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(19)

(54) A PHARMACEUTICAL PREPARATION IN THE FORM OF A FOIL HAVING AN ACTIVE SUBSTANCE INCORPORATED THEREIN

(71) We, SCHERING AKTIENGESELLSCHAFT, a body corporate organised according to the laws of Germany, of Berlin and Bergkamen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a pharmaceutical preparation in the form of a foil having an active substance incorporated therein, for internal and external use.

Belgian Specification No. 637,363 describes paper foils coated with active substances suitable for oral use. The foils consist of cellulose fibres insoluble in water and a water-soluble binding agent. As water-soluble binding agent there is preferably used sodium carboxymethyl-cellulose. The active substance may be applied to the paper foil by dropping onto it a solution of the active substance, by spreading the solid active substance on the foil or by drawing the foil through a solution of the active substance. The discontinuous process of separately making the foil and applying the active substance has the disadvantage that the accuracy of the dosage is not very good, accuracy being of great importance as active substances are generally administered in small doses at the present time. Inaccuracies arise not only in applying the active substance, but also in the manufacture and pretreatment of the foil and owing to variations during storage of the foil material. Thus, for example, it has been found that in using foil drawing machines as prescribed in Belgian Specification No. 637,363 non-uniform layers of foil are formed, and that the foil shrinks during drying. However, it is easy to understand that with non-uniform material the take-up of active substance is also not uniform. Moreover, an active substance bound only on the surface can be partially removed during the handling of the foils, for example, during packing. The sodium carboxymethyl-cellulose used as binding agent becomes detached in the stomach and there is liberated carboxymethyl-cellulose, which includes some of the active substance and liberates it only slowly or not at all.

The present invention is based on the observation that foils having a constant thickness and a uniform distribution of active substance can be obtained by making foils having the active substance incorporated therein and using foil formers that are soluble in water or certain organic solvents.

The present invention provides a pharmaceutical preparation in the form of a foil (as hereinafter defined), wherein the foil incorporates from a foil forming material or materials that is or are soluble in at least one of the following solvents:— water, aliphatic alcohols containing up to 6 carbon atoms, chlorinated aliphatic hydrocarbons containing up to 8 carbon atoms, aliphatic ketones containing from 3 to 7 carbon atoms and mixtures of any two or more of these solvents. There are preferably used foil forming materials that are soluble in water, ethyl alcohol, isopropanol, acetone or methylene chloride, or in a mixture of any two or more of such solvents. Especially suitable are foil forming materials that are soluble both in water and in at least one of the organic solvent selected from aliphatic alcohols containing up to 6 carbon atoms, chlorinated aliphatic hydrocarbons containing up to 6 carbon atoms and aliphatic ketones containing

from 3 to 7 carbon atoms, more particularly those that are soluble in mixtures of ethyl alcohol and water.

The term "foil" as used herein includes a lamina strip and a film.

As foil formers there come into consideration, for example, poly-N-vinyl-pyrrolidone, vinylpyrrolidone-vinyl acetate, methyl- and ethyl-cellulose, but preferably non-ionic water-soluble hydroxyalkyl ethers of cellulose such, for example, as hydroxypropyl-cellulose, hydroxyethyl-cellulose and methylhydroxy-propyl-cellulose.

In addition to the active substance or substances the foil may contain fillers and advantageously a small amount of a release agent.

Suitable release agents are, *inter alia,* polyoxyethylene-polyoxypropylene polymer (PLURONIC F 68), polyoxyl stearates, alkyl- or acyl-substituted polyaddition products of ethylene oxide, for example, CREMOPHOR EL, silicones and silicone parting emulsions, glycerine, propylene glycol and metal soaps. The terms PLURONIC F 68 and CREMOPHOR EL are Registered Trade Marks.

As fillers there may be mentioned, for example, cellulose, sugars, for example, lactose, dextrose and cane sugar, starches, polyhydric alcohols, for example, mannitol, calcium carbonate, calcium phosphate, talcum and dyestuffs in water-soluble form or as pigments. The fillers used in the preparations of the invention are generally insoluble or only sparingly soluble in water and organic solvents. When fillers and active substances are used which are soluble in water or organic solvents a transparent smooth foil is formed, and when insoluble fillers, especially cellulose, or insoluble active substances are used a white or coloured paper-like foil is formed.

All active substances used in human and veterinary medicine can be used in accordance with the invention. For internal use there comes into consideration especially oral administration. As external use there is to be understood, more especially, topical administration on the skin and in body cavities such, for example, as the nose, ears and vagina. As active substances there may be mentioned, for example: Gestagens, oestrogens, mixtures of gestagens and oestrogens, tranquillizers, anti-diabetics, sulphonamides, antibiotics, trichomonal agents and inflammation inhibitors, for example corticoids.

The medicaments may be present in the carrier materials in a dissolved or uniformly suspended state. The proportion of active substance in the foil may be up to 60 per cent by weight of the foil. The surfaces may be cut or perforated to form unit dosage portions which can be readily separated and which contain quantities of active substance such as are usually present also in tablets, dragées, salves and suppositories. Thus, the quantity of active substance per single dose may be as high as desired depending on the mode of use and from 1 μ gram to 0.5 gram, and the lower and upper dose may easily be smaller or greater.

For the production of the medicinal preparations in foil form of the invention the active substance and/or parting compound is dissolved or suspended, the foil former and optionally the filler is introduced, optionally homogenised, and the solution or suspension is drawn out on a foil drawing machine to a sheet. The foil obtained by drying the sheet is divided into sections (units).

Into the solution or suspension are introduced the foil former in a proportion by weight of from 6 to 20 per cent, the filler in a proportion by weight of up to 30 per cent and the release agent preferably in a proportion by weight of 0.01 to 2 per cent, the percentages being calculated on the total weight of the solution or suspension.

The content of solvent or suspension medium is from 48 to 84 per cent by weight and consists of water and/or one or more organic solvents. As organic solvents there come into consideration physiologically tolerable solvents or solvents that are removed except for a physiologically unobjectionable residue. Such solvents are, for example, aliphatic alcohols containing up to 6 carbon atoms, chlorinated hydrocarbons, especially chlorinated aliphatic hydrocarbons containing up to 6 carbon atoms, aliphatic ketones containing from 3 to 7 carbon atoms and mixtures of any two or more of such solvents. There may be mentioned, more especially, ethyl alcohol, isopropanol, acetone and methylene chloride, and mixtures thereof. There are preferably used water and ethyl alcohol or mixtures of water and ethyl alcohol.

The layer thickness of the wet sheet is generally 0.1 to 2 mm and that of the dry foil is from 0.05 to 1 mm, and preferably 0.07 to 0.3 mm.

The process of making the medicinal preparation in foil form in one operation

(a continuous process) has the advantage that the active substance is homogeneously and uniformly distributed in the medicament carrier. By varying the concentration of the active substance in the carrier, the thickness of the foil and the area of the foil the unit dose can be varied in a very simple manner.

The pharmaceutical preparations of the invention may be in the form of a two-phase or multi-phase preparation wherein the foil contains different active ingredients and/or different concentrations of active ingredient in different sections or zones of the foil, and/or in which one or more sections or zones may contain no active ingredient. Thus, foils can be made with a sheet in which different active substances and/or varying concentrations of active substance are incorporated side by side over the width of the web of foil. By means of a special doctor, which consists of two or more compartments, different solutions or suspensions can be drawn out without mixing to form a coherent sheet. The width and thickness of the sheet is separately adjustable for each compartment. If desired, zones (strips) having different active substances or different concentrations are made visible by different dyestuffs. By drying the wet sheet there is obtained a foil, which by being divided in an appropriate way, for example, by perforation, yields units containing different active substances and/or concentrations of active substance or units containing no active substance. Foils containing different active substances and/or different concentrations of active substance are required for making multi-phase preparations, for example, for making contraceptive preparations. The possibility of the spatial separation of active substances that are incompatible with one another in one foil unit improves the stability of the individual active substances. Foils for intravaginal application may, for example, also be rolled round an ordinary commercial tampon.

The invention also provides a process for the manufacture of a pharmaceutical preparation in the form of a foil, wherein two or more solutions or suspensions are prepared each containing a different active ingredient and/or different concentrations of active ingredient and in which one or more solutions or suspensions may contain no active ingredient, the solutions or suspensions are drawn on a suitable foil drawing apparatus having doctor means to give a sheet containing in different sections or zones of the sheet different active ingredients and/or different concentrations of active ingredient (including zero concentration), and the foil is appropriately divided by cutting, perforation or other means to give a two-phase or multi-phase preparation in which unit dosage portions can be readily detached.

The following Examples 1 to 19 illustrate the invention; with the exception of Examples 5 and 15 the preparations described in the Examples are primarily suitable for oral administration.

Example 1.

Preparation for 1000 units:

0.25 gram of *d*-norgestrel,
0.05 gram of ethinyl-oestradiol and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in
95.00 grams of ethyl alcohol while stirring, and into this is introduced a powdered mixture of
16.93 grams of hydroxypropyl-cellulose and
16.93 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.

The composition of one unit:

0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.93 mg of hydroxypropyl-cellulose
16.93 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 2.

A preparation for 1000 units:
1.10 grams of Cremophor EL are dissolved in
152.00 grams of water. In this solution are suspended
0.25 gram of micronised *d*-norgestrel and
0.05 gram of micronised ethinyl-oestradiol and if necessary homogenised.
Into the suspension are introduced
22.10 grams of hydroxypropyl-cellulose and
16.50 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition for one unit:
0.25 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
1.10 mg of Cremophor EL
22.10 mg of hydroxypropyl-cellulose
16.50 mg of cellulose

40.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 3.

A preparation for 1000 units:
0.03 gram of *d*-norgestrel and
0.84 gram of polyoxyl-40-stearate are dissolved, while stirring, in
95.00 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
16.93 grams of hydroxypropyl-cellulose and
17.20 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition of one unit:
0.03 mg of *d*-norgestrel
0.84 mg of polyoxyl-40-stearate
16.93 mg of hydroxypropyl-cellulose
17.20 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 4.

A preparation for 1000 units:
1.10 grams of polyoxyethylene-polyoxypropylene polymer are dissolved in
152.00 grams of demineralised water. In this solution is suspended
0.03 gram of micronised *d*-norgestrel, and if necessary homogenised. Into the suspension are introduced
22.10 grams of hydroxypropyl-cellulose and
16.77 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition for one unit:
0.03 mg of *d*-norgestrel
1.10 mg of polyoxyethylene-polyoxypropylene polymer
22.10 mg of hydroxypropyl-cellulose
16.77 mg of cellulose

40.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 5.

A preparation for 1000 units:
0.025 gram of fluocortolone trimethylacetate and
0.183 gram of glycerine are dissolved in
30.000 grams of ethyl alcohol. Into this solution are introduced
7.292 grams of hydroxypropyl-cellulose.

The solution so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition of one unit:
0.025 mg of fluocortolone trimethylacetate
0.183 mg of glycerine
7.292 mg of hydroxypropyl-cellulose

7.500 mg

One unit corresponds to an area of about 1 cm^2.
Appearance of the foil: transparent.
The dry foil has a thickness of about 70 μm.
The foil is suitable for topical use.

Example 6.

A preparation for 1000 units:
10.00 grams of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzo-diazepine-4-oxide and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in
95.00 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
16.93 grams of hydroxypropyl-cellulose and
7.23 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition of one unit:
10.00 mg of 7-chloro-2-methylamino-5-phenyl-3H-1,4-benzo-diazepine-4-oxide
0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.93 mg of hydroxypropyl-cellulose
7.23 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: yellow, paper-like.
The dry foil has a thickness of about 170 μm.

Example 7.

A preparation for 1000 units:
1.00 gram of norethisterone acetate,
0.03 gram of ethinyl-oestradiol and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in
95.00 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
16.93 grams of hydroxypropyl-cellulose and
16.20 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition for one unit:
1.00 mg of norethisterone acetate
0.03 mg of ethinyl-oestradiol

0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.93 mg of hydroxypropyl-cellulose
16.20 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 8.

A preparation for 1000 units:
1.00 gram of norethisterone acetate
0.03 gram of ethinyl-oestradiol and
0.84 gram of propylene glycol are dissolved in a mixture of
101.60 grams of methylene chloride and
26.40 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
8.47 grams of hydroxypropyl-cellulose
8.47 grams of hydroxyethyl-cellulose and
16.19 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition for one unit:
1.00 mg of norethisterone acetate
0.03 mg of ethinyl-oestradiol
0.84 mg of propylene glycol
8.47 mg of hydroxypropyl-cellulose
16.19 mg of cellulose

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 9.

A preparation for 1000 units:
1.00 gram of norethisterone acetate,
0.03 gram of ethinyl-oestradiol and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in
101.60 grams of methylene chloride and
25.40 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
16.93 grams of hydroxyethyl-cellulose and
16.20 grams of starch.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.
The composition for one unit:
1.00 mg of norethisterone acetate
0.03 mg of ethinyl-oestradiol
0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.93 mg of hydroxyethyl-cellulose and
16.20 mg of starch

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 10.

A preparation for 1000 units:
1.00 gram of norethisterone acetate
0.03 gram of ethinyl-oestradiol and
0.84 gram of polyoxyl-40-stearate are dissolved in
95.00 grams of ethyl alcohol. Into this solution is introduced a powdered mixture of
16.93 grams of hydroxypropyl-cellulose
8.10 grams of lactose and
8.10 grams of maize starch.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm, and is then dried.

The composition for one unit:
1.0 mg of norethisterone acetate
0.03 mg of ethinyl-oestradiol
0.84 mg of polyoxyl-40-stearate
16.93 mg of hydroxypropyl-cellulose
8.10 mg of lactose
8.10 mg of maize starch

35.00 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 11.

A preparation for 1000 units:
1.00 gram of norethisterone (17α-ethinyl-19-nor-testosterone)
0.03 gram of ethinyl-oestradiol and
0.22 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
84.75 grams of ethyl alcohol and
4.00 grams of water. Into this solution is introduced a powdered mixture of
16.00 grams of hydroxypropyl-cellulose and
16.00 grams of cellulose.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 600 μm and then dried.

The composition for one unit:
1.00 mg of norethisterone (17α-ethinyl-19-nor-testosterone)
0.03 mg of ethinyl-oestradiol
0.22 mg of polyoxyethylene-polyoxypropylene polymer
16.00 mg of hydroxypropyl-cellulose
16.00 mg of cellulose

33.25 mg

One unit corresponds to an area of about 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of approx. 230 μm.

Example 12.

A preparation for 1000 units:
4.00 grams of glisoxepide * in micronised form are suspended in
0.9 gram of polyoxyl-40-stearate dissolved in
152.0 grams of water, and if necessary homogenised. Into the suspension are introduced
15.0 grams of hydroxyethyl-cellulose and
15.1 grams of calcium carbonate.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm and dried.

The composition for one unit:
4.00 mg of glisoxepide *
0.90 mg of polyoxyl-40-stearate
15.00 mg of hydroxyethyl-cellulose
15.00 mg of calcium carbonate

35.00 mg

One unit corresponds to an area of about 3 cm².
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

* 4 - {4 - [β - (5 - methyl - isoxazol - 3 - carboxamido) - ethyl] - benzosulphonyl}-1,1 - hexamethylene - semicarbazide.

Example 13.

A preparation for 1000 units:
0.030 gram of *d*-norgestrel are dissolved in
40.000 grams of methylene chloride and
55.000 grams of ethanol. Into this solution are introduced
0.840 gram of silicone oil
6.930 grams of methyl-cellulose and
10.000 grams of poly-N-vinyl-pyrrolidone and
17.200 grams of starch, and if necessary homogenised.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 500 μm and dried.
The composition of one unit:
0.030 mg of *d*-norgestrel
0.840 mg of silicone oil
6.930 mg of methyl-cellulose
10.000 mg of poly-N-vinyl-pyrrolidone
17.200 mg of starch

35.000 mg

One unit corresponds to an area of about 3 cm².
Appearance of the foil: white, paper-like.
The dry foil has a thickness of about 170 μm.

Example 14.

A preparation for 1000 units:
0.04 gram of saccharin
0.04 gram of cream essence and
0.40 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
79.00 grams of ethyl alcohol and
4.00 grams of water. Into this solution are introduced
30.00 grams of iron (II) fumarate,
15.00 grams of hydroxypropyl-cellulose,
5.52 grams of cocoa and
4.00 grams of cellulose, and if necessary homogenised.

The suspension so obtained is drawn on a suitable foil drawing apparatus to a sheet having a thickness of 0.5 mm, and then dried.
The composition for one unit:
30.00 mg of iron (II) fumarate
15.00 mg of hydroxypropyl-cellulose
4.00 mg of cellulose
0.40 mg of polyoxyethylene-polyoxypropylene polymer
5.52 mg of cocoa
0.04 mg of saccharin
0.04 mg of cream essence

55.00 mg. Weight per unit.

One unit corresponds to an area of about 3 cm².
Appearance of the foil: pale red-brown.

Example 15.

Foils for intravaginal application:
The foil is prepared in accordance with Example 11.
The composition of one unit:

100.0 mg of 5-morpholinomethyl-3-(5-nitro-1-methyl-2-imidazolyl)-methyleneamino-2-oxazolidone. HCl
8.4 mg of Cremophor EL
169.2 mg of methylhydroxypropyl-cellulose
72.4 mg of cellulose

350.0 mg. Weight of one unit.

One unit corresponds to an area of about 8 × 4 cm.
Appearance of the foil: pale yellow.
The foil (1 unit) is either rolled round an ordinary commercial tampon or is itself rolled to form a narrow tube.

Example 16.

A two phase preparation
Part 1: 21 units containing active substance.
Part 2: 7 units without active substance.

A preparation for 3000 units. Part 1.
0.75 gram of *d*-norgestrel
0.15 gram of ethinyl-oestradiol and
0.54 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
237.00 grams of ethyl alcohol and
12.00 grams of water. Into this solution are introduced
44.28 grams of hydroxypropyl-cellulose and
44.28 grams of cellulose, and if necessary homogenised.

A preparation for 1000 units. Part 2.
0.18 gram of polyoxyethylene-polyoxypropylene polymer is dissolved in a mixture of
79.00 grams of ethyl alcohol and
4.00 grams of water. Into this solution are introduced
14.91 grams of hydroxypropyl-cellulose and
14.91 grams of cellulose, and if necessary homogenised.

The suspensions so obtained are drawn on a suitable foil drawing apparatus having a two compartment special doctor (widths of the compartments: 1 = 54 mm; 2 = 18 mm) to form a sheet of 0.5 mm and then dried. By appropriate division into units measuring 18 × 18 mm, for example, by perforation, the foil can be divided over its width into three units containing active substance and one unit free from active substance. There may be produced in the web of foil any desired number of sections having a ratio of three units containing active substance to one unit containing no active substance.
The composition of each unit:

Part 1 (containing active substance)	Part 2 (free from active substance)
0.25 mg of *d*-norgestrel	—
0.05 mg of ethinyl-oestradiol	—
14.76 mg of hydroxypropyl-cellulose	14.91 mg
14.76 mg of cellulose	14.91 mg
0.18 mg of polyoxyethylene-polyoxypropylene polymer	0.18 mg
30.00 mg weight per unit	30.00 mg

Area per unit: about 3 cm².
Appearance: white.

Example 17.

Three phase preparation (two active substance stage preparation).
Part 1: 11 Units containing 0.05 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol.
Part 2: 10 Units containing 0.125 mg of *d*-norgestrel
0.050 mg of ethinyl-oestradiol.
Part 3: 7 Units without active substance.

A preparation for 1100 units. Part 1:
0.055 gram of *d*-norgestrel,
0.055 gram of ethinyl-oestradiol and
0.198 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
86.900 grams of ethyl alcohol and
4.400 grams of water. Into this solution are introduced
16.346 grams of hydroxypropyl-cellulose and
16.346 grams of cellulose, and if necessary homogenised.

A preparation for 1000 units. Part 2.
0.125 gram of *d*-norgestrel
0.050 gram of ethinyl-oestradiol and
0.180 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
79.000 grams of ethyl alcohol and
4.000 grams of water. Into this solution are introduced
14.823 grams of hydroxypropyl-cellulose and
14.822 grams of cellulose, and if necessary homogenised.

