as pullulan and elsinan. The ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Glucans are generally desirable materials for edible film because of their high water solubility, rapid dissolution and excellent mouth-feel.

The edible water-soluble delivery system of the present invention further include an anti-foaming or defoaming agent, such as simethicone, which is a combination of a polymethylsiloxane and silicon dioxide. Simethicone acts as either an anti-foaming or defoaming agent which reduces or eliminates air from the film composition. An anti-foaming agent will aid in preventing the introduction of air into a composition, while a defoaming agent will aid in removing air from the composition.

The edible water-soluble delivery system of the present invention further include an active component selected from cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof. The active component may be present in any amount effective for the intended treatment. It is particularly desirable and an advantage of the present invention that the active component can be included in high loads. For example, the active component may be present in amounts up to about 60% by weight of the total composition and desirably in amounts of 0.01% to about 50% by weight of total composition.

The pharmaceutically or bioeffecting active components that may be incorporated into the films of the present invention include a wide variety of medicaments and pharmaceutical compositions. Examples of useful drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmátics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines,

anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium

hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^H-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as , but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

The pharmaceutically active agents employed in the present invention may be incorporated into the film compositions of the present invention in a taste-masked form. For example, particles of drug may be coated with taste-masking agents, for example polymers, oils and waxes. Additionally, organoleptic agents, such as, but not limited to sweeteners and/or flavors, may also be employed in such taste-masked compositions, including in the coating layer of the taste masking agent.

Suitable sweeteners include both natural and artificial sweeteners. Non-limiting examples of suitable sweeteners include, e.g.:

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

b. water-soluble artificial sweeteners such as the soluble saccharin salts, i.e., sodium or calcium saccharin salts, cyclamate salts, the sodium, ammonium or calcium salt of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2, 2-dioxide, the potassium salt

of 3,4-dihydro-6-methyl-1,2,3-oxathiazine-4-one-2,2-dioxide (acesulfame-K), the free acid form of saccharin and the like;

c. dipeptide based sweeteners, such as L-aspartic acid derived sweeteners, such as L-aspartyl-L-phenylalanine methyl ester (aspartame), L-alpha-aspartyl-N-(2,2,4,4-tetramethyl-3-thietanyl)-D-alaninamide hydrate, methyl esters of L-aspartyl-L-phenylglycerin and L-aspartyl-L-2,5,dihydrophenylglycine, L-aspartyl-2,5-dihydro-L-phenylalanine, L-aspartyl-L-(1-cyclohexyen)-alanine, and the like;

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

e. protein based sweeteners such as thaurnatoccous danielli(Thaurnatin I and II).

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with the sweetener selected. This amount will normally be 0.01 % to about 10 % by weight of the composition. These amounts may be used to achieve a desired level of sweetness independent from the flavor level achieved from any optional flavor oils used. Of course, sweeteners need not be added to films intended for non-oral administration.

Useful flavors or flavoring agents include natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Non-limiting flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit, and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot and the like. These flavorings can be used individually or in combination. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in combination. Flavorings such as aldehydes and esters including cinnamylacetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and the like may also be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamicaldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral,

i.e. beta citral(lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream);heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese);valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal(citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits);aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla);12,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2 dimethyloctanal (greenfruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference, subject to such factors as flavor type, individual flavor, and strength desired. The amount may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt% are useful with the practice of the present invention.

A variety of polymeric and non-polymeric materials can be employed for taste masking pharmaceutically active agents. Non-limiting examples of polymers include acrylic polymers, cellulosic polymers or vinyl polymers. Non-limiting examples of non-polymeric materials include crown ethers, fully hydrogenated oils and waxes. Moreover, the taste masking agents may be water soluble, water insoluble or partially water soluble.

Useful non-limiting acrylic polymers include those available under the trade name Eudragit® from Röhm America, LLC, such as methacrylic acid co-polymers sold under the trade names Eudragit E®, Eudragit L®, Eudragit RD® and Eudragit S®, and polyethylacrylate-methylmethacrylate sold under the trade name, Eudragit NE®. These acrylic polymers are generally water soluble materials.

Useful non-limiting cellulosic polymers include, alkylcelluloses, such as, methyl or ethyl cellulose and, hydroxyalkylcelluloses, such as hydroxylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxymethylpropyl cellulose, and combinations thereof. Useful alkylcelluloses include those sold under the trade names Methocel E™ by Dow Chemicals. Additionally, useful ethylcelluloses are commercially available commercially available from FMC Corporation under brand name Aquacoat ECD. These acrylic polymers are generally water soluble materials.