A preparation for 700 units. Part 3:
0.189 gram of polyoxyethylene-polyoxypropylene polymer is dissolved in a mixture of
82.950 grams of ethyl alcohol and
4.200 grams of water. Into this solution are introduced
15.656 grams of hydroxypropyl-cellulose and
15.655 grams of cellulose, and if necessary homogenised.

The suspensions so obtained are drawn on a suitable foil drawing apparatus having a three compartment special doctor (width per compartment 18 mm) to a sheet and dried. By appropriate division, for example, by perforation, there can be distributed over the width of the foil three units of 18 × 18 mm for Part 1, of 18 × 19.8 mm for Part 2 and of 18 × 28 for Part 3, having different contents of active substance. There can be separated from the foil web preparations having 11 units of Part 1, 10 units of Part 2 and 7 units of Part 3.

The composition per unit:

Part 1	Part 2	Part 3	Ingredients
0.050 mg	0.125 mg	—	*d*-norgestrel
0.050 mg	0.050 mg	—	ethinyl-oestradiol
0.180 mg	0.180 mg	0.270 mg	polyoxyethylene-polyoxypropylene polymer
14.860 mg	14.823 mg	22.366 mg	hydroxypropyl-cellulose
14.860 mg	14.822 mg	22.364 mg	cellulose
30.000 mg	30.000 mg	45.000 mg	weight per unit
about 3 cm^2	about 3.5 cm^2	about 5 cm^2	area per unit
white	white	white	appearance

Example 18.

Three phase preparation:
Part 1: 11 Units containing 0.05 mg of *d*-norgestrel
0.05 mg of ethinyl-oestradiol
Part 2: 10 Units containing 0.125 mg of *d*-norgestrel
0.050 mg of ethinyl-oestradiol
Part 3: 7 Units containing 0.050 mg of iron (II) fumarate.

A preparation for 1100 units. Part 1:
0.066 gram of food colour yellow No. 2 (tartrazine; E 102) is dissolved in
4.400 grams of water, and then introduced into
86.900 grams of ethyl alcohol. In this solution are dissolved
0.055 gram of *d*-norgestrel
0.055 gram of ethinyl-oestradiol and
0.198 gram of polyoxyethylene-polyoxypropylene polymer. Into this solution are introduced
16.313 grams of hydroxypropyl-cellulose and
16.313 grams of cellulose, and if necessary homogenised.

A preparation for 1000 units. Part 2:
0.065 gram of food colour orange No. 2 (Sunset Yellow; E 110) is dissolved in
4.000 grams of water, and then introduced into
79.000 grams of ethyl alcohol. In this solution are dissolved
0.125 gram of *d*-norgestrel
0.050 gram of ethinyl-oestradiol and
0.180 gram of polyoxyethylene-polyoxypropylene polymer. Into this solution are introduced
14.790 grams of hydroxypropyl-cellulose and
14.790 grams of cellulose, and if necessary homogenised.

A preparation for 700 units. Part 3:
0.042 gram of saccharin
0.042 gram of cream essence and
0.406 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in a mixture of
55.300 grams of ethyl alcohol and
2.800 grams of water. Into this solution are introduced
35.000 grams of iron (II) fumarate
17.500 grams of hydroxypropyl-cellulose
5.950 grams of cocoa and
4.060 grams of cellulose, and if necessary homogenised.

The suspensions so prepared are drawn on a suitable foil drawing apparatus having a three compartment special doctor (width per compartment 18 mm) to a sheet and dried. By appropriate division, for example, by perforation, there can be distributed over the width of the foil three units of 18 × 18 mm for Part 1, of 18 × 19.8 mm for Part 2 and of 18 × 28 mm for Part 3, having different contents of active substance. There can be separated from the foil web preparations having 11 units of Part 1, 10 units of Part 2 and 7 units of Part 3.
The composition per unit:

Part 1	Part 2	Part 3	Ingredients
0.050 mg	0.125 mg	—	*d*-norgestrel
0.050 mg	0.050 mg	—	ethinyl-oestradiol
—	—	50.000 mg	iron (II) fumarate
0.180 mg	0.180 mg	0.580 mg	polyoxyethylene-polyoxypropylene polymer
0.060 mg	—	—	food colour yellow No. 2
—	0.065 mg	—	food colour orange No. 2
14.830 mg	14.790 mg	25.000 mg	hydroxypropyl-cellulose
14.830 mg	14.790 mg	5.800 mg	cellulose
—	—	8.500 mg	cocoa
—	—	0.060 mg	saccharin
—	—	0.060 mg	cream essence
30.000 mg	30.000 mg	90.000 mg	weight per unit
about 3 cm^2	about 3.5 cm^2	about 5 cm^2	area per unit
yellow	orange	brown	appearance

Example 19.

Preparation for 1000 units:

0.15 gram of *d*-norgestrel
0.03 gram of ethinyl-oestradiol and
0.84 gram of polyoxyethylene-polyoxypropylene polymer are dissolved in 95.00 grams of ethyl alcohol while stirring and a powdered mixture of 16.99 grams of hydroxypropyl-cellulose and 16.99 grams of cellulose is introduced into this solution.

The suspension obtained is drawn out on a suitable foil drawing apparatus to a very thin foil having a thickness of 500 μm, and is then dried.

The composition of one unit:

0.15 mg of *d*-norgestrel
0.03 mg of ethinyl-oestradiol
0.84 mg of polyoxyethylene-polyoxypropylene polymer
16.99 mg of hydroxypropyl-cellulose
16.99 mg of cellulose

35.00

One unit corresponds to an area of approx. 3 cm^2.
Appearance of the foil: white, paper-like.
The dry foil has a thickness of approx. 170 μm.

WHAT WE CLAIM IS:—

1. A pharmaceutical preparation in the form of a foil (as hereinbefore defined), wherein the foil incorporates one or more pharmacologically active ingredients and is obtained from a foil forming material or materials that is or are soluble in at least one of the following solvents:— water, aliphatic alcohols containing up to 6 carbon atoms, chlorinated aliphatic hydrocarbons containing up to 6 carbon atoms, aliphatic ketones containing from 3 to 7 carbon atoms and mixtures of any two or more of these solvents.

2. A preparation as claimed in claim 1, wherein the foil is obtained from a foil forming material or materials that is or are soluble in at least one of the following solvents: water, ethyl alcohol, isopropanol, acetone, methylene chloride and mixtures of any two or more of such solvents.

3. A preparation as claimed in claim 1, wherein the foil is obtained from a foil forming material or materials that is or are soluble in mixtures of water and ethyl alcohol.

4. A preparation as claimed in claim 1, wherein the foil forming material is hydroxypropyl-cellulose, hydroxyethyl-cellulose or methylhydroxypropyl-cellulose or a mixture of any two or all of such compounds.

5. A preparation as claimed in claim 1, wherein the foil forming material is poly-N-vinyl-pyrrolidone, vinylpyrrolidone-vinylacetate copolymer, methyl-cellulose or ethyl-cellulose.

6. A preparation as claimed in any one of claims 1 to 5, wherein the foil has a thickness of from 0.05 to 1 mm.

7. A preparation as claimed in claim 6, wherein the foil has a thickness of from 0.07 to 0.3 mm.

8. A preparation as claimed in any one of claims 1 to 7, which contains up to 60 per cent by weight of the active ingredient or ingredients.

9. A preparation as claimed in any one of claims 1 to 8, wherein the active ingredient is a gestagen, oestrogen or a mixture of a gestagen and an oestrogen, a tranquilliser, an anti-diabetic, a sulphonamide, an antibiotic, a trichomonal agent or an inflammation inhibitor.

10. A preparation as claimed in any one of claims 1 to 9, wherein the pharmacologically active ingredient is dissolved or uniformly suspended in the foil material.

11. A preparation as claimed in any one of claims 1 to 10, which also contains a filler and/or a release agent.

12. A preparation as claimed in any one of claims 1 to 11, which is in the form of a two-phase or multi-phase preparation wherein the foil contains different active ingredients and/or different concentrations of active ingredient in different sections or zones of the foil, and/or in which one or more sections or zones may contain no active ingredient.

13. A preparation as claimed in claim 12, wherein the zones having different active ingredients and/or different concentrations of active ingredient are indicated by means of different dyestuffs.

14. A preparation as claimed in any one of claims 1 to 13, wherein the surface of the foil is cut or perforated in order to provide unit dosage portions which can be readily separated.

15. A preparation as claimed in any one of claims 1 to 12, which is in unit dosage form.

16. A preparation as claimed in any one of claims 1 to 15, which is suitable for oral administration.

17. A preparation as claimed in any one of claims 1 to 15, which is suitable for topical administration on the skin or in body cavities.

18. A preparation as claimed in claim 17, which is suitable for intravaginal application.

19. A preparation as claimed in any one of claims 1 to 18, which is a contraceptive preparation.

20. A preparation as claimed in claim 1 and substantially as described in any one of Examples 1 to 13 and 15 to 20 herein.

21. A process for the manufacture of a pharmaceutical preparation in the form of a foil as hereinbefore defined, wherein one or more pharmacologically active ingredients is or are dissolved or suspended in a liquid medium, a foil forming material or materials, that is or are soluble in at least one of the solvents specified in claim 1, is or are incorporated in the medium, the solution or suspension is drawn on a foil drawing machine to a sheet and the foil so obtained is dried and, if desired, divided into sections or zones.

22. A process as claimed in claim 21, wherein a release agent and, if desired, a filler is or are incorporated in the liquid medium.

23. A process as claimed in claim 22, wherein the foil former is used in a proportion of from 6 to 20 percent by weight, the filler in a proportion of up to 30 per cent by weight and the release agent in a proportion of from 0.01 to 2 per cent by weight.

24. A process as claimed in any one of claims 21 to 23, wherein the liquid medium is water and/or an organic solvent.

25. A process as claimed in claim 24, wherein the organic solvent is ethyl alcohol, isopropanol, acetone or methylene chloride or a mixture of any two or more of such solvents.

26. A process as claimed in claim 24, wherein the liquid medium is a mixture of water and ethyl alcohol.

27. A process as claimed in any one of claims 21 to 26, wherein the liquid medium is used in a proportion of from 48 to 84 per cent by weight.

28. A process as claimed in any one of claims 21 to 27, wherein the wet sheet has a thickness of from 0.1 to 2 mm and the dry foil has a thickness of from 0.05 to 1 mm.

29. A process as claimed in any one of claims 21 to 28, wherein the foil forming material is as specified in claim 4.

30. A process as claimed in any one of claims 21 to 28, wherein the foil forming material is as specified in claim 5.

31. A process as claimed in any one of claims 21 to 30, wherein the active ingredient is as specified in claim 9.

32. A process as claimed in any one of claims 21 to 31, wherein two or more solutions or suspensions are prepared each containing a different active ingredient and/or different concentrations of active ingredient and in which one or more solutions or suspensions may contain no active ingredient, the solutions or suspensions are drawn on a suitable foil drawing apparatus having doctor means to give a sheet containing in different sections or zones of the sheet different active ingredients and/or different concentrations of active ingredient (including zero concentration), and the foil is appropriately divided by cutting, perforation or other means to give a two-phase or multi-phase preparation in which unit dosage portions can be readily detached.

33. A process as claimed in claim 21, substantially as described in any one of Examples 1 to 19 herein.

34. A contraceptive pack which comprises a contraceptive preparation as claimed in claim 19 or as described in any one of Examples 1 to 4, 7 to 11, 13, and 16 to 19, and instructions or indications for its use in the treatment of human females.

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(54) Title: GLUCAN BASED FILM DELIVERY SYSTEMS

(57) Abstract: An ingestible water-soluble delivery system in the form of a film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Delivery system films of the present invention include a low content of pullulan and can include a relatively high content of a pharmaceutical, cosmetic, or biologically-active agent.

GLUCAN BASED FILM DELIVERY SYSTEMS

FIELD OF THE INVENTION

The invention relates to film delivery systems, especially suitable for oral delivery, which can be formed during manufacture in the form of large film strips or sheets and subsequently cut into uniform dosage units, each dosage unit being uniform in content and having distributed therein a glucan, such as pullulan, a water-soluble polymer and optionally an active component.

BACKGROUND OF RELATED TECHNOLOGY

Self-supporting glucan films, such as those made from pullulan and elsinan, are known as being useful for the delivery of edible or ingestible components, for packaging and wrapping as well as other uses. For example, U.S. Patent No. 4,562,020 to Haijiya, et al. discloses a continuous process for producing such self-supporting glucan films formed from aqueous glucan solutions whereby the solution is deposited on a corona-treated plastic conveyor belt and air dried to form thin films. A variety of additional ingredients, such as flavors, colors, seasonings, cyclodextrine, protein, fat, vitamin, hormones, anti-genic substances, antibiotics, biologically active substances, viruses, lecithin, plasticizers, micro-organisms, spores, seeds and the like are disclosed as being useful additives.

Pullulan is a desirable material for forming edible films because of its high water solubility, rapid dissolution and excellent mouth-feel. However, due to its relatively low molecular weight as compared to many polymeric film forming materials, it is difficult to achieve films having low pullulan content. This is because, due to the low viscosity of pullulan, high amounts of pullulan must be present in the aqueous solution for good film casting. Generally, the pullulan content must be greater than 20% by weight in order to form a useful film. When insoluble additives are to be added to such pullulan solutions, even more pullulan must be used in order to achieve sufficient viscosity to prevent separation of the insoluble particulate from the solution prior to or during the film forming process. For example, many useful pharmaceutical and cosmetic active agents are water insoluble particulates. These particulates must be uniformly dispersed throughout the pullulan solution and must remain uniformly dispersed in the film forming process, such that the resultant

films have uniform drug content. For example, by uniform content it is meant that unit dosages cut from larger pieces of film will not substantially vary in the amount of drug content. In particular, the drug content of any one unit dosage should not vary more than 10% in order to be acceptable for sale under regulations by the U.S. Federal Drug Administration (FDA) or other world regulatory authorities regulations.

Films made from pullulan to-date also suffer the limitation that in order to put higher drug levels in the film, increased pullulan content is necessary in order to achieve uniformity in film content.

U.S. Patent No. 4,927,636 to Haijiya, et al. discloses pullulan films which have decreased solubility in water. These films are made from a combination of pullulan and polyethylene glycol (PEG) which form an "association complex" to produce this effect. Polyethylene glycols within the molecular range of 400 to 10,000 are disclosed as useful. The ratio of pullulan to PEG is disclosed as being 1 part by weight (pbw) pullulan to 0.01 to 100 part by weight (pbw) PEG. This patent discloses that pullulan in combination with other water-soluble polymers does not form such an association complex useful for decreasing solubility and reducing adhesive and stickiness properties of aqueous pullulan.

U.S. Patent No. 5,411,945 to Ozaki, et al. discloses a pullulan binder composition made from a combination of pullulan and a mono-saccharide or lower molecular weight oligo-saccharide in a ratio of 85:15 to 65:35 pullulan/saccharide. These films are disclosed as being gradually dissolvable.

U.S. Patent No. 5,518,902 to Ozaki, et al. discloses high pullulan content products made by cultivating micro-organisms capable of producing pullulan at a pH exceeding 2.0 but not higher than 4.0 in a nutrient culture medium containing 10-20 w/v % of a polysaccharide to produce pullulan, while controlling the viscosity of the nutrient culture to below 30 cps.

U.S. Patent Application Publication No. 2001/0022964 A1 to Leung, et al. discloses edible films made from pullulan and which include anti-microbial effective amounts of essential oils. A variety of polymers may be used as film formers in addition to pullulan.

Various drugs may be included in the films. The content of pullulan used is very high and the drug loading is very low, as is typical of pullulan films.

It would be desirable to have film products made from pullulan which can include high content active ingredients, such as pharmaceutical and/or cosmetic agents, and which have relatively low pullulan content. It would also be advantageous to provide water-soluble, edible films which have uniformity of active content, both in the manufacturing scale and in the unit dosage, final product form.

SUMMARY OF THE INVENTION

The present invention seeks to attain low content, high pharmaceutical and/or cosmetic 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 uniform distribution of 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 there is included an edible water-soluble delivery system in the form of a film composition which includes a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5. Desirably, a pharmaceutical and/or cosmetic active components is present in the delivery system in amounts effective for its intended use, desirably, due to the advantages of the aforementioned glucan/water-soluble polymer ratio, high amounts of active components may be present without disrupting the uniformity of content of the overall film and subsequently the individual dosage forms cut therefrom. Significantly lower amounts of pullulan, as compared to conventional pullulan films, can be used while maintaining a high load of active components. Increased flexibility as compared to pullulan or the water-soluble polymers being used along is achieved, as well as enhanced tensile strength and overall structural integrity. Elongation of the resultant film is substantially unaffected as compared to pullulan alone.

In another aspect of the present invention there is included a pharmaceutical composition in the form of a film for enteral or topical administration, which includes a composition having a uniformly distributed combination of a glucan, a water-soluble polymer, a polar solvent, and a pharmaceutical active, wherein said glucan and said water-soluble polymer are present in a ratio of about 40:1 to about 0.1:5, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

In another aspect of the present invention there is included a pharmaceutical and/or cosmetic dosage form which includes a film having a uniformly dispersed composition including a glucan and a water-soluble polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

In a further aspect of the present invention there is provided a pharmaceutical and/or cosmetic dosage form including an edible water-soluble film composition which includes a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5 having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

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

Glucans useful in the present invention include pullulan and elsinan. These materials substantially contain repeating maltotriose units and are produced by culturing a strain of species *Aureobasidium pullulans* or genus *Elsino* on a nutrient medium containing sugars under aeration and agitation conditions. The cellular debris is removed and the resultant supernatant is purified and filtrated to yield the resultant glucan. The molecular weight of the glucan may vary widely, but generally are commercially available at molecular weights of 50,000 to 100,000. Due to the relatively low molecular weight, water solubility is very high and attaining useful viscosities for film forming requires a high content of pullulan;

Water-soluble polymers useful in the present invention cellulosic materials, gums, proteins, starches, and combinations thereof.

Examples of cellulosic materials include, without limitation, carboxymethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose hydroxypropylmethyl 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 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 tapioca, rice, corn, potato, wheat and combinations thereof.

Useful water-soluble protein polymers 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 or combinations thereof, and polydextrose.

To achieve the desired results of the present invention of film content uniformity, the ratio of glucan to water-soluble polymer is about 40:1 to 0.1:5, desirable about 20:1 to 0.5:5 and more desirably 10:1 to about 1:5.

The ingestible 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 edible water-soluble delivery system of the present invention further includes one or more members selected from taste-masking agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents and combinations thereof.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal,

ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10'may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in

Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

Rheology and Films Properties

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to

Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o = (2gr^r)(\rho_p - \rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of

particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o = 1/(1 + \kappa\varphi)$$

where κ = a constant, and φ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_o^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n} (2\pi/\lambda)^{(3+n)/n} h^{(2n+1)/n} t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart

or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps ("cps" or "centipoise") to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be

adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

Film Component Mixing:

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch

22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30, 30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in

other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed "Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of

heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first ½ minute to about the first 4 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared

radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1mils to about 10mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot

break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions, low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and

sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the

film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Uses of Thin Films

The thin films of the present invention are well suited for many uses. The high degree of uniformity of the components of the film makes them particularly well suited for incorporating pharmaceuticals. Furthermore, the polymers used in construction of the films may be chosen to allow for a range of disintegration times for the films. A variation or extension in the time over which a film will disintegrate may achieve control over the rate that the active is released, which may allow for a sustained release delivery system. In addition, the films may be used for the administration of an active to any of several body surfaces, especially those including mucous membranes, such as oral, anal, vaginal, ophthalmological, the surface of a wound, either on a skin surface or within a body such as during surgery, and similar surfaces.

The films may be used to orally administer an active. This is accomplished by preparing the films as described above and introducing them to the oral cavity of a mammal. This film may be prepared and adhered to a second or support layer from which it is removed prior to use, i.e. introduction to the oral cavity. An adhesive may be used to attach the film to the support or backing material which may be any of those known in the art, and is preferably not water soluble. If an adhesive is used, it will desirably be a food grade adhesive that is ingestible and does not alter the properties of the active. Mucoadhesive compositions are particularly useful. The film compositions in many cases serve as mucoadhesives themselves.

The films may be applied under or to the tongue of the mammal. When this is desired, a specific film shape, corresponding to the shape of the tongue may be preferred. Therefore the film may be cut to a shape where the side of the film corresponding to the back of the tongue will be longer than the side corresponding to the front of the tongue. Specifically, the desired shape may be that of a triangle or trapezoid. Desirably, the film will adhere to the oral cavity preventing it from being ejected from the oral cavity and permitting more of the active to be introduced to the oral cavity as the film dissolves.

Another use for the films of the present invention takes advantage of the films' tendency to dissolve quickly when introduce to a liquid. An active may be introduced to a liquid by preparing a film in accordance with the present invention, introducing it to a liquid, and allowing it to dissolve. This may be used either to prepare a liquid dosage form of an active, or to flavor a beverage.

The films of the present invention are desirably packaged in sealed, air and moisture resistant packages to protect the active from exposure oxidation, hydrolysis, volatilization and interaction with the environment. Referring to Figure 1, a packaged pharmaceutical dosage unit 10, includes each film 12 individually wrapped in a pouch or between foil and/or plastic laminate sheets 14. As depicted in Figure 2, the pouches 10, 10' can be linked together with tearable or perforated joints 16. The pouches 10, 10'may be packaged in a roll as depicted in Figure 5 or stacked as shown in Figure 3 and sold in a dispenser 18 as shown in Figure 4. The dispenser may contain a full supply of the medication typically prescribed for the intended therapy, but due to the thinness of the film and package, is smaller and more

convenient than traditional bottles used for tablets, capsules and liquids. Moreover, the films of the present invention dissolve instantly upon contact with saliva or mucosal membrane areas, eliminating the need to wash the dose down with water.

Desirably, a series of such unit doses are packaged together in accordance with the prescribed regimen or treatment, e.g., a 10-90 day supply, depending on the particular therapy. The individual films can be packaged on a backing and peeled off for use.

Rheology and Films Properties

For the purposes of the present invention the term non-self-aggregating uniform heterogeneity refers to the ability of the films of the present invention, which are formed from one or more components in addition to a polar solvent, to provide a substantially reduced occurrence of, i.e. little or no, aggregation or conglomeration of components within the film as is normally experienced when films are formed by conventional drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The term heterogeneity, as used in the present invention, includes films that will incorporate a single component, such as a polymer, as well as combinations of components, such as a polymer and an active. Uniform heterogeneity includes the substantial absence of aggregates or conglomerates as is common in conventional mixing and heat drying methods used to form films.

Furthermore, the films of the present invention have a substantially uniform thickness, which is also not provided by the use of conventional drying methods used for drying water-based polymer systems. The absence of a uniform thickness detrimentally affects uniformity of component distribution throughout the area of a given film.

The film products of the present invention are produced by a combination of a properly selected polymer and a polar solvent, optionally including an active ingredient as well as other fillers known in the art. These films provide a non-self-aggregating uniform heterogeneity of the components within them by utilizing a selected casting or deposition method and a controlled drying process. Examples of controlled drying processes include, but are not limited to, the use of the apparatus disclosed in U.S. Patent No. 4,631,837 to Magoon ("Magoon"), herein incorporated by reference, as well as hot air impingement across the bottom substrate and bottom heating plates. Another drying technique for obtaining the

films of the present invention is controlled radiation drying, in the absence of uncontrolled air currents, such as infrared and radio frequency radiation (i.e. microwaves).

The objective of the drying process is to provide a method of drying the films that avoids complications, such as the noted "rippling" effect, that are associated with conventional drying methods and which initially dry the upper surface of the film, trapping moisture inside. In conventional oven drying methods, as the moisture trapped inside subsequently evaporates, the top surface is altered by being ripped open and then reformed. These complications are avoided by the present invention, and a uniform film is provided by drying the bottom surface of the film first or otherwise preventing the formation of polymer film formation (skin) on the top surface of the film prior to drying the depth of the film. This may be achieved by applying heat to the bottom surface of the film with substantially no top air flow, or alternatively by the introduction of controlled microwaves to evaporate the water or other polar solvent within the film, again with substantially no top air flow. Yet alternatively, drying may be achieved by using balanced fluid flow, such as balanced air flow, where the bottom and top air flows are controlled to provide a uniform film. In such a case, the air flow directed at the top of the film should not create a condition which would cause movement of particles present in the wet film, due to forces generated by the air currents. Additionally, air currents directed at the bottom of the film should desirably be controlled such that the film does not lift up due to forces from the air. Uncontrolled air currents, either above or below the film, can create non-uniformity in the final film products. The humidity level of the area surrounding the top surface may also be appropriately adjusted to prevent premature closure or skinning of the polymer surface.

This manner of drying the films provides several advantages. Among these are the faster drying times and a more uniform surface of the film, as well as uniform distribution of components for any given area in the film. In addition, the faster drying time allows viscosity to quickly build within the film, further encouraging a uniform distribution of components and decrease in aggregation of components in the final film product. Desirably, the drying of the film will occur within about ten minutes or fewer, or more desirably within about five minutes or fewer.

The present invention yields exceptionally uniform film products when attention is paid to reducing the aggregation of the compositional components. By avoiding the

introduction of and eliminating excessive air in the mixing process, selecting polymers and solvents to provide a controllable viscosity and by drying the film in a rapid manner from the bottom up, such films result.

The products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film. More particularly, a greater viscosity of components in the mixture is particularly useful when the active is not soluble in the selected polar solvent in order to prevent the active from settling out. However, the viscosity must not be too great as to hinder or prevent the chosen method of casting, which desirably includes reverse roll coating due to its ability to provide a film of substantially consistent thickness.

In addition to the viscosity of the film or film-forming components or matrix, there are other considerations taken into account by the present invention for achieving desirable film uniformity. For example, stable suspensions are achieved which prevent solid (such as drug particles) sedimentation in non-colloidal applications. One approach provided by the present invention is to balance the density of the particulate (ρ_p) and the liquid phase (ρ_l) and increase the viscosity of the liquid phase (μ). For an isolated particle, Stokes law relates the terminal settling velocity (Vo) of a rigid spherical body of radius (r) in a viscous fluid, as follows:

$$V_o = (2gr^r)(\rho_p - \rho_l)/9\mu$$

At high particle concentrations, however, the local particle concentration will affect the local viscosity and density. The viscosity of the suspension is a strong function of solids volume fraction, and particle-particle and particle-liquid interactions will further hinder settling velocity.

Stokian analyses has shown that the incorporation of a third phase, dispersed air or nitrogen, for example, promotes suspension stability. Further, increasing the number of particles leads to a hindered settling effect based on the solids volume fraction. In dilute particle suspensions, the rate of sedimentation, v, can be expressed as:

$$v/V_o = 1/(1 + \kappa\varphi)$$

where κ = a constant, and φ is the volume fraction of the dispersed phase. More particles suspended in the liquid phase results in decreased velocity. Particle geometry is also an important factor since the particle dimensions will affect particle-particle flow interactions.

Similarly, the viscosity of the suspension is dependent on the volume fraction of dispersed solids. For dilute suspensions of non-interaction spherical particles, an expression for the suspension viscosity can be expressed as:

$$\mu/\mu_o = 1 + 2.5\phi$$

where μ_o is the viscosity of the continuous phase and ϕ is the solids volume fraction. At higher volume fractions, the viscosity of the dispersion can be expressed as

$$\mu/\mu_o = 1 + 2.5\varphi + C_1\varphi^2 + C_2\varphi^3 + ...$$

where C is a constant.

The viscosity of the liquid phase is critical and is desirably modified by customizing the liquid composition to a viscoelastic non-Newtonian fluid with low yield stress values. This is the equivalent of producing a high viscosity continuous phase at rest. Formation of a viscoelastic or a highly structured fluid phase provides additional resistive forces to particle sedimentation. Further, flocculation or aggregation can be controlled minimizing particle-particle interactions. The net effect would be the preservation of a homogeneous dispersed phase.

The addition of hydrocolloids to the aqueous phase of the suspension increases viscosity, may produce viscoelasticity and can impart stability depending on the type of hydrocolloid, its concentration and the particle composition, geometry, size, and volume fraction. The particle size distribution of the dispersed phase needs to be controlled by selecting the smallest realistic particle size in the high viscosity medium, i.e., <500μm. The presence of a slight yield stress or elastic body at low shear rates may also induce permanent stability regardless of the apparent viscosity. The critical particle diameter can be calculated from the yield stress values. In the case of isolated spherical particles, the maximum shear stress developed in settling through a medium of given viscosity can be given as

$$\tau_{max} = 3V\mu/2r$$

For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

A stable suspension is an important characteristic for the manufacture of a pre-mix composition which is to be fed into the film casting machinery film, as well as the maintenance of this stability in the wet film stage until sufficient drying has occurred to lock-in the particles and matrix into a sufficiently solid form such that uniformity is maintained. For viscoelastic fluid systems, a rheology that yields stable suspensions for extended time period, such as 24 hours, must be balanced with the requirements of high-speed film casting operations. A desirable property for the films is shear thinning or pseudoplasticity, whereby the viscosity decreases with increasing shear rate. Time dependent shear effects such as thixotropy are also advantageous. Structural recovery and shear thinning behavior are important properties, as is the ability for the film to self-level as it is formed.

The rheology requirements for the inventive compositions and films are quite severe. This is due to the need to produce a stable suspension of particles, for example 30-60 wt%, in a viscoelastic fluid matrix with acceptable viscosity values throughout a broad shear rate range. During mixing, pumping, and film casting, shear rates in the range of $10 - 10^5$ sec.$^{-1}$ may be experienced and pseudoplasticity is the preferred embodiment.

In film casting or coating, rheology is also a defining factor with respect to the ability to form films with the desired uniformity. Shear viscosity, extensional viscosity, viscoelasticity, structural recovery will influence the quality of the film. As an illustrative example, the leveling of shear-thinning pseudoplastic fluids has been derived as

$$\alpha^{(n-1/n)} = \alpha_o{}^{(n-1/n)} - ((n-1)/(2n-1))(\tau/K)^{1/n}\,(2\pi/\lambda)^{(3+n)/n}h^{(2n+1)/n}t$$

where α is the surface wave amplitude, α_o is the initial amplitude, λ is the wavelength of the surface roughness, and both "n" and "K" are viscosity power law indices. In this example, leveling behavior is related to viscosity, increasing as n decreases, and decreasing with increasing K.

Desirably, the films or film-forming compositions of the present invention have a very rapid structural recovery, i.e. as the film is formed during processing, it doesn't fall apart or become discontinuous in its structure and compositional uniformity. Such very rapid structural recovery retards particle settling and sedimentation. Moreover, the films or film-forming compositions of the present invention are desirably shear-thinning pseudoplastic

fluids. Such fluids with consideration of properties, such as viscosity and elasticity, promote thin film formation and uniformity.

Thus, uniformity in the mixture of components depends upon numerous variables. As described herein, viscosity of the components, the mixing techniques and the rheological properties of the resultant mixed composition and wet casted film are important aspects of the present invention. Additionally, control of particle size and particle shape are further considerations. Desirably, the size of the particulate a particle size of 150 microns or less, for example 100 microns or less. Moreover, such particles may be spherical, substantially spherical, or non-spherical, such as irregularly shaped particles or ellipsoidally shaped particles. Ellipsoidally shaped particles or ellipsoids are desirable because of their ability to maintain uniformity in the film forming matrix as they tend to settle to a lesser degree as compared to spherical particles.

Although a variety of different polymers may be used, it is desired to select polymers to provide a desired viscosity of the mixture prior to drying. For example, if the active or other components are not soluble in the selected solvent, a polymer that will provide a greater viscosity is desired to assist in maintaining uniformity. On the other hand, if the components are soluble in the solvent, a polymer that provides a lower viscosity may be preferred.

The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps ("cps" or "centipoise") to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

The viscosity may be adjusted based on the selected active depending on the other components within the matrix. For example, if the component is not soluble within the selected solvent, a proper viscosity may be selected to prevent the component from settling which would adversely affect the uniformity of the resulting film. The viscosity may be adjusted in different ways. To increase viscosity of the film matrix, the polymer may be chosen of a higher molecular weight or crosslinkers may be added, such as salts of calcium, sodium and potassium. The viscosity may also be adjusted by adjusting the temperature or

by adding a viscosity increasing component. Components that will increase the viscosity or stabilize the emulsion/suspension include higher molecular weight polymers and polysaccharides and gums, which include without limitation, alginate, carrageenan, hydroxypropyl methyl cellulose, locust bean gum, guar gum, xanthan gum, dextran, gum arabic, gellan gum and combinations thereof.

Film Component Mixing:

A number of techniques may be employed in the mixing stage to prevent bubble inclusions in the final film. To provide a composition mixture with substantially no air bubble formation in the final product, anti-foaming or surface-tension reducing agents are employed. Additionally, the speed of the mixture is desirably controlled to prevent cavitation of the mixture in a manner which pulls air into the mix. Finally, air bubble reduction can further be achieved by allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film. Desirably, the inventive process first forms a masterbatch of film-forming components without active ingredients such as drug particles or volatile materials such as flavor oils. The actives are added to smaller mixes of the masterbatch just prior to casting. Thus, the masterbatch pre-mix can be allowed to stand for a longer time without concern for instability in drug or other ingredients.

When the matrix is formed including the film-forming polymer and polar solvent in addition to any additives and the active ingredient, this may be done in a number of steps. For example, the ingredients may all be added together or a pre-mix may be prepared. The advantage of a pre-mix is that all ingredients except for the active may be combined in advance, with the active added just prior to formation of the film. This is especially important for actives that may degrade with prolonged exposure to water, air or another polar solvent.

Figure 6 shows an apparatus 20 suitable for the preparation of a pre-mix, addition of an active and subsequent formation of a film. The pre-mix or master batch 22, which includes the film-forming polymer, polar solvent, and any other additives except a drug active is added to the master batch feed tank 24. The components for pre-mix or master batch 22 are desirably formed in a mixer (not shown) prior to their addition into the master batch feed tank 24. Then a pre-determined amount of the master batch is controllably fed via a first metering pump 26 and control valve 28 to either or both of the first and second mixers, 30,

30'. The present invention, however, is not limited to the use of two mixers, 30, 30', and any number of mixers may suitably be used. Moreover, the present invention is not limited to any particular sequencing of the mixers 30, 30', such as parallel sequencing as depicted in Figure 6, and other sequencing or arrangements of mixers, such as series or combination of parallel and series, may suitably be used. The required amount of the drug or other ingredient, such as a flavor, is added to the desired mixer through an opening, 32, 32', in each of the mixers, 30, 30'. Desirably, the residence time of the pre-mix or master batch 22 is minimized in the mixers 30, 30'. While complete dispersion of the drug into the pre-mix or master batch 22 is desirable, excessive residence times may result in leaching or dissolving of the drug, especially in the case for a soluble drug. Thus, the mixers 30, 30' are often smaller, i.e. lower residence times, as compared to the primary mixers (not shown) used in forming the pre-mix or master batch 22. After the drug has been blended with the master batch pre-mix for a sufficient time to provide a uniform matrix, a specific amount of the uniform matrix is then fed to the pan 36 through the second metering pumps, 34, 34'. The metering roller 38 determines the thickness of the film 42 and applies it to the application roller. The film 42 is finally formed on the substrate 44 and carried away via the support roller 46.

Forming the Film

The films of the present invention must be formed into a sheet prior to drying. After the desired components are combined to form a multi-component matrix, including the polymer, water, and an active or other components as desired, the combination is formed into a sheet or film, by any method known in the art such as extrusion, coating, spreading, casting or drawing the multi-component matrix. If a multi-layered film is desired, this may be accomplished by co-extruding more than one combination of components which may be of the same or different composition. A multi-layered film may also be achieved by coating, spreading, or casting a combination onto an already formed film layer.

Although a variety of different film-forming techniques may be used, it is desirable to select a method that will provide a flexible film, such as reverse roll coating. The flexibility of the film allows for the sheets of film to be rolled and transported for storage or prior to being cut into individual dosage forms. Desirably, the films will also be self-supporting or in other words able to maintain their integrity and structure in the absence of a separate support. Furthermore, the films of the present invention may be selected of materials that are edible or ingestible.

Coating or casting methods are particularly useful for the purpose of forming the films of the present invention. Specific examples include reverse roll coating, gravure coating, immersion or dip coating, metering rod or meyer bar coating, slot die or extrusion coating, gap or knife over roll coating, air knife coating, curtain coating, or combinations thereof, especially when a multi-layered film is desired.

Roll coating, or more specifically reverse roll coating, is particularly desired when forming films in accordance with the present invention. This procedure provides excellent control and uniformity of the resulting films, which is desired in the present invention. In this procedure, the coating material is measured onto the applicator roller by the precision setting of the gap between the upper metering roller and the application roller below it. The coating is transferred from the application roller to the substrate as it passes around the support roller adjacent to the application roller. Both three roll and four roll processes are common.

The gravure coating process relies on an engraved roller running in a coating bath, which fills the engraved dots or lines of the roller with the coating material. The excess coating on the roller is wiped off by a doctor blade and the coating is then deposited onto the substrate as it passes between the engraved roller and a pressure roller.

Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

In the simple process of immersion or dip coating, the substrate is dipped into a bath of the coating, which is normally of a low viscosity to enable the coating to run back into the bath as the substrate emerges.

In the metering rod coating process, an excess of the coating is deposited onto the substrate as it passes over the bath roller. The wire-wound metering rod, sometimes known as a Meyer Bar, allows the desired quantity of the coating to remain on the substrate. The quantity is determined by the diameter of the wire used on the rod.

In the slot die process, the coating is squeezed out by gravity or under pressure through a slot and onto the substrate. If the coating is 100% solids, the process is termed

"Extrusion" and in this case, the line speed is frequently much faster than the speed of the extrusion. This enables coatings to be considerably thinner than the width of the slot.

The gap or knife over roll process relies on a coating being applied to the substrate which then passes through a "gap" between a "knife" and a support roller. As the coating and substrate pass through, the excess is scraped off.

Air knife coating is where the coating is applied to the substrate and the excess is "blown off" by a powerful jet from the air knife. This procedure is useful for aqueous coatings.

In the curtain coating process, a bath with a slot in the base allows a continuous curtain of the coating to fall into the gap between two conveyors. The object to be coated is passed along the conveyor at a controlled speed and so receives the coating on its upper face.

Drying the Film

While the proper viscosity, uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

When a controlled or rapid drying process is desired, this may be through a variety of methods. A variety of methods may be used including those that require the application of heat. The liquid carriers are removed from the film in a manner such that the uniformity, or more specifically, the non-self-aggregating uniform heterogeneity, that is obtained in the wet film is maintained.

Desirably, the film is dried from the bottom of the film to the top of the film. Substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first ½ minute to about the first 4 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

The temperature at which the films are dried is about 100°C or less, desirably about 90°C or less, and most desirably about 80°C or less.

Another method of controlling the drying process, which may be used alone or in combination with other controlled methods as disclosed above includes controlling and modifying the humidity within the drying apparatus where the film is being dried. In this manner, the premature drying of the top surface of the film is avoided.

A specific example of an appropriate drying method is that disclosed by Magoon. Magoon is specifically directed toward a method of drying fruit pulp. However, the present inventors have adapted this process toward the preparation of thin films.

The method and apparatus of Magoon are based on an interesting property of water. Although water transmits energy by conduction and convection both within and to its surroundings, water only radiates energy within and to water. Therefore, the apparatus of Magoon includes a surface onto which the fruit pulp is placed that is transparent to infrared radiation. The underside of the surface is in contact with a temperature controlled water bath. The water bath temperature is desirably controlled at a temperature slightly below the boiling temperature of water. When the wet fruit pulp is placed on the surface of the apparatus, this

creates a "refractance window." This means that infrared energy is permitted to radiate through the surface only to the area on the surface occupied by the fruit pulp, and only until the fruit pulp is dry. The apparatus of Magoon provides the films of the present invention with an efficient drying time reducing the instance of aggregation of the components of the film.

The films may initially have a thickness of about 500 μm to about 1,500 μm, or about 20 mils to about 60 mils, and when dried have a thickness from about 3 μm to about 250 μm, or about 0.1mils to about 10mils. Desirably, the dried films will have a thickness of about 2 mils to about 8 mils, and more desirably, from about 3 mils to about 6 mils.

The wet film is then dried using controlled bottom drying or controlled microwave drying, desirably in the absence of external air currents or heat on the top (exposed) surface of the film 48 as described herein. Controlled bottom drying or controlled microwave drying advantageously allows for vapor release from the film without the disadvantages of the prior art. Conventional convection air drying from the top is not employed because it initiates drying at the top uppermost portion of the film, thereby forming a barrier against fluid flow, such as the evaporative vapors, and thermal flow, such as the thermal energy for drying. Such dried upper portions serve as a barrier to further vapor release as the portions beneath are dried, which results in non-uniform films. As previously mentioned some top air flow can be used to aid the drying of the films of the present invention, but it must not create a condition that would cause particle movement or a rippling effect in the film, both of which would result in non-uniformity. If top air is employed, it is balanced with the bottom air drying to avoid non-uniformity and prevent film lift-up on the carrier belt. A balance top and bottom air flow may be suitable where the bottom air flow functions as the major source of drying and the top air flow is the minor source of drying. The advantage of some top air flow is to move the exiting vapors away from the film thereby aiding in the overall drying process. The use of any top air flow or top drying, however, must be balanced by a number of factors including, but not limited, to rheological properties of the composition and mechanical aspects of the processing. Any top fluid flow, such as air, also must not overcome the inherent viscosity of the film-forming composition. In other words, the top air flow cannot break, distort or otherwise physically disturb the surface of the composition. Moreover, air velocities are desirably below the yield values of the film, i.e., below any force level that can move the liquids in the film-forming compositions. For thin or low viscosity compositions,

low air velocity must be used. For thick or high viscosity compositions, higher air velocities may be used. Furthermore, air velocities are desirable low so as to avoid any lifting or other movement of the film formed from the compositions.

Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, which may have a low degradation temperature. In such cases, the drying temperature may be decreased while increasing the drying time to adequately dry the uniform films of the present invention. Furthermore, bottom drying also tends to result in a lower internal film temperature as compared to top drying. In bottom drying, the evaporating vapors more readily carry heat away from the film as compared to top drying which lowers the internal film temperature. Such lower internal film temperatures often result in decreased drug degradation and decreased loss of certain volatiles, such as flavors.

Furthermore, particles or particulates may be added to the film-forming composition or matrix after the composition or matrix is cast into a film. For example, particles may be added to the film 42 prior to the drying of the film 42. Particles may be controllably metered to the film and disposed onto the film through a suitable technique, such as through the use of a doctor blade (not shown) which is a device which marginally or softly touches the surface of the film and controllably disposes the particles onto the film surface. Other suitable, but non-limiting, techniques include the use of an additional roller to place the particles on the film surface, spraying the particles onto the film surface, and the like. The particles may be placed on either or both of the opposed film surfaces, i.e., the top and/or bottom film surfaces. Desirably, the particles are securably disposed onto the film, such as being embedded into the film. Moreover, such particles are desirably not fully encased or fully embedded into the film, but remain exposed to the surface of the film, such as in the case where the particles are partially embedded or partially encased.

The particles may be any useful organoleptic agent, cosmetic agent, pharmaceutical agent, or combinations thereof. Desirably, the pharmaceutical agent is a taste-masked or a controlled-release pharmaceutical agent. Useful organoleptic agents include flavors and sweeteners. Useful cosmetic agents include breath freshening or decongestant agents, such as menthol, including menthol crystals.

Although the inventive process is not limited to any particular apparatus for the above-described desirable drying, one particular useful drying apparatus 50 is depicted in Figure 7. Drying apparatus 50 is a nozzle arrangement for directing hot fluid, such as but not limited to hot air, towards the bottom of the film 42 which is disposed on substrate 44. Hot air enters the entrance end 52 of the drying apparatus and travels vertically upward, as depicted by vectors 54, towards air deflector 56. The air deflector 56 redirects the air movement to minimize upward force on the film 42. As depicted in Figure 7, the air is tangentially directed, as indicated by vectors 60 and 60', as the air passes by air deflector 56 and enters and travels through chamber portions 58 and 58' of the drying apparatus 50. With the hot air flow being substantially tangential to the film 42, lifting of the film as it is being dried is thereby minimized. While the air deflector 56 is depicted as a roller, other devices and geometries for deflecting air or hot fluid may suitable be used. Furthermore, the exit ends 62 and 62' of the drying apparatus 50 are flared downwardly. Such downward flaring provides a downward force or downward velocity vector, as indicated by vectors 64 and 64', which tend to provide a pulling or drag effect of the film 42 to prevent lifting of the film 42. Lifting of the film 42 may not only result in non-uniformity in the film or otherwise, but may also result in non-controlled processing of the film 42 as the film 42 and/or substrate 44 lift away from the processing equipment.

Monitoring and control of the thickness of the film also contributes to the production of a uniform film by providing a film of uniform thickness. The thickness of the film may be monitored with gauges such as Beta Gauges. A gauge may be coupled to another gauge at the end of the drying apparatus, i.e. drying oven or tunnel, to communicate through feedback loops to control and adjust the opening in the coating apparatus, resulting in control of uniform film thickness.

The film products are generally formed by combining a properly selected polymer and polar solvent, as well as any active ingredient or filler as desired. Desirably, the solvent content of the combination is at least about 30% by weight of the total combination. The matrix formed by this combination is formed into a film, desirably by roll coating, and then dried, desirably by a rapid and controlled drying process to maintain the uniformity of the film, more specifically, a non-self-aggregating uniform heterogeneity. The resulting film will desirably contain less than about 10% by weight solvent, more desirably less than about 8% by weight solvent, even more desirably less than about 6% by weight solvent and most

desirably less than about 2%. The solvent may be water, a polar organic solvent including, but not limited to, ethanol, isopropanol, acetone, methylene chloride, or any combination thereof.

It has also been unexpectedly discovered that high temperature fat materials, e.g. M.P. 55°C or greater, can be used to encapsulate dry particles before or after enteric coating. The drying process temperatures are sufficiently rapid and low, and evaporative cooling effect as a result of water vapor loss is sufficiently high enough, that the fat does not appreciably melt.

Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples 1-8:

A variety of films were produced using the aforementioned inventive ratios of pullulan to water-soluble polymer. As an insoluble active component, calcium carbonate was used.

The compositions in Table 1 below were made in accordance with the process set forth in co-pending U.S. Application No. 10/074,272. The resultant uncut film exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom.

TABLE 1

Films Containing Pullulan/Water-Soluble Polymer Combinations With Insoluble Calcium Carbonate Active				
	Grams (% by weight)			
Components	**1**	**2**	**3**	**4**
Pullulan[1]	5.0 (15.5)	10.0 (23.5)	20.0 (42.1)	15.0 (35.2)
Modified Cellulose	3.0 (9.3)	--	--	--
Starches	--	10.0 (23.5)	--	--
Carageenan Gum	--	--	4.0 (8.4)	--
Xantham Gum	--	--	--	3.0 (7.0)
Alginate	--	--	--	--
Polyvinyl-pyrrolidone	--	--	--	--
Loratidine	--	--	--	--
Calcium Carbonate	10.0 (31.0)	10.0 (23.5)	10.0 (21.1)	10.0 (23.5)
Mint Flavor	2.5 (7.7)	2.0 (4.7)	2.0 (4.2)	2.5 (5.9)
Artificial Sweeteners	2.0 (6.2)	1.5 (3.5)	1.5 (3.2)	2.0 (4.7)
Tween 80	3.0 (9.3)	2.5 (5.9)	2.5 (5.3)	2.5 (5.9)
Antifoaming agent	0.2 (0.6)	0.2 (0.5)	0.2 (0.4)	0.2 (0.5)
Propylene Glycol	4.0 (12.4)	3.0 (7.0)	3.5 (7.4)	4.0 (9.4)
Water [1], Potable	180 (8.0)	80 (8.0)	100 (8.0)	120 (8.0)

[1] The dried film was assumed to have a moisture content of about 6.0-8.0% by weight.

[2] Other non-limiting Gums/Food Polymers may be used in combination with Pullulan: Pectin, Carboxymethyl Cellulose, Hydroxypropyl Cellulose, Polyvinyl Alcohol, Gum Arabic, Polyacrylic Acid, Dextrim, Gelatin, Zein, Soy Protein Isolate, Whey Protein Isolate, Milk Casein and combinations thereof.

TABLE 1 cont'd

Films Containing Pullulan/Water-Soluble Polymer Combinations With Insoluble Calcium Carbonate Active				
	Grams (% by weight)			
Components	**5**	**6**	**7**	**8**
Pullulan[1]	25.0 (39.1)	30.0 (8.7)	20.0 (43.6)	0.4 (1.6)
Modified Cellulose	--	--	2.0 (4.4)	2.0 (8.0)
Starches	--	--	--	--
Carageenan Gum	--	--	--	--
Xantham Gum	--	--	--	--
Alginate	3.0 (4.6)	--	--	--
Polyvinyl-pyrrolidone	--	8.0 (2.3)	--	--
Loratidine	--	--	10.0 (21.8)	12.0 (47.8)
Calcium Carbonate	10.0 (15.4)	10.0 (12.5)	--	--
Mint Flavor	2.5 (3.9)	2.0 (3.1)	2.0 (4.4)	1.5 (6.0)
Artificial Sweeteners	2.0 (3.1)	2.0 (3.1)	2.0 (4.4)	1.5 (6.0)
Tween 80	3.0 (4.6)	2.5 (3.9)	2.0 (4.4)	1.5 (6.0)
Antifoaming agent	0.2 (0.3)	0.2 (0.3)	0.2 (0.4)	0.2 (0.8)
Propylene Glycol	4.0 (6.2)	4.0 (6.2)	4.0 (8.7)	4.0 (15.9)
Water [1], Potable	140 (8.0)	100 (8.0)	150 (8.0)	120 (8.0)

[1] The dried film was assumed to have a moisture content of about 6.0-8.0% by weight.

[2] Other non-limiting Gums/Food Polymers may be used in combination with Pullulan: Pectin, Carboxymethyl Cellulose, Hydroxypropyl Cellulose, Polyvinyl Alcohol, Gum Arabic, Polyacrylic Acid, Dextrim, Gelatin, Zein, Soy Protein Isolate, Whey Protein Isolate, Milk Casein and combinations thereof.

Examples 9-11:

The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be

essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 2

Ingredient	(parts by wt.) 9
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
Xanthan Gum	1.14
SURFACTANT[2]:	2.0
PLASTICIZER[3]:	11.67
ANTI-FOAM AGENT[4]	2.44
OTHER	
Spearmint Flavor	10.43
Loratadine (drug)	16.62
Calcium Carbonate	5.54
Sweetener	9.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Ethoxylated caster oil, Cremophor® EL available from BASF
[3] Propylene Glycol
[4] Silicone Emulsion

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 45 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over 45 min.

After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 3

Ingredient	(parts by wt.) 10
POLYMERS:	
Hydroxypropylmethyl cellulose	15.6
Cornstarch[1]	10.41
Polyvinylpyrrolidone	10.41
PLASTICIZER/SOLVENT[2]:	22.1
ANTI-FOAM AGENT[3]	2.44
OTHER	
Raspberry Flavor	0.3
Calcium Carbonate[4]	30.38
Sweetener	8.36

[1] Available from Grain Processing Corporation as Pure Cote B792
[2] Propylene Glycol
[3] Polydimethyl Siloxane Emulsion
[4] Functioned to mimic drug loading

The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 4

Ingredient	(parts by wt.) 11
POLYMERS:	
Hydroxypropylmethyl cellulose	7.8
Hydroxypropyl cellulose	7.8
ANTI-FOAM AGENT[1]	0.75
OTHER	
Peppermint & Bittermint Flavor	2.25
Tastemasking Flavor[2]	0.3
Calcium Carbonate[3]	15.2
Sweeteners	0.9

[1] Polydimethyl Siloxane Emulsion
[2] Prosweet from Virginia Dave
[3] Functioned to mimic drug loading

The above ingredients were added at 30% to 70% water and stirred until polymers were fully hydrated which took 20 min. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner up to 760 mm over 35 min.

After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The tastemasking flavor is an ingredient that effects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Examples 12-15:

The following examples of the present invention describe film-forming compositions analyzed for uniformity and stability. Film-forming compositions were formed as shown below in Table 5.

TABLE 5

Ingredient	(grams)			
	12	13	14	15
Pullulan	7.0	7.0		
Hydroxypropylmethyl cellulose		7.0	7.0	10.5
Hydroxypropyl cellulose			7.0	3.5
Polydimethylsiloxane emulsion	0.14	0.14	0.14	0.14
Water	86	86	86	86

The above ingredients were stirred and mixed under vacuum to eliminate entrapped air. Seventy grams of each solution and five grams of glass beads were combined into four ounce jars and manually shook for about one minute to completely mix the glass beads into the solutions. The mixed samples were placed aside for ten minutes. After ten minutes a 10 ml sample was obtained from the top surface of each jar by use of a syringe.

The 10 ml samples were filtered through a funnel containing filter paper. The materials collected on the filter were washed with water to leave the glass beads on the paper. The filter papers with the glass beads were then dried for ten minutes at 90°C. The weight of the filter and the resulting glass beads were measured, as shown below in Table 6.

TABLE 6

Ingredient	(grams)			
	12	13	14	15
Weight of filter paper and glass beads collected after drying	0.332	0.509	0.839	0.831
Initial weight of filter paper	0.151	0.143	0.143	0.140
Weight of glass beads collected	0.181	0.366	0.696	0.691

Samples 14 and 15 contained considerably more glass beads that sample 12, which was made from pullulan. This indicated the significant particulate, i.e. glass beads, settling occurred with composition containing only pullulan as the polymer. The viscosity of pullulan is thus too low to provide a film-forming matrix that can maintain uniformity of particulates therein. Increasing the amount of other polymers, such as hydroxypropylmethyl cellulose, significantly increases the film stability and uniformity, as noted by the increased weight of the glass beads.

While there have been described what are presently believed to be the certain desirable embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. An ingestible water-soluble delivery system in the form of a film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5.

2. The ingestible water-soluble delivery system of claim 1, wherein the ratio is about 10:1 to about 1:5.

3. The ingestible water-soluble delivery system of claim 1, wherein said glucan is selected from the group consisting of pullulan, elsinan and combinations thereof.

4. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a cellulosic material, a gum, a protein, a starch, and combinations thereof.

5. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of carboxymethyl cellulose, hydroxyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose hydroxypropylmethyl cellulose, and combinations thereof.

6. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of gum arabic, xanthan gum, tragacanth, acacia, carageenan, guar gum, locust bean gum, pectin, alginates and combinations thereof.

7. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of polyvinyl alcohol, polyacrylic acid, polyvinyl pyrrolidone, poly(meth)acrylate, poly(meth)copolymers and combinations thereof.

8. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a starch selected from the group consisting of tapioca, rice, corn, potato, wheat and combinations thereof.

9. The ingestible water-soluble delivery system of claim 8, wherein said starch is gelatinized, modified or unmodified.

10. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is a protein selected from the group consisting of gelatin, zein, gluten, soy protein, soy protein isolate, whey protein, whey protein isolate, casein, levin, collagen and combinations thereof.

11. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of dextrin, dextran and combinations thereof.

12. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of chitin, chitosin or combinations thereof.

13. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is polydextrose.

14. The ingestible water-soluble delivery system of claim 1, wherein said water-soluble polymer is selected from the group consisting of dextrin, dextran and combinations thereof.

15. The ingestible water-soluble delivery system of claim 1, further comprising an active component selected from the group consisting of cosmetic agents, pharmaceutical agents, bioactive agents and combinations thereof.

16. The ingestible water-soluble delivery system of claim 1, wherein said active component is present in amounts of up to about 60% by weight of the total composition.

17. The ingestible water-soluble delivery system of claim 1, wherein said active component is present in amounts of up to about 0.1% to about 60% by weight of the total composition.

18. The ingestible water-soluble delivery system of claim 1, further comprising one or more members selected from the group consisting of taste-masking agents, plasticizing agents, surfactants, emulsifying agents, thickening agents, binding agents, cooling agents, saliva-stimulating agents, sweetening agents, antimicrobial agents and combinations thereof.

19. A dried film formed from the composition of claim 1.

20. A dried film formed from the composition of claim 15.

21. A dried film formed from the composition of claims 1 or 15 having a thickness up to about 5mm.

22. The dried film of claims 19 or 20 having a polymeric carrier backing.

23. The dried film of claims 19 or 20 in unit dosage form sealed in a pouch.

24. A pharmaceutical and/or cosmetic dosage form comprising an ingestible water-soluble film composition comprising a glucan and a water-soluble polymer, wherein the ratio of glucan to water soluble polymer is about 40:1 to about 0.1:5 having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area.

25. A pharmaceutical and/or cosmetic dosage form comprising a film having a uniformly dispersed composition comprising a glucan and a water-soluble polymer, a pharmaceutical and/or cosmetic active and a solvent, said film being formed by depositing a wet film of said composition onto a substrate surface and controllably drying the wet film from the side contacting the substrate to prevent self-aggregation and achieve compositional uniformity.

26. A pharmaceutical composition in the form of a film for enteral or topical administration, comprising a composition having a uniformly distributed combination of a glucan, a water-soluble polymer, a polar solvent, and a pharmaceutical active, wherein said glucan and said water-soluble polymer are present in a ratio of about 40:1 to about 0.1:5, said composition in its dried film form maintaining the uniform distribution of components through the application of controlled bottom drying of the film.

27. The ingestible water-soluble delivery system of claim 15, wherein said pharmaceutical active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-

parkinsonism drugs, narcotics, analgesics, anti-pyretics, psychopharmacological drugs and combinations thereof.

28. The ingestible water-soluble delivery system of claim 1, wherein the film composition is essentially free of a surfactant.

29. The ingestible water-soluble delivery system of claims 1 or 28, wherein the film composition is essentially free of a plasticizer.

30. The ingestible water-soluble delivery system of claims 1, 28 or 29, wherein the film composition is essentially free of a polyalcohol.

31. The pharmaceutical and/or cosmetic dosage form of claims 24 or 25 , wherein the film is essentially free of a surfactant.

32. The pharmaceutical and/or cosmetic dosage form of claims 24, 25, or 31, wherein the film is essentially free of a plasticizer.

33. The pharmaceutical and/or cosmetic dosage form of claims 24, 25, 31 or 32, wherein the film is essentially free of a polyalcohol.

34. The pharmaceutical composition of claim 26 , wherein the film is essentially free of a surfactant.

35. The pharmaceutical composition of claims 26 or 34, wherein the film is essentially free of a plasticizer.

36. The pharmaceutical composition of claims 26, 34 or 35, wherein the film is essentially free of a polyalcohol.

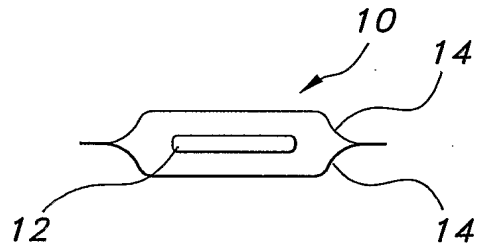

FIG. 1

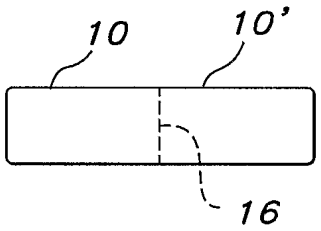

FIG. 2

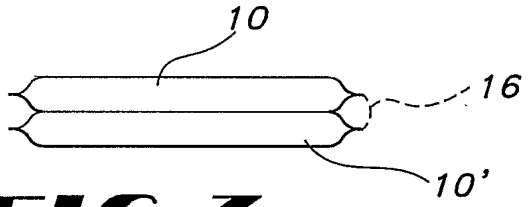

FIG. 3

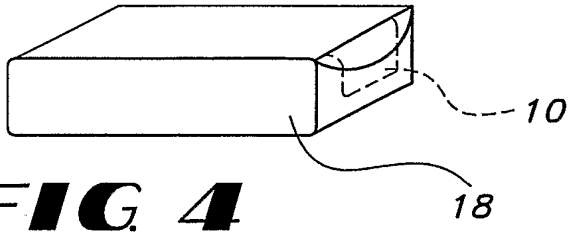

FIG. 4

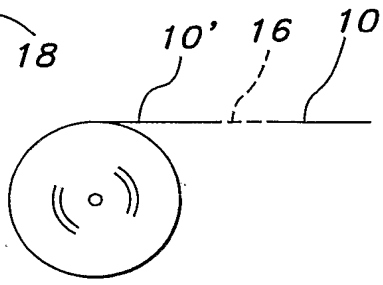

FIG. 5

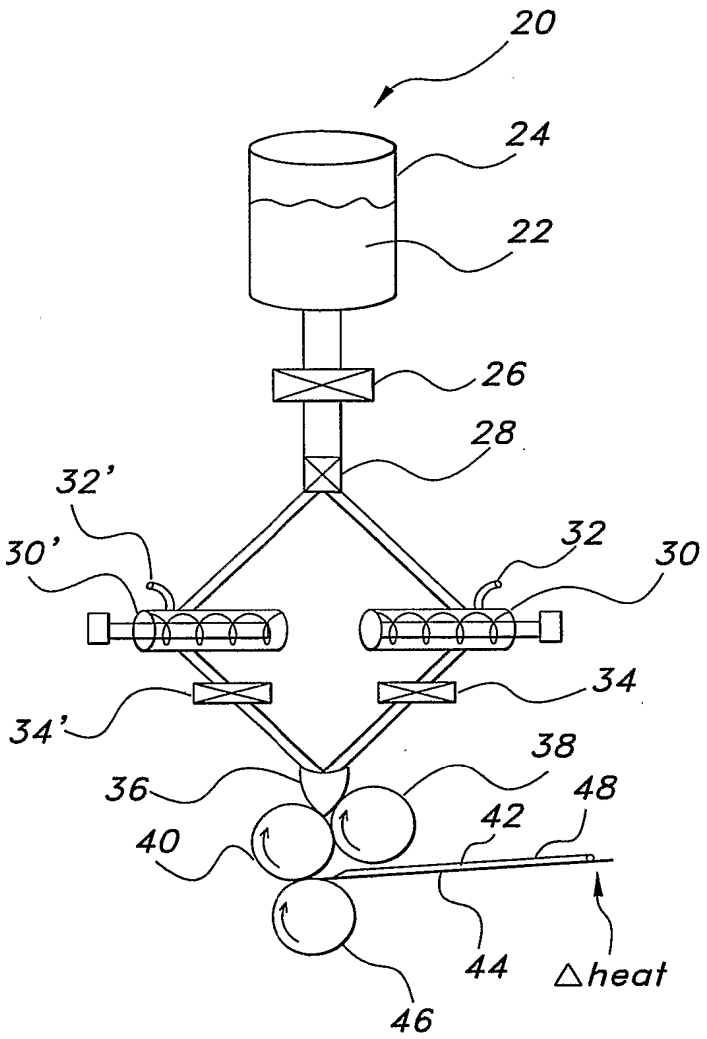

FIG. 6

3/3

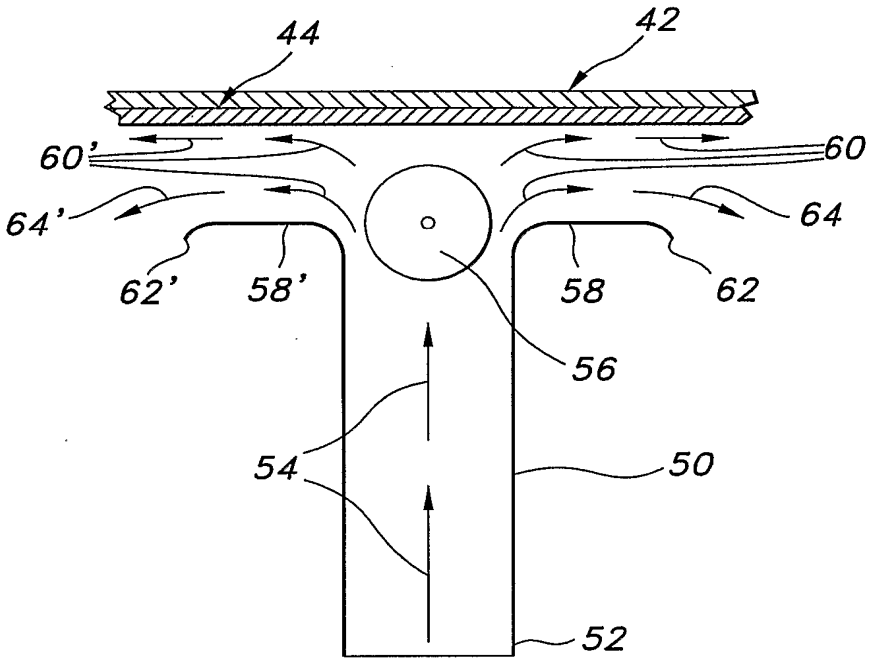

FIG. 7

INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/70 A61K9/00 A61K47/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, FSTA, 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	US 4 562 020 A (HIJIYA HIROMI ET AL) 31 December 1985 (1985-12-31) cited in the application examples 4,5 claim 10	1-36
X	US 5 518 902 A (MIYAKE TOSHIO ET AL) 21 May 1996 (1996-05-21) cited in the application example B8	1-36
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-/--

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

[X] Patent family members are listed in annex.

° Special categories of cited documents :

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

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

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

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 January 2003	06/02/2003

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

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INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

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 00 18365 A (WARNER LAMBERT CO) 6 April 2000 (2000-04-06) abstract claims tables 1-4	1-36
X	WO 01 70194 A (WARNER LAMBERT CO) 27 September 2001 (2001-09-27) claims; tables	1-36
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X	US 4 623 394 A (NAKAMURA SATOSHI ET AL) 18 November 1986 (1986-11-18) example 1	1-36
P,X	LAZARIDOU A ET AL: "Thermophysical properties of chitosan, chitosan-starch and chitosan-pullulan films near the glass transition" CARBOHYDRATE POLYMERS, APPLIED SCIENCE PUBLISHERS, LTD. BARKING, GB, vol. 48, no. 2, 1 May 2002 (2002-05-01), pages 179-190, XP004333230 ISSN: 0144-8617 abstract; table 1	1-36
X	US 4 981 693 A (HIGASHI KIYOTSUGU ET AL) 1 January 1991 (1991-01-01) abstract example 4	1-36
A	US 4 631 837 A (MAGOON RICHARD E) 30 December 1986 (1986-12-30) cited in the application the whole document	1-36

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

PCT/US 02/32542

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

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

2. ☒ Claims Nos.: 1, 19, 24-26 (in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

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

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

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

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

Remark on Protest

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

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1, 19, 24-26 (in part)

Present claims 1, 24-26, by using the functional definition "water-soluble polymer", relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the delivery systems where the water-souble polymer is as listed in claims 4-14.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/US 02/32542

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
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INTERNATIONAL SEARCH REPORT

Information on patent family members

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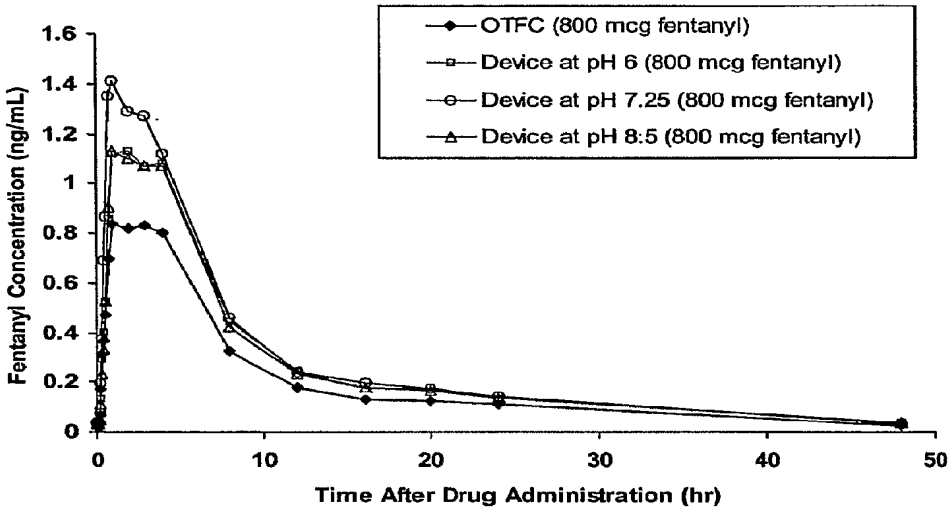
(54) Title: TRANSMUCOSAL DELIVERY DEVICES WITH ENHANCED UPTAKE

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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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.

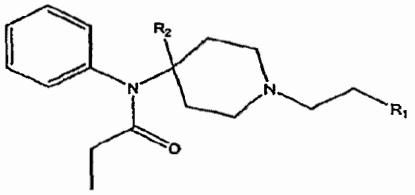
[0027] As used herein, the term "acute pain" refers to pain characterized by a short duration, e.g., three to six months. Acute pain is typically associated with tissue damage, and manifests in ways that can be easily described and observed. It can, for example, cause sweating or increased heart rate. 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:

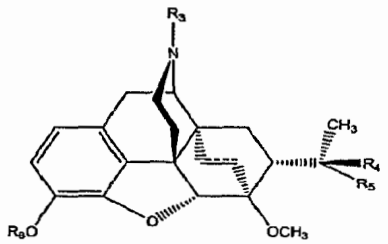


or pharmaceutically acceptable salts or esters thereof, wherein

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

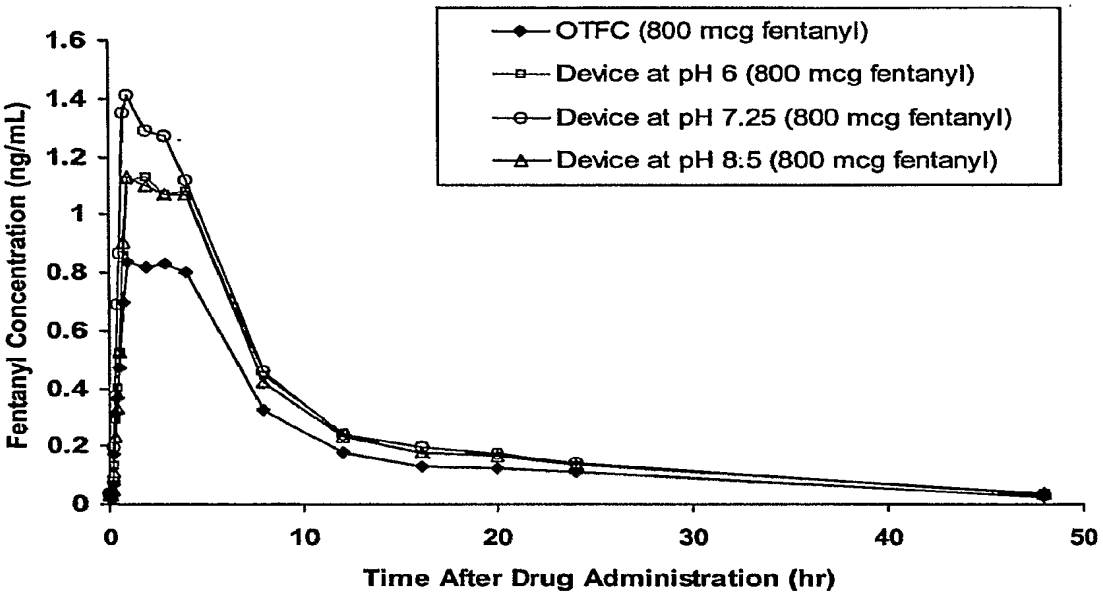


Figure 2. Mean (SD) Fentanyl Concentration Over Time Comparing an Exemplary Device According To The Present Invention and OTFC

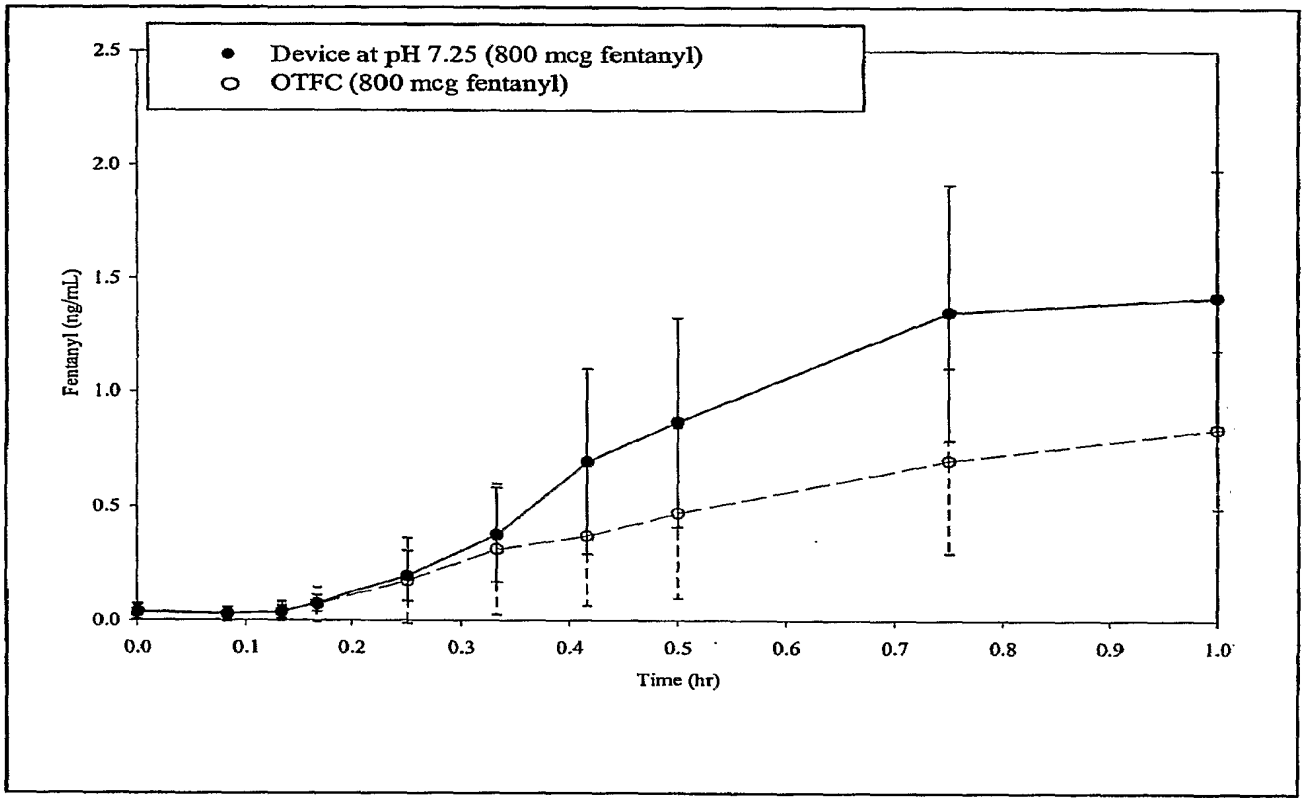


Figure 3. Mean (SD) Buprenorphine Concentration Over Time Comparing an Exemplary Device According To The Present Invention and Conventional Buprenorphine Delivery

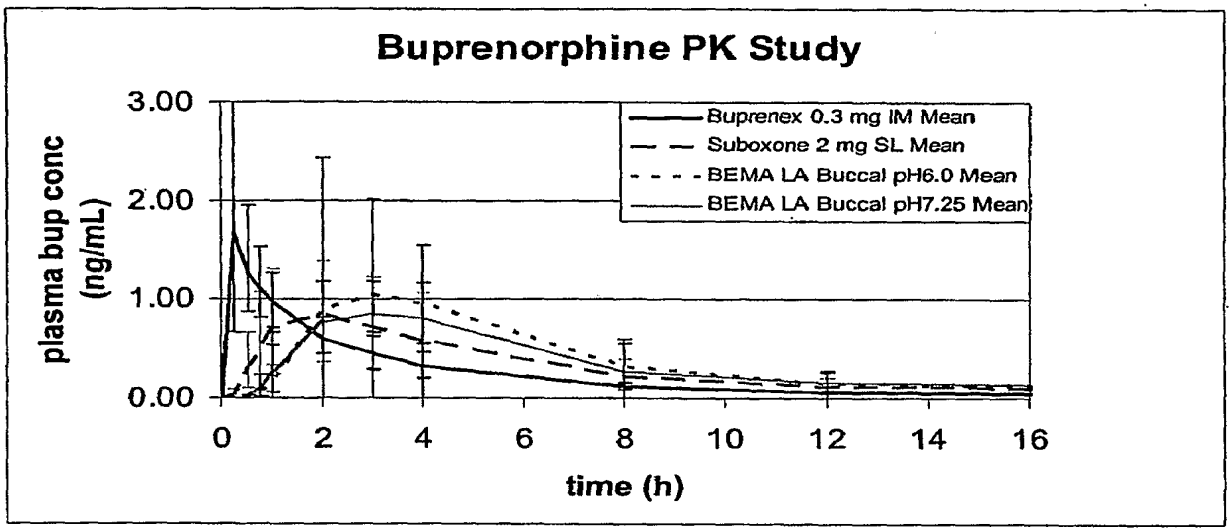


Figure 4: Exemplary Embodiments of the Present Invention

Figure 4A

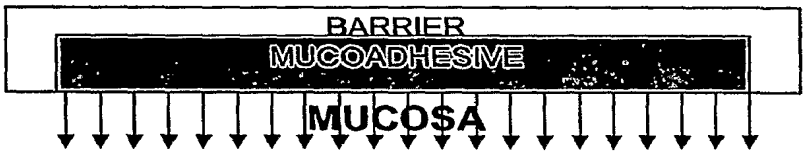


Figure 4B

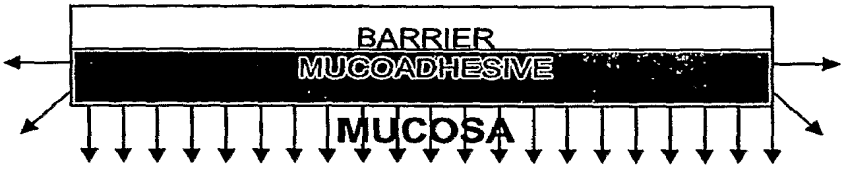
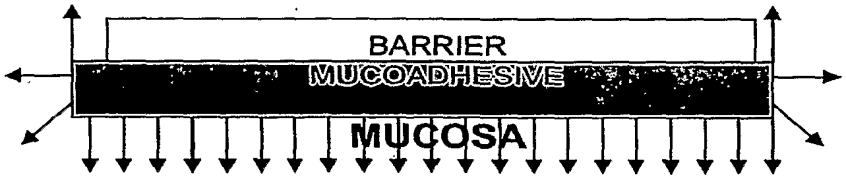


Figure 4C



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(72) Inventors; and

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(74) Agents: **HANLEY, Elizabeth, A.** et al.; Lahive & Cockfield, Llp, One Post Office Square, Boston, MA 02109-2127 (US).

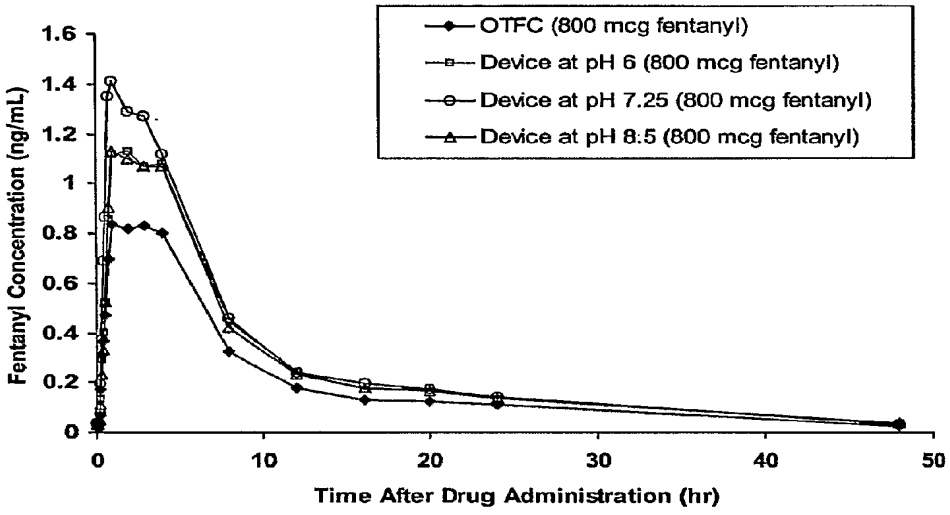
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, 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.

(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.

WO 2008/011194 A3

PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
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(88) Date of publication of the international search report:
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International application No
PCT/US2007/016634

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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)
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.

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

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

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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

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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
X	WO 00/19987 A (3M INNOVATIVE PROPERTIES CO [US]; MATSON CHARLES J [US]; CHEN YEN LANE) 13 April 2000 (2000-04-13) page 8, line 24 - line 31 page 16, line 1 - line 13; claims	1-8,10, 14, 16-18, 20-22, 28,30, 32,35, 37,38,43
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

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2007/016634

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Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Julie Tabarovsky/Marcy Mancuso
Attorney Docket Number:	1199-4B CIP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Submission- Information Disclosure Stmt	1806	1	180	180
		Total in USD ($)		**180**

Electronic Acknowledgement Receipt

EFS ID:	9041114
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	15-DEC-2010
Filing Date:	10-JUL-2007
Time Stamp:	14:43:31
Application Type:	Utility under 35 USC 111(a)

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Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$180
RAM confirmation Number	1099
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Warnings:					
Information:					
2	Information Disclosure Statement (IDS) Filed (SB/08)	IDS_form_PTO-SB-08a.pdf	3167859 3ab4513c2f0351864893ff7adfac2991beeeff1f	no	5
Warnings:					
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3	Foreign Reference	GB1510999A.pdf	821700 9c0172b7fd6ada39a296cd84155e2c30555cde20	no	14
Warnings:					
Information:					
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Warnings:					
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5	Foreign Reference	WO2008011194A2A3.pdf	2717019 bf87e090175b518b68adc771a5f4ca708deb2ee7	no	53
Warnings:					
Information:					
6	Fee Worksheet (PTO-875)	fee-info.pdf	30549 56999ee54347ea25e542d20b9e3ccdc3c260a777	no	2
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If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	December 15, 2010

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: December 15, 2010

Signature: /Marcy Mancuso/

SUPPLEMENTAL INFORMATION DISCLOSURE STATEMENT

Sir:

In fulfillment of the requirements of candor and good faith set forth in 37 C.F.R. §1.56, Applicants submit herewith the following Supplemental Information Disclosure Statement in accordance with the provisions of 37 C.F.R. §1.97 and §1.98. It is understood that the information provided herein is solely for the purpose of fulfilling Applicants' obligations under the law and should not be construed as, nor is it intended to be, an admission of prior art.

Copies of the U.S. patent documents and U.S. publications listed on the attached Form PTO/SB/08a are not provided as the United States Patent and Trademark Office has waived the requirement for paper submission of such documents. Copies of the foreign patent documents are attached.

It is believed that the $180.00 fee pursuant to 37 C.F.R. §1.17 is due. Please charge the $180.00 fee due for submission of this Supplemental Information Disclosure Statement to Deposit Account No. 08-2461. The Commissioner also is hereby authorized to charge any additional fees deemed due or to credit any overpayment to Deposit Account No. 08-2461.

If the Examiner has any questions or comments relating to the present application, he or she is respectfully invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
Registration No.: 60,808

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 02/02/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
02/02/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA S. MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 December 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 10-36* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-24,35 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12-15-10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of Applicants Remarks and Amended Claims filed on December 9, 2010 is acknowledged. Claims 1-8 and 10-36 remain pending in this application. Claims 25-34 remain withdrawn from consideration. Claims 1-8, 10-24, and 35-36 remain under prosecution in this application.

Information Disclosure Statement

Receipt of the Information Disclosure Statement filed December 15, 2010 is acknowledged. A signed copy is attached to this office action.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

The rejection of claims 1-17 and 35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been withdrawn in view of Applicants arguments regarding the combined particle sizes and Applicants amendment to the claims to remove the terminology "such as" and "including".

Maintained Rejections

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-5, 8-12, 14-19, 22, and 35-36 are rejected under 35 U.S.C. 102 (b) and (e) as being anticipated by Bess et al. (US Patent 7,067,116).

Bess discloses fast dissolving orally consumable solid film containing a taste masking agent and a pharmaceutically active agent at weight ratio of dissolving 1:3 to 3:1 (Title). The films include a water soluble film forming polymer and a taste masked pharmaceutically active agent (abstract).

Examples of water soluble film forming polymers include pullulan, HPMC, hydroxyethyl cellulose, hydropropyl cellulose, PVP, carboxymethyl cellulose PVA, sodium alginate, PEG, xanthan gum, for example (column 5, lines 1-16).

The active agents include antimicrobial agents, NSAIDS, anti-tussives, decongestants, anti-histamines, expectorants, anti-diarrheals, PPI's, CNS depressants and stimulants (columns 2 and 3).

The taste masking agent is an ion exchange resin includes synthetic polymer of acrylic acid, methacrylic acid, sulfonated styrene, and sulfonated divinylbenzene or

partially synthetic polymers of modified celluloses and dextrans (column 4, lines 1-24). Less preferred embodiments partially taste masking agents of magnesium trisilicate and polymers such as Eudragit E and/or cellulosics, such as ethylcellulose (column 4, lines 60-67).

The active agents adsorbed to the ion exchange resin is in the range from about 25-75% by weight of the pharmaceutically active agent/resin adsorption complex, thereby meeting the limitations of claims 14-15. The recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent.

The pharmaceutically active agent/resin adsorption complex can also be coated in the range from about 40 to about 70% w/w pharmaceutically active agents/resin complex. Variation in the amount of coating and/or the use of coating/uncoated complex mixtures can be employed to selectively modify the dissolution profile (column 11, lines 43-53).

The particle size of the coated and uncoated pharmaceutically active agent/resin adsorption complex is about 60-200 microns (column 11, lines 54-58).

Plasticizers, surfactants, and polyalcohol's are optional ingredients; therefore, they are not required by Bess in order for the film to perform as disclosed.

The films can additionally include polyethylene oxide compound (column 8, line 15-18).

Regarding claim 19, Bess discloses his formulations are cast on a suitable substrate and dried to form a film (column 8, lines 47-48); however, this is considered a product by process limitation. Applicant is directed to MPEP 2112 which discloses

"[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Since the methods of preparing the films disclosed in the reference recite numerous mixing steps of the same structural elements as recited in the instant claims, it is the position of the Examiner that absent of showing of evidence to the contrary, the films would possess the same uniformity as recited in instant claims. Applicant is invited to provide evidence that the uniformity of the film does not have a variation of drug content of less than 10% per film unit.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Bess does not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Bess does not disclose the drug content uniformity, Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the same components prepared as a film. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order

to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims.

***The ion exchange resin does not necessary result in a coating.**

The Examiner respectfully disagrees. Adsoprtion, by definition is adhesion to a surface, therefore, the disclosure of the active agent adsorbed onto the ion exchange resin, at the very least is an intimate admixture, and however, it is the positon of the Examiner that it is also a coating. The claims do not recite that they entire surface be coating, therefore any adhesion to the surface meets the limitations of the claims.

The rejection is therefore maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8, 10-12, 17, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (WO 00/42992) in view of Ghana et al (US Patent 5,653,993).

Chen discloses a water soluble hydrocolloid; mucosal surface coated forming film, having an effective dose of an active agent (page 3, lines 30-33).

The hydrocolloid includes a polymer selected from the group consisting of natural, semi-natural and synthetic biopolymers (page 4, lines 1-3).

The active agents is selected from the group consisting of therapeutic agents, dietary supplements, and hygiene aids, for example sildenafil citrate, nicotine, hydromorphone, oxybutynine, or estradiol (page 4, lines 7-10). The active agent can be encapsulated in a material that is different than the hydrocolloid. Encapsulation is additionally utilized to achieve masking of taste of active agents that are bitter (page 9, lines 13-15).

The hydrocolloid is a water soluble non gelling natural polysaccharide, polypeptide or protein (page 14, lines 12-31).

The films can be cast or extruded (page 15-16).

Chen does not disclose the particle size of the encapsulated active agents.

Ghanta discloses the preparation of taste masked microcapsules. The encapsulating material is cellulose acetate phthalate and gelatin (abstract).

The average/mean microcapsule diameter ranges from about 25 to about 600 microns (column 3, lines 59-62).

The gelatin used can be of any origin so long as it is of pharmaceutical grade. The gelatin, for example, can have a number average molecular weight of about 27,000 to 70,000 (column 4, lines 43-47).

It would have been within the skill of the ordinary practitioner to have used the particle size disclosed by Ghanta in order to make the encapsulated active agents utilized by Chen since both references discloses the particles are suitable for taste masking and Ghanta discloses they do not form agglomerates (column 3, lines 33-35), thereby allowing for a more uniform distribution.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the particle size of the microcapsules in Chen since Ghanta discloses in order to make wider use of NSAIDs while substantially eliminating the bitter taste, aftertaste and adverse mouth feel and make these drugs more pleasant upon taking them orally, there has long been desired a way to insure delivery of these drugs in their desired concentrations while avoiding their extremely bitter taste, lingering aftertaste and adverse mouth feel effects referred to above connected with their ingestion orally, thereby encouraging patient compliance.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Chen and Ghanta do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Chen and Ghanta do not disclose the drug content uniformity, Chen and Ghanta are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims.

The rejection is therefore maintained.

Claims 1-4, 10-13, 17-20, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Grass et al. (US Patent 3,237,596).

Schiraldi discloses a bioadhesive extruded single or multilayered thin film having a water soluble or swell able polymer matrix, bioadhesive layer consists essentially of 40-95% by weight of a hydroxypropyl cellulose, 5-60% of a homopolymer of ethylene oxide, 0-10% of a water-insoluble polymer such as ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and 2-10% of a plasticizer, said film having

incorporated therein a medicament, such as anesthetics, analgesics, anticaries agents, anti-inflammatories, antihistamines, antibiotics, antibacterials, fungistats, etc (abstract).

Schiraldi does not disclose the medicament being coated with a taste masking polymer having a particle size of 200 microns or less.

Grass discloses a method of coating discrete solids. The solids have a particle size of about 5 to about 200 microns (column 1, lines 10-15). Spherical particles of acetaminophen coated with 12-hydroxystearyl alcohol are disclosed in the Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have employed the method of coating medicaments as disclosed by Grass for incorporation into the films disclosed by Schiraldi in order to achieve the taste masking, sustained dissolution, enteric properties, improved stability, delayed interaction, wettability, and improved flow properties of the active agent for incorporation into drug formulation.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***The films of Schiraldi must be extruded and therefore teach away from the casted film product of the instant claims.**

It is unclear to the Examiner how the method of preparation is a teaching away to the composition claims of the instant application. The claims are drawn to a composition and not a method of making said composition, which is a non elected invention.

Applicant is requested to clarify the arguments. The combined teachings of Schiraldi and Grass render the instant claims obvious and the rejection is therefore maintained.

Claims 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Thakur et al. (US 2004/0156901).

The teaching of Schiraldi are discussed above and applied in the same manner.

Schiraldi does not disclose the medicament being coated with a taste masking water soluble polymer

Thakur discloses particulate cores of active agents coated with a taste masking polymer, preferably cellulose acetate (paragraph 0034), which is a water soluble polymer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used coated active agents, as discussed by Thakur in order to provide dosage forms in which pharmaceutical agents with unappealing tastes can be masked and allow for increased patient compliance.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Schiraldi and Thakur do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Schiraldi and Thakur do not disclose the drug content uniformity, Schiraldi and Thakur are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims.

The rejection is therefore maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA S. MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
January 30, 2011

Notice of References Cited	Application/Control No. 11/775,484	Applicant(s)/Patent Under Reexamination YANG ET AL.	
	Examiner MELISSA S. MERCIER	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-4,067,116	01-1978	Bryner et al.	33/343
*	B	US-5,653,993	08-1997	Ghanta et al.	424/440
*	C	US-4,713,243	12-1987	Schiraldi et al.	424/676
*	D	US-3,237,596	03-1966	GRASS JR GEORGE M et al.	118/62
*	E	US-2004/0156901	08-2004	Thakur et al.	424/471
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
*	N	WO0042992	07-2000	WIPO	Chen	A61K 9/70
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/MM/	1	3007848		1961-11-07	J.H. Stroop	
/MM/	2	4478658		1984-10-23	Wittwer	
/MM/	3	5044761		1991-09-03	Yuhki et al.	
/MM/	4	5605696		1997-02-25	Eury et al.	
/MM/	5	5733575		1998-03-31	Mehra et al.	
/MM/	6	5800832		1998-09-01	Tapolsky et al.	
/MM/	7	5806284		1998-09-15	Gifford	
/MM/	8	5881476		1999-03-16	Strobush et al.	

/Melissa Mercier/ (01/21/2011)

Receipt date: 12/15/2010	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Mercier, Melissa S.	
	Attorney Docket Number	1199-4 B CIP	

/MM/	9	6660292	B2	2003-12-09	Zerbe et al.	
/MM/	10	6800239	B2	2004-10-05	Horstmann et al.	
/MM/	11	6824829	B2	2004-11-30	Berry et al.	
/MM/	12	7005142	B2	2006-02-28	Leon et al.	
/MM/	13	7579019	B2	2009-08-25	Tapolsky et al.	

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U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/MM/	1	20050048102	A1	2005-03-03	Tapolsky et al.	
/MM/	2	20070148097	A1	2007-06-28	Finn et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

/Melissa Mercier/ (01/21/2011)

Receipt date: 12/15/2010	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Mercier, Melissa S.	
	Attorney Docket Number	1199-4 B CIP	

/MM/	1	1 510 999	GB		1978-05-17	Schering Aktiengesellschaft		☐
/MM/	2	WO 03/030881	WO	A1	2003-04-17	Kosmos Pharma		☐
/MM/	3	WO 2008/011194	WO	A2	2008-01-24	Biodelivery Sciences International, Inc.		☐

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Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

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EXAMINER SIGNATURE

Examiner Signature	/Melissa Mercier/ (01/21/2011)	Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	April 4, 2011

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Dated: April 4, 2011

Signature: Shannon Farischon/Shannon Farischon/

AMENDMENT AND RESPONSE PURSUANT TO 37 C.F.R. §1.116

Sir:

This is in response to the final Office Action dated February 2, 2011, a reply to which is due April 4, 2011 under the weekend rule.

Amendments to the Claims as reflected in the listing of claims; and

Remarks begin on page 12 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently Amended) A drug delivery composition comprising:

(i) a flowable water-soluble or water swellable film forming matrix comprising two or more substantially water soluble or water swellable polymers; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate bioeffecting agent uniformly stationed ~~therein~~ in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and

wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film unit.

11. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film unit.

12. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists,

proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently Amended) A thin film drug delivery composition comprising:

(a) an edible water-soluble or water swellable film forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component uniformly stationed ~~therein~~ in the matrix;

wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone;

poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer

agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (New) The drug delivery composition of claim 1, wherein the two or more water soluble or water swellable polymers have the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

Remarks

Claims 1-8 and 10-37 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claims 1 and18 are amended and new claim 37 is added. Support for the amendments to the claims and the new claim may be found, for example, in the original claims, and the specification at paragraph [0160]. No new matter is added.

Entry of the amendments is proper under 37 CFR §1.116 because the amendments: (a) place the application in condition for allowance for the reasons discussed herein; (b) do not raise any new issue requiring further search and/or consideration as the amendments amplify issues previously discussed throughout prosecution; (c) satisfy a requirement of form asserted in the previous Office Action; and (d) place the application in better form for appeal, should an appeal be necessary. The amendments are necessary and were not earlier presented because they are made in response to arguments raised in the final rejection. Entry of the amendments is thus respectfully requested.

In view of the foregoing amendments and following remarks, reconsideration and allowance are respectfully requested.

I. Rejection Under 35 U.S.C. §102

The Office Action rejects claims 1-5, 8-12, 14-19, 22, and 35-36 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 7,067,116 to Bess et al. ("Bess"). Applicants respectfully traverse the rejection.

By this Amendment, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Bess teach or suggest such features.

In particular, Bess fails to teach or suggest a matrix that comprises at least two water soluble or water swellable polymers and that the active present in the matrix is capable of being maintained with the aid of particular viscosity.

Nowhere does Bess teach or suggest that specific viscosity can be used to aid in maintaining non-self aggregating uniformity of the active in the matrix. At most Bess discloses that "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." However, Bess fails to teach or suggest a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as Bess does not appreciate the need for specific uniformity, as claimed.

The Office Action acknowledges that "Bess does not disclose the active component is uniformly distributed in the film composition; and wherein the infirmity is determined by the composition having a variation of drug content of less than 10% per film unit." *See* Office Action page 5, 3rd and 4th paragraphs.

Nonetheless, the Office Action asserts that because "Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the composition the same components prepared as a film,…one skilled in the art would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient." *See* Office Action page 5 last paragraph through page 6, 1st paragraph. Applicants respectfully disagree.

As is well settled:

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.'

In re Robertson, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted). In other words, it must be clear to one of ordinary skill in the art that the film matrix discussed in Bess **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection. As will be discussed below, evidence found, e.g., in the instant specification precludes such a determination.

The Examples and Comparative Example found of the instant specification illustrate how films having compositions recited in the independent claims, but are manufactured by two different processes, can exhibit different properties. *See* pages 22-37 of the published specification.

The missing elements of Bess cannot be inherent because the processes Bess uses to make its composition is clearly different from the novel process disclosed in the present application.

The ability to achieve the uniformity of content within the claimed range is directly related to Applicants' drying technique which is disclosed in must be carefully controlled. Conventional drying of cast films in ovens will not preserve uniformity.

As described in the present invention, a number of techniques are employed to avoid bubbles and provide uniform heterogeneity. In particular, the present specification obtains, "a composition mixture with substantially no air bubble formation in the final product" by utilizing "anti-foaming or surface-tension reducing agents" and controlling the speed of the mixture to prevent cavitation and "allowing the mix to stand for a sufficient time for bubbles to escape prior to drying the film". (Instant specification, paragraph [0075]) (emphasis added).

Bess fail to disclose the difficulties of achieving uniformity of content in cast films, nor steps or processes to overcome the inherent difficulties in doing so.

Applicants' process forms a visco-elastic matrix rapidly to "lock-in" the uniformity of the flowable matrix during the drying process. Bess merely recites air drying or drying under warm air, without any suggestion or even hint of the problem relating to uniformity. Uniformity, as recited by Applicants is clearly not taught nor suggested, nor is it at all predictable.

The film of Bess is dried using one of the "conventional" drying techniques, i.e. air-dried or dried under warm air. The method of drying as described by Bess would trap moisture inside the film. (Bess, col. 8, lines 47-50). Once the trapped moisture begins to evaporate, the surface of the film will rip open and reform. As such, a film that includes uniform heterogeneity is not expected in films that are dried according to the methods described in Bess. Uniform distribution of actives within the final film would not be expected with Bess's process. In fact, conventional processing does not produce films with uniformity of content, as further described below.

In contrast, the present specification utilizes a controlled drying process that avoids the formation of bubbles and a rippling effect by evaporating or removing at least a portion of the liquid carrier in a faster drying time than those conventionally used in the art. The faster drying time encourages uniform distribution of the actives because viscosity of the film increases at a quicker rate utilizing this method.

For at least the reasons mentioned, Bess fails to teach or suggest all the features of the independent claims. Accordingly Bess does not anticipate independent claims 1 and 18. Claims 2-5, 8-12, 14-17, 19, 22, and 35-36 variously depend from claims 1 and 18 and, thus, also are not anticipated by Bess. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

II. Rejections Under 35 U.S.C. §103

A. Chen in view of Ghana

The Office Action rejects claims 1–8, 10-12, 17, and 35-36 under 35 U.S.C. §103(a) over PCT Publication No. WO 00/42992 to Chen et al. ("Chen") in view of U.S. Patent No. 5,653,993 to Ghana et al. ("Ghana").

Without conceding the propriety of the rejection, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Chen teach or suggest such features. Ghana fails to cure the deficiencies of Chen, as it also fails to teach or suggest such features.

Whether considered independently or combined, Chen and Ghana fail to teach or suggest that specific viscosity can be used to aid in maintaining non-self aggregating uniformity of the active in the matrix and that uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit, as claimed.

The Office Action acknowledges that Chen and Ghana do not disclose the drug content uniformity but asserts that because "Chen and Ghana are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation….the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient." *See* Office Action page 9, 2nd paragraph.

As mentioned above, in order to support an inherency rejection, it must be clear to one of ordinary skill in the art that the film matrix discussed in Chen and Ghana **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection. As will be discussed below, evidence found, e.g., in the instant specification precludes such a determination.

The Examples and Comparative Example found of the instant specification illustrate how films having compositions recited in the independent claims, but are manufactured by two different processes, can exhibit different properties. *See* pages 22-37 of the published specification.

The claimed invention is directed to solving the problems associated with achieving a taste-masked drug which is uniformly distributed throughout a film, such that individual dosage units cut from the film will have the same amount of drug in them and will be pleasant tasting.

As described in the present invention, "the products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film." *See* paragraph [0160].

Although Chen discloses the use of taste-modifying agents in a film dosage form, Chen merely mixes taste modifying agents into the film-forming mix without recognizing the problem of separation or aggregation of the taste-modifying agents from the unpleasant tasting pharmaceutical agents. Therefore, Chen does not recognize the problem to be solved by the claimed invention, i.e. attaining low adjuvant content, high-taste-masked pharmaceutical active content films which have enhanced flexibility, structural integrity and **uniformity** (emphasis added). *See* page 3, lines 20-22.

As further evidence that Chen completely fails to appreciate uniformity, Chen merely discloses conventional hot air oven drying. Chen describes that the film is "dried under aeration at a temperature between 40-100°C so as to avoid destabilizing the agents contained within the formulation." (page 15, lines 28-29). Chen, however, does not disclose or even contemplate

using the specific controlled, bottom-drying methods presently claimed. The only means of drying disclosed in the cited reference is the method of drying that the present application specifically seeks to avoid (uncontrolled air drying).

Ghana is cited for its alleged disclosure of a diameter ranges from about 25 to 600 microns. Ghana is directed to preparation of individual taste-masked microcapsules. Nowhere does Ghana teach or suggest film that is uniform in content, as required by the claims. Therefore, Ghana fails to cure the deficiencies of Chen. Therefore, Chen and Ghana, whether considered independent or combines fails to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit" and a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

Thus, claim 1 would not have been rendered obvious by Chen and Ghana. Claims 2–12, 17, and 35-36 depend from claim 1 and, thus, also would not have been rendered obvious by Chen and Ghana. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

B. Schiraldi in view of Grass

The Office Action rejects claims 1–4, 10-13, 17-20, and 22-23 under 35 U.S.C. §103(a) over U.S. Patent No. 4,713,243 to Schiraldi et al. ("Schiraldi") in view of U.S. Patent No. U.S. Patent No. 3,237,596 to Grass et al. ("Grass"). Applicants respectfully traverse the rejection.

The Examiner acknowledges that Schiraldi does not teach all the limitations provided by the claims, but alleges that Grass remedies the deficiencies of Schiraldi. The Examiner asserts that Grass teaches a method of coating discrete solids that have a particle size of 5 to 200 microns thus is easily combinable with Schiraldi. Applicants respectfully disagree.

Without conceding the propriety of the rejection, the independent claims are amended to recite that the "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix; (ii) a particulate bioeffecting agent uniformly stationed in the matrix." Nowhere does Schiraldi teach or suggest such features. Grass fails to cure the deficiencies of Schiraldi, as it also fails to teach or suggest such features.

In particular, Schiraldi and Grass fail to teach or suggest a matrix that comprises at least two water soluble or water swellable polymers and that the active present in the matrix is capable of being maintained with the aid of particular viscosity. At most Schiraldi discloses that "for the uses for the present invention contemplated here, the plasticizer should be non-toxic. The purpose of the plasticizer is to improve polymer melt processing by reducing the polymer melt viscosity and to impart flexibility to the final product." However, Schiraldi fails to teach or suggest a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as Schiraldi does not appreciate the need for specific uniformity, as claimed.

As described in the present invention, "the products and processes of the present invention rely on the interaction among various steps of the production of the films in order to provide films that substantially reduce the self-aggregation of the components within the films. Specifically, these steps include the particular method used to form the film, making the composition mixture to prevent air bubble inclusions, controlling the viscosity of the film forming composition and the method of drying the film." *See* paragraph [0160].

Schiraldi describes a process for obtaining their bioadhesive extruded films. The components are all described as "powders" that are blended and then extruded by passing them through heated stainless steel rollers. Nothing in the reference suggests that simply blending components guarantees uniformity to any level. Nowhere in Schiraldi is it disclosed or suggested that the components are uniformly distributed throughout the final product, let alone that the final product has a uniformity that is no more than 10% variance per unit area nor that

the matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

As mentioned above, in order to support an inherency rejection, it must be clear to one of ordinary skill in the art that the film matrix discussed in Schiraldi and Grass **necessarily** possesses all of the properties and characteristics of the film matrix recited in the independent claims to support an inherency rejection.

As mentioned in the previous response, the Examiner has not provided any teaching to suggest that the extruded film of the Schiraldi is uniform. Nothing in the references suggests that simply blending components guarantees uniformity.

Grass is merely cited for its alleged disclosure of the particle size of about 5 to about 200 microns. Grass is directed to a method of coating discrete solids having a particular particle size. Nowhere does Grass teach or suggest film that is uniform in content nor does it teach a matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as required by the claims. Therefore, Grass fails to cure the deficiencies of Schiraldi.

Accordingly, independent claims 1 and 18 would not have been rendered obvious by Schiraldi and Grass. Claims 2–4, 9-13, 17, 19, 20, 22, and 23 variously depend from claims 1 and 18 and, thus, also would not have been rendered obvious by Schiraldi and Grass. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

C. Schiraldi in view of Thakur

The Office Action rejects claims 18-21 and 23-24 under 35 U.S.C. §103(a) over Schiraldi in view of U.S. Patent No. U.S. Publication No. 2004/0156901 to Thakur e al. ("Thakur").

The Examiner acknowledges that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. *See* Office Action, page 11 last paragraph. Nevertheless, the Examiner cites Thakur as allegedly curing Schiraldi's deficiencies. Applicants respectfully traverse the rejection.

For at least the reasons mentioned above, Schiraldi fails to teach or suggest all the features of claims 1 and 18. Thakur is cited for its alleged teaching particulate cores of actives agents coated with taste-masking polymer. Thakur's disclosure is directed to "a solid dosage formulation of topiramate intended primarily for use by pediatric patients, or for patients who have difficulty swallowing tablets." *See* Abstract. Nowhere does Thakur teach or suggest film that is uniform in content and a matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as required by the claims. Therefore, Thakur fails to cure the deficiencies of Schiraldi. Therefore, Schiraldi and Thakur, whether considered independent or combined fail to teach that "the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit" and a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix."

Moreover, similar to the arguments stated above in regards to Grass, there is no rationale in Schiraldi or Thakur to modify their teachings. Furthermore, there is no predictability in the teachings of Schiraldi or Thakur to lead one of skill in the art to arrive at the present invention with any expectation of success. Moreover, the combination of Schiraldi and Thakur does not teach all the claim limitations. Applicants therefore respectfully request reconsideration and withdrawal of the Section 103 rejection based thereon.

III. New Claim

By this Amendment, new claim 37 is presented. New claim 37 depends from claim 1 and, thus, distinguishes over the applied references for at least the reasons discussed above with respect to claim 1. Prompt examination and allowance of new claim 37 are respectfully requested.

IV. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
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Electronic Acknowledgement Receipt

EFS ID:	9803973
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Shannon Farischon
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	04-APR-2011
Filing Date:	10-JUL-2007
Time Stamp:	16:19:40
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1199-4B_CIP_Amendment_Response_04_04_11.pdf	156414 8102e3030436f5f4cbc1947c63f5c4c759f6f90c	yes	22

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	11
	Applicant Arguments/Remarks Made in an Amendment	12	22
Warnings:			
Information:			
	Total Files Size (in bytes):	156414	

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	04/04/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 37	Minus	** 36	= 1	X $26 =	26	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	26	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TINA J. BARDEN/

Document code: WFEE

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	April 15, 2011

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Dated: April 15, 2011

Signature: Marcy Mancuso */Marcy Mancuso/*

SUPPLEMENTAL AMENDMENT AND RESPONSE

Sir:

The Applicant previously submitted an Amendment and Response on April 4, 2011. Prior to examination of the newly-amended claims, the Applicant submits the following supplemental amendment:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Previously presented) A drug delivery composition comprising:

(i) a flowable water-soluble or water swellable film forming matrix comprising two or more substantially water soluble or water swellable polymers; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate bioeffecting agent uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and

wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film dosage unit.

11. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film dosage unit.

12. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Previously presented) A thin film drug delivery composition comprising:

(a) an edible water-soluble or water swellable film forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; said matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is uniformly distributed in the film composition; and

wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film dosage unit.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics,

prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (Previously presented) The drug delivery composition of claim 1, wherein the two or more water soluble or water swellable polymers have the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

Remarks

Claims 1-8 and 10-37 are pending in this application. Claims 25-34 have been withdrawn from consideration by the Examiner. By this Amendment, claims 10-12 are amended. Amendments to the dependent claims 10-12 were made to replace "per film unit" with "per film dosage unit" in order to improve the clarity of the claims and for consistency with the independent claims.

Support for the amendments may be found, for example, in the original claims, specification, and drawings. No new matter is added.

I. Conclusion

In view of the previously-submitted Amendment and Response, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should any additional fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time pursuant to 37 C.F.R. § 1.136, and includes fees for consideration of any IDS.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
Registration No. 60,808

HOFFMANN & BARON, LLP
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Electronic Acknowledgement Receipt

EFS ID:	9892400
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	15-APR-2011
Filing Date:	10-JUL-2007
Time Stamp:	16:12:03
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		Supplemental_Amendment_and_Response.pdf	124140 75aa84a2efd5532beaf37b3081a6bac6d17e6156	yes	11

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Supplemental Response or Supplemental Amendment	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	11
Warnings:			
Information:			
	Total Files Size (in bytes):	124140	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
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Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT 04/15/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	* 36	Minus	** 37	= 0	X $26 =	0	OR	X $ =	
Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)		RATE ($)	ADDITIONAL FEE ($)
Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
☐ Application Size Fee (37 CFR 1.16(s))									
☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
					TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/FLORENCE PATTERSON/

DO NOT ENTER: /MM/ (05/02/2011)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	April 15, 2011

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: April 15, 2011

Signature: Marcy Mancuso */Marcy Mancuso/*

SUPPLEMENTAL AMENDMENT AND RESPONSE

Sir:

The Applicant previously submitted an Amendment and Response on April 4, 2011. Prior to examination of the newly-amended claims, the Applicant submits the following supplemental amendment:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 05/10/2011
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
05/10/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Advisory Action Before the Filing of an Appeal Brief	**Application No.** 11/775,484	**Applicant(s)** YANG ET AL.	
	Examiner MELISSA MERCIER	**Art Unit** 1615	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 4/4/11; 4/15/11 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *3* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-8,10-24,35 and 36*.
   Claim(s) withdrawn from consideration: *25-34*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

/ANAND U DESAI/
Primary Examiner, Art Unit 1656

Continuation of 3. NOTE: Applicant has presented additonal claim limitations to a water swellable polymer. to be used in combination with or in place of the water soluble polymers which were previously presented. The additional limitations will require additional search and consideration. .

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

REQUEST FOR CONTINUED EXAMINATION(RCE)TRANSMITTAL
(Submitted Only via EFS-Web)

Application Number	11/775,484	Filing Date	2007-07-10	Docket Number (if applicable)	1199-4B CIP/RCE	Art Unit	1615
First Named Inventor	Robert K. Yang			Examiner Name	Mercier, Melissa S.		

This is a Request for Continued Examination (RCE) under 37 CFR 1.114 of the above-identified application.
Request for Continued Examination (RCE) practice under 37 CFR 1.114 does not apply to any utility or plant application filed prior to June 8, 1995, or to any design application. The Instruction Sheet for this form is located at WWW.USPTO.GOV

SUBMISSION REQUIRED UNDER 37 CFR 1.114

Note: If the RCE is proper, any previously filed unentered amendments and amendments enclosed with the RCE will be entered in the order in which they were filed unless applicant instructs otherwise. If applicant does not wish to have any previously filed unentered amendment(s) entered, applicant must request non-entry of such amendment(s).

☒ Previously submitted. If a final Office action is outstanding, any amendments filed after the final Office action may be considered as a submission even if this box is not checked.

☐ Consider the arguments in the Appeal Brief or Reply Brief previously filed on _____

☒ Other Amendments filed on April 4, 2011 and April 15, 2011

☒ Enclosed

☐ Amendment/Reply

☐ Information Disclosure Statement (IDS)

☐ Affidavit(s)/ Declaration(s)

☒ Other Request for Extension of Time

MISCELLANEOUS

☐ Suspension of action on the above-identified application is requested under 37 CFR 1.103(c) for a period of months _____ (Period of suspension shall not exceed 3 months; Fee under 37 CFR 1.17(i) required)

☐ Other _____

FEES

The RCE fee under 37 CFR 1.17(e) is required by 37 CFR 1.114 when the RCE is filed.

☒ The Director is hereby authorized to charge any underpayment of fees, or credit any overpayments, to Deposit Account No 082461

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

☒ Patent Practitioner Signature

☐ Applicant Signature

PTO/SB/30EFS (07-09)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Signature of Registered U.S. Patent Practitioner			
Signature	/Julie Tabarovsky, Reg. No. 60,808/	Date (YYYY-MM-DD)	2011-06-01
Name	Julie Tabarovsky	Registration Number	60808

This collection of information is required by 37 CFR 1.114. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether the Freedom of Information Act requires disclosure of these records.

2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.

3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.

4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).

5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.

6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspections or an issued patent.

9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Mercier, Melissa S.
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	June 1, 2011

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: June 1, 2011

Signature: Marcy Mancuso */Marcy Mancuso/*

PETITION FOR EXTENSION OF TIME

Sir:

Pursuant to 37 C.F.R. §1.136(a), an extension of time of one month is hereby requested to file a Request for Continued Examination. An Advisory Action was mailed on May 10, 2011, and a final Office Action was mailed on February 2, 2011. A Request for Continued Examination is being filed concurrently herewith.

A one-month extension is respectfully requested, making the due date June 2, 2011. Accordingly, this petition is timely filed on June 1, 2011. The requisite fee in the amount of $65.00 for a small entity pursuant to 37 C.F.R. §1.17 is believed to be due.

The Commissioner is hereby authorized to charge payment of $65.00 and any additional fees associated with this communication, or credit any overpayment, to Deposit Account

No. 08-2461. Such authorization includes authorization to charge fees for extensions of time under 37 C.F.R. § 1.17 and also should be treated as a constructive petition for an extension of time in this submission or any future submission pursuant to 37 C.F.R. § 1.136.

Respectfully submitted,

/Julie Tabarovsky/
Julie Tabarovsky
Registration No.: 60,808

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
(973) 331-1700

Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Julie Tabarovsky/Marcy Mancuso
Attorney Docket Number:	1199-4B CIP

Filed as Small Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 1 month with $0 paid	2251	1	65	65

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
Request for continued examination	2801	1	405	405
		Total in USD ($)		**470**

Electronic Acknowledgement Receipt

EFS ID:	10207319
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Julie Tabarovsky/Marcy Mancuso
Filer Authorized By:	Julie Tabarovsky
Attorney Docket Number:	1199-4B CIP
Receipt Date:	01-JUN-2011
Filing Date:	10-JUL-2007
Time Stamp:	14:49:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$470
RAM confirmation Number	1306
Deposit Account	082461
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Continued Examination (RCE)	RCE_Transmittal.pdf	983567 803c51553d92f8eb19db0e01844570e1bcedf8e0	no	3
Warnings:					
Information:					
2	Extension of Time	Extension_of_Time.pdf	91222 0800a8d5c2b2c3864fb5822d0c000c9d20f94cd2	no	2
Warnings:					
Information:					
3	Fee Worksheet (PTO-875)	fee-info.pdf	32689 10742ab97105613cd110e380b32579921388699a	no	2
Warnings:					
Information:					
		Total Files Size (in bytes):	1107478		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	06/01/2011	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 37	= 0	X $26 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $110 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/LINDA HUMES/

PTO/SB/08a (01-10)
Approved for use through 07/31/2012. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP/RCE

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5118508		1992-06-02	Kikuchi et al	
	2	5891461		1999-04-06	Jona et al	
	3	6103266		2000-08-15	Tapolsky et al	
	4	6667060	B1	2003-12-23	Vandecruys et al	

If you wish to add additional U.S. Patent citation information please click the Add button. Add

U.S.PATENT APPLICATION PUBLICATIONS Remove

Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030124176	A1	2003-07-03	Hsu et al	
	2	20050118217	A1	2005-06-02	Barnhart et al	

If you wish to add additional U.S. Published Application citation information please click the Add button. Add

FOREIGN PATENT DOCUMENTS Remove

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP/RCE

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] ¡	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
	1							☐

If you wish to add additional Foreign Patent Document citation information please click the Add button Add

NON-PATENT LITERATURE DOCUMENTS Remove

Examiner Initials*	Cite No	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc), date, pages(s), volume-issue number(s), publisher, city and/or country where published.	T[5]
	1		☐

If you wish to add additional non-patent literature document citation information please click the Add button Add

EXAMINER SIGNATURE

Examiner Signature		Date Considered	

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through a citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

[1] See Kind Codes of USPTO Patent Documents at www.USPTO.GOV or MPEP 901.04. [2] Enter office that issued the document, by the two-letter code (WIPO Standard ST.3). [3] For Japanese patent documents, the indication of the year of the reign of the Emperor must precede the serial number of the patent document. [4] Kind of document by the appropriate symbols as indicated on the document under WIPO Standard ST.16 if possible. [5] Applicant is to place a check mark here if English language translation is attached.

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

CERTIFICATION STATEMENT

Please see 37 CFR 1.97 and 1.98 to make the appropriate selection(s):

☐ That each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(1).

OR

☐ That no item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in 37 CFR 1.56(c) more than three months prior to the filing of the information disclosure statement. See 37 CFR 1.97(e)(2).

☐ See attached certification statement.

☐ The fee set forth in 37 CFR 1.17 (p) has been submitted herewith.

☒ A certification statement is not submitted herewith.

SIGNATURE

A signature of the applicant or representative is required in accordance with CFR 1.33, 10.18. Please see CFR 1.4(d) for the form of the signature.

Signature	/Jon A. Chiodo Reg. No. 52,739/	Date (YYYY-MM-DD)	2012-02-23
Name/Print	Jon A. Chiodo	Registration Number	52,739

This collection of information is required by 37 CFR 1.97 and 1.98. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1 hour to complete, including gathering, preparing and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

Privacy Act Statement

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6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).

7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.

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9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	12145360
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Jessica Colicchio
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-4B CIP
Receipt Date:	23-FEB-2012
Filing Date:	10-JUL-2007
Time Stamp:	16:11:04
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Form (SB08)	1199-4B-CIP-RCE_IDS.pdf	4930861 a85067e4d14ce401aea837dc17dc4b716bd013b3	no	4

Warnings:	
Information:	

Total Files Size (in bytes):	4930861

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 06/19/2012
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
06/19/2012	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2011*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-8 and 10-37* is/are pending in the application.

5a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8, 10-24, 35-37* is/are rejected.

8)☐ Claim(s) _____ is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

12)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2-23-12*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 4, 2011 has been entered.

Information Disclosure Statement

Receipt of the Information Disclosure Statement filed on February 23, 2012 is acknowledged. A signed copy is attached to this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 37 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 37 recites the “two or more water soluble or water swell able polymers have a viscosity in an amount sufficient to substantially prevent an active from setting out during mixing or coating”. Applicant has not particularly pointed out exactly how the

viscosity of a polymer is measured. It is the understanding of the examiner that a polymer "solution" can be determined based on the size and concentration of the polymer in the solution, but a polymer alone does not have a viscosity value. Therefore, exactly what the viscosity is a measure of has not been particularly pointed out.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8-12, 14-19, 22, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bess et al. (US Patent 7,067,116).

Bess discloses fast dissolving orally consumable solid film containing a taste masking agent and a pharmaceutically active agent at weight ratio of dissolving 1:3 to 3:1 (Title). The films include a water soluble film forming polymer and a taste masked pharmaceutically active agent (abstract).

Examples of water soluble film forming polymers include pullulan, HPMC, hydroxyethyl cellulose, hydropropyl cellulose, PVP, carboxymethyl cellulose PVA, sodium alginate, PEG, xanthan gum, and mixtures thereof, for example (column 5, lines 1-16).

The active agents include antimicrobial agents, NSAIDS, anti-tussives, decongestants, anti-histamines, expectorants, anti-diarrheals, PPI's, CNS depressants and stimulants (columns 2 and 3).

The taste masking agent is an ion exchange resin includes synthetic polymer of acrylic acid, methacrylic acid, sulfonated styrene, and sulfonated divinylbenzene or partially synthetic polymers of modified celluloses and dextrans, which is water soluble (column 4, lines 1-24). Less preferred embodiments partially taste masking agents of magnesium trisilicate and polymers such as Eudragit E and/or cellulosics, such as ethylcellulose (column 4, lines 60-67).

The active agents adsorbed to the ion exchange resin is in the range from about 25-75% by weight of the pharmaceutically active agent/resin adsorption complex, thereby meeting the limitations of claims 14-15. The recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent.

The pharmaceutically active agent/resin adsorption complex can also be coated in the range from about 40 to about 70% w/w pharmaceutically active agents/resin complex. Variation in the amount of coating and/or the use of coating/uncoated complex mixtures can be employed to selectively modify the dissolution profile (column 11, lines 43-53).

The particle size of the coated and uncoated pharmaceutically active agent/resin adsorption complex is about 60-200 microns (column 11, lines 54-58).

Plasticizers, surfactants, and polyalcohol's are optional ingredients; therefore, they are not required by Bess in order for the film to perform as disclosed.

The films can additionally include polyethylene oxide compound (column 8, line 15-18).

Regarding claim 19, Bess discloses his formulations are cast on a suitable substrate and dried to form a film (column 8, lines 47-48); however, this is considered a product by process limitation. Applicant is directed to MPEP 2112 which discloses "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is

unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Since the methods of preparing the films disclosed in the reference recite numerous mixing steps of the same structural elements as recited in the instant claims, it is the position of the Examiner that absent of showing of evidence to the contrary, the films would possess the same uniformity as recited in instant claims. Applicant is invited to provide evidence that the uniformity of the film does not have a variation of drug content of less than 10% per film unit.

.Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Bess does not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Bess does not disclose the drug content uniformity, Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the same components prepared as a film. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. Again, it is suggested that Applicant provide evidence that the film does not

have a different drug variation than that claims in the instant claims. Arguments of council do not replace the showing of evidence when evidence is needed to distinguish the instant film from that disclosed in the prior art. Applicant has provided speculative properties of the film of Bess but not any actual measurements or comparisons between the two. Bess does not disclose the difficulty in achieving a uniform film; however, there is nothing of record, with Bess or presented by applicant to show that Bess's film is not uniform.

Applicant appears to be arguing the claims as a process of making and not the final composition. The method in which the composition is made does not hold patentable weight in a composition claims. Applicant has elected the composition and not the method of making the composition in this application.

Claims 1-8, 10-12, 17, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (WO 00/42992) in view of Ghana et al (US Patent 5,653,993).

Chen discloses a water soluble hydrocolloid; mucosal surface coated forming film, having an effective dose of an active agent (page 3, lines 30-33).

The hydrocolloid includes a polymer selected from the group consisting of natural, semi-natural and synthetic biopolymers (page 4, lines 1-3).

The active agents is selected from the group consisting of therapeutic agents, dietary supplements, and hygiene aids, for example sildenafil citrate, nicotine, hydromorphone, oxybutynine, or estradiol (page 4, lines 7-10). The active agent can be

encapsulated in a material that is different than the hydrocolloid. Encapsulation is additionally utilized to achieve masking of taste of active agents that are bitter (page 9, lines 13-15).

The hydrocolloid is a water soluble non gelling natural polysaccharide, polypeptide or protein (page 14, lines 12-31).

The films can be cast or extruded (page 15-16).

Chen does not disclose the particle size of the encapsulated active agents.

Ghanta discloses the preparation of taste masked microcapsules. The encapsulating material is cellulose acetate phthalate and gelatin (abstract).

The average/mean microcapsule diameter ranges from about 25 to about 600 microns (column 3, lines 59-62).

The gelatin used can be of any origin so long as it is of pharmaceutical grade. The gelatin, for example, can have a number average molecular weight of about 27,000 to 70,000 (column 4, lines 43-47).

It would have been within the skill of the ordinary practitioner to have used the particle size disclosed by Ghanta in order to make the encapsulated active agents utilized by Chen since both references discloses the particles are suitable for taste masking and Ghanta discloses they do not form agglomerates (column 3, lines 33-35), thereby allowing for a more uniform distribution.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the particle size of the microcapsules in Chen since Ghanta discloses in order to make wider use of NSAIDs while substantially

eliminating the bitter taste, aftertaste and adverse mouth feel and make these drugs more pleasant upon taking them orally, there has long been desired a way to insure delivery of these drugs in their desired concentrations while avoiding their extremely bitter taste, lingering aftertaste and adverse mouth feel effects referred to above connected with their ingestion orally, thereby encouraging patient compliance.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Chen and Ghanta do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Chen and Ghanta do not disclose the drug content uniformity, Chen and Ghanta are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims. As discussed above, Arguments of council do not replace the showing of evidence when evidence is needed to distinguish the instant film from that disclosed in the prior art. Applicant has

provided speculative properties of the film of Chen and Ghanta but not any actual measurements or comparisons between the two. Chen and Ghanta do not disclose the difficulty in achieving a uniform film, however, there is nothing of record, in the prior art references or presented by applicant to show that the film is not uniform.

Claims 1-4, 10-13, 17-20, and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Grass et al. (US Patent 3,237,596).

Schiraldi discloses a bioadhesive extruded single or multilayered thin film having a water soluble or swell able polymer matrix, bioadhesive layer consists essentially of 40-95% by weight of a hydroxypropyl cellulose, 5-60% of a homopolymer of ethylene oxide, 0-10% of a water-insoluble polymer such as ethyl cellulose, propyl cellulose, polyethylene and polypropylene, and 2-10% of a plasticizer, said film having incorporated therein a medicament, such as anesthetics, analgesics, anticaries agents, anti-inflammatories, antihistamines, antibiotics, antibacterials, fungistats, etc (abstract).

Schiraldi does not disclose the medicament being coated with a taste masking polymer having a particle size of 200 microns or less.

Grass discloses a method of coating discrete solids. The solids have a particle size of about 5 to about 200 microns (column 1, lines 10-15). Spherical particles of acetaminophen coated with 12-hydroxystearyl alcohol are disclosed in the Examples.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have employed the method of coating medicaments as disclosed

by Grass for incorporation into the films disclosed by Schiraldi in order to achieve the taste masking, sustained dissolution, enteric properties, improved stability, delayed interaction, wettability, and improved flow properties of the active agent for incorporation into drug formulation.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

*** Schiraldi and Grass do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

As discussed with each rejection above, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims. As discussed above, Arguments of council do not replace the showing of evidence when evidence is needed to distinguish the instant film from that disclosed in the prior art. Applicant has provided speculative properties of the film of Schiraldi and Grass but not any actual measurements or comparisons between the two. Schiraldi and Grass do not disclose the difficulty in

achieving a uniform film, however, there is nothing of record, in the prior art references or presented by applicant to show that the film is not uniform.

Claims 18-21 and 23-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schiraldi et al. (US Patent 4,713,243) in view of Thakur et al. (US 2004/0156901).

The teaching of Schiraldi are discussed above and applied in the same manner.

Schiraldi does not disclose the medicament being coated with a taste masking water soluble polymer .

Thakur discloses particulate cores of active agents coated with a taste masking polymer, preferably cellulose acetate (paragraph 0034), which is a water soluble polymer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to have used coated active agents, as discussed by Thakur in order to provide dosage forms in which pharmaceutical agents with unappealing tastes can be masked and allow for increased patient compliance.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Schiraldi and Thakur do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Schiraldi and Thakur do not disclose the drug content uniformity, Schiraldi and Thakur are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
June 15, 2012

Notice of References Cited	Application/Control No. 11/775,484	Applicant(s)/Patent Under Reexamination YANG ET AL.	
	Examiner MELISSA MERCIER	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,067,116	06-2006	Bess et al.	424/78.1
*	B	US-5,653,993	08-1997	Ghanta et al.	424/440
*	C	US-4,713,243	12-1987	Schiraldi et al.	424/676
*	D	US-3,237,596	03-1966	GRASS JR GEORGE M et al.	118/62
*	E	US-2004/0156901	08-2004	Thakur et al.	424/471
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
S1	254	edible SAME film AND coated SAME (active drug medicant medicament)	USPAT	OR	OFF	2010/09/04 15:11
S2	281	edible SAME film AND coated SAME (active drug medicant medicament)	USPAT	OR	ON	2010/09/04 15:11
S3	13	edible SAME film AND coated SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/04 15:13
S4	0	edible SAME film AND taste adj1 mask$ SAME coated SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/04 15:49
S5	4	edible SAME film AND taste adj1 mask$ SAME coated SAME (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 15:49
S6	47	film AND taste adj1 mask$ SAME coated SAME (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:05
S7	0	WO0042992A	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:08
S8	0	0042992A	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:08
S9	132	"4136145"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:17

EAST Search History (Prior Art)

S10	2266	film AND coated SAME (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:26
S11	1358	film AND coated SAME (active drug medicant medicament) SAME particle adj1 size	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:26
S12	27	edible SAME film AND coated SAME (active drug medicant medicament) SAME particle adj1 size	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/04 16:27
S13	96	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 10:47
S14	291	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND micron	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 11:02
S15	308	edible SAME film AND (active drug medicant medicament) SAME (particle particulate) AND (coat encapsulate)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:23
S16	177	"4713243"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:28
S17	52	"6284264"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:46

EAST Search History (Prior Art)

S18	47	"5393528"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:49
S19	17	"1110546"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:52
S20	19068	film AND (active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:53
S21	5583	film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:54
S22	89	edible WITH film AND (active drug medicant medicament) SAME particle adj1 size SAME (coat coating coated encapsulate encapsulated)	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 13:55
S23	45	"4849246"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:02
S24	3	"0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:09

S25	0	"0514691A"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
S26	0	"EP0514691"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:10
S27	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:20
S28	19	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size AND film	USPAT	OR	ON	2010/09/05 14:24
S29	37	taste adj1 masking SAME (active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:29
S30	21	taste adj1 masking SAME (drugactive drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
S31	37	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	USPAT	OR	ON	2010/09/05 14:35
S32	159	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 14:35
S33	45	"5215755"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:14
S34	47	taste adj1 masking SAME (drug active drug medicant medicament) SAME particle adj1 size AND spherical	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2010/09/05 15:41

EAST Search History (Prior Art)

S35	1	film SAME "drug uniformity"	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	OR	ON	2011/01/21 14:41
S36	428	drug content uniformity	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2011/01/21 14:44
S37	223	drug content uniformity AND film	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2011/01/21 14:44
S38	223	(drug content uniformity) AND film	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2011/01/21 14:44
S39	51	(drug content uniformity) AND film	USPAT	WITH	ON	2011/01/21 14:44
S40	0	(drug content uniformity) SAME film	USPAT	WITH	ON	2011/01/22 13:25
S41	24	(drug content uniformity) SAME film	US-PGPUB; USPAT; USOCR; FPRS; EPO; JPO; DERWENT; IBM_TDB	WITH	ON	2011/01/22 13:25

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	Art Unit
	MELISSA S MERCIER	1615

SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
East-see attached	6-15-12	MMercier

INTERFERENCE SEARCH			
Class	Subclass	Date	Examiner

/MELISSA S MERCIER/ Examiner.Art Unit 1615	

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Mercier, Melissa S.
Attorney Docket Number	1199-4 B CIP/RCE

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	5118508		1992-06-02	Kikuchi et al	
	2	5891461		1999-04-06	Jona et al	
	3	6103266		2000-08-15	Tapolsky et al	
	4	6667060	B1	2003-12-23	Vandecruys et al	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	20030124176	A1	2003-07-03	Hsu et al	
	2	20050118217	A1	2005-06-02	Barnhart et al	

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Receipt date: 02/23/2012	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Mercier, Melissa S.	
	Attorney Docket Number	1199-4 B CIP/RCE	

Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP
Confirmation No.	5059	Dated:	December 19, 2012

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

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Dated: December 19, 2012

Signature: Ivory Edwards /Ivory Edwards/

AMENDMENT AND RESPONSE

Madam:

In response to the Office Action dated June 19, 2012, a response to which is due December 19, 2012, with a three-month extension of time, the following amendments and remarks are provided:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 10 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently amended) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising two or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has ~~having~~ a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate bioeffecting agent uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the bioeffecting agent;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of uniformity in the stationing of said particulate bioeffecting agent therein; and

wherein the uniformity subsequent to casting and drying is measured ~~determined~~ by substantially equally sized individual unit doses which do not vary by more ~~the composition having a variation of drug content of less~~ than 10% of said desired amount of said at least one active~~per dosage unit~~.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said bioeffecting agent.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film dosage unit.

11. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film dosage unit.

12. (Currently amended) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

13. (Original) The drug delivery composition of claim 1, wherein the coated particulate bioeffecting agent has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Original) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently amended) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has ~~having~~ a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is uniformly distributed in the film composition;

and

wherein the uniformity ~~is determined~~ subsequent to casting and drying is measured by substantially equally sized individual unit doses which do not vary by more ~~the composition having a variation of drug content of less~~ than 10% of said desired amount of said at least one active~~per film dosage unit~~.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

24. (Original) The drug delivery composition of claim 18, wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said bioeffecting agent is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids,

amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (Currently amended) The drug delivery composition of claim 1, wherein the ~~two or more water-swellable polymers have~~ film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

Remarks

Claims 1, 18, and 37 have been amended. Support for these amendments may be found throughout the specification. No new matter has been added.

35 U.S.C. § 112, Second Paragraph Rejection

Claim 37 was rejected under 35 U.S.C. § 112, second paragraph as indefinite for the recitation of "viscosity" without "particularly [pointing] out exactly how the viscosity of a polymer is measure." Applicants respectfully traverse the rejection.

Claim 1, from which claim 37 depends, has been amended to recite an explicit parameters for the measure of uniformity. By extension, the parameters provide a measure for the viscosity of the matrix, which is sufficient to maintain this uniformity of the active. Accordingly, Applicants respectfully submit that claim 37 fully complies with the requirements of 35 U.S.C. § 112. Reconsideration and withdrawal of the rejection are respectfully solicited.

35 U.S.C. § 103 Rejections

Bess

Claims 1-5, 8-12, 14-19, 22, and 35-36 have been rejected under 35 U.S.C. § 103 as obvious over Bess et al., U.S. Patent No. 7,067,116. Applicants respectfully traverse the rejection.

The Examiner conceded that Bess does not teach the uniformity limitations of the present claims. However, the Examiner then alleged that Bess teaches the same components as claimed and "numerous mixing steps of the same structural elements as recited in the instant claims, it is the position of the Examiner that absent of showing evidence to the contrary, the films would possess the same uniformity as recited in instant claims." However, the Examiner offers nothing to support her "position." Unable to make out a *prima facie* case for the obviousness of the claims, the Examiner attempts to shift the burden to the Applicants to provide evidence that the Bess compositions do not meet the express limitations of the claims.

Simply put, the Examiner has not met her burden to make out a *prima facie* case for obviousness. And, no amount of unsupported supposition can cure the fatal flaw in Bess – there is simply no disclosure in Bess of the claimed limitation or any other teaching to arrive at the claimed invention.

Nowhere does Bess teach or suggest the viscosity of the polymer matrix can be used to aid in maintaining non-self aggregating uniformity of the active in the matrix. At most Bess discloses that "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." However, Bess fails to teach or suggest a "matrix having a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix," as Bess does not appreciate the need for specific uniformity, as claimed.

Recognizing this fatal shortcoming, the Examiner acknowledged that Bess does not disclose uniformity limitations of the claims. Nonetheless, the Examiner asserted that "Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the composition the same components prepared as a film,…the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient."

Not surprisingly, the Examiner doesn't appear come to any conclusion as to what these observations mean with regard to the present claims. It is not enough for one of skill in the art to desire what the applicant has done. In fact, such a desire coupled with the inability to achieve the desire result is actually evidence of non-obviousness, e.g., failure of others, long felt need. For example, the desire to produce a medicine that cures cancer, does not render a composition that achieves this goal obvious.

Moreover, the Examples and Comparative Example in the instant specification illustrate that films having the components recited in the independent claims, but manufactured by two different processes, exhibit different properties. (*See* pages 22-37 of the published specification.) The elements missing from Bess are not obvious because the same components can result in

vastly different uniformities. Thus, the fact that Bess uses similar components and "numerous mixing steps" is simply not enough to render the present claim obvious.

In view of the forgoing, it is clear that Bess is insufficient to support a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully solicited.

Chen in view of Ghana

Claims 1–8, 10-12, 17, and 35-36 were rejected under 35 U.S.C. §103(a) as obvious over Chen et al., WO 00/42992 in view of Ghanta et al., U.S. Patent No. 5,653,993. Applicants respectfully traverse the rejection.

In making the rejection, the Examiner has alleged that Chen teaches a film including all the components of the claimed films. The Examiner acknowledged that "Chen does not disclose the claimed particle size of the encapsulated active agents." The Examiner relied on Ghanta as disclosing gelatin encapsulated actives to close this gap.

However, the Examiner conceded that Chen and Ghanta, even in combination, do not teach the uniformity limitations of the present claims. Similar to the previous rejection over Bess, the Examiner alleged that "Chen and Ghanta are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation,…the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient."

Not surprisingly, the Examiner doesn't appear come to any conclusion as to what these observations mean with regard to the present claims. It is not enough for one of skill in the art to desire what the applicant has done. In fact, such a desire coupled with the inability to achieve the desire result is actually evidence of non-obviousness, e.g., failure of others, long felt need.

Unable to make out a *prima facie* case for the obviousness of the claims, the Examiner again attempts to shift the burden to the Applicants to provide evidence that the Chen and Ghanta compositions do not meet the express limitations of the claims. However, the Examiner has not met her burden to make out a *prima facie* case for obviousness. And, no amount of unsupported

supposition can cure the fatal flaw in the combination of Chen and Ghanta – there is simply no disclosure therein of the claimed limitation or any other teaching to arrive at the claimed invention.

As previously discussed, the Examples and Comparative Example in the instant specification illustrate that films having the components recited in the independent claims, but manufactured by two different processes, exhibit different properties. (*See* pages 22-37 of the published specification.) The elements missing from Chen and Ghanta are not obvious because the same components can result in vastly different uniformities. Thus, the fact that the cited references similar components and mixing is simply not enough to render the present claim obvious.

In view of the forgoing, it is clear that Chen and Ghanta, even in combination, are insufficient to support a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully solicited.

Schiraldi in view of Grass

Claims 1–4, 10-13, 17-20, and 22-23 were rejected under 35 U.S.C. §103(a) as obvious over Schiraldi et al., U.S. Patent No. 4,713,243 in view of Grass et al., U.S. Patent No. U.S. Patent No. 3,237,596. Applicants respectfully traverse the rejection.

In making the rejection, the Examiner asserted that Schiraldi teaches a film composition including most of the claimed components. However, the Examiner acknowledged that Schiraldi does not teach the active agent being coating with a taste masking polymer having a particle size of 200 μm or less. The Examiner relied on Grass to fill this gap as teaching a method of coating discrete solids that have a particle size of 5 to 200 microns.

However, the Examiner apparently conceded that Schiraldi and Glass, even in combination, do not teach the uniformity limitations of the present claims. Similar to the previous rejections, the Examiner alleged that "the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient."

Not surprisingly, the Examiner doesn't appear come to any conclusion as to what this observations means with regard to the present claims. It is not enough for one of skill in the art to desire what the applicant has done. In fact, such a desire coupled with the inability to achieve the desire result is actually evidence of non-obviousness, e.g., failure of others, long felt need.

Unable to make out a *prima facie* case for the obviousness of the claims, the Examiner again attempts to shift the burden to the Applicants to provide evidence that the Schiraldi and Glass compositions do not meet the express limitations of the claims. However, the Examiner has not met her burden to make out a *prima facie* case for obviousness. And, no amount of unsupported supposition can cure the fatal flaw in the combination of Schiraldi and Glass – there is simply no disclosure therein of the claimed limitation or any other teaching to arrive at the claimed invention.

As previously discussed, the Examples and Comparative Example in the instant specification illustrate that films having the components recited in the independent claims, but manufactured by two different processes, exhibit different properties. (*See* pages 22-37 of the published specification.) The elements missing from Schiraldi and Glass are not obvious because the same components can result in vastly different uniformities. Thus, the fact that the cited references similar components and mixing is simply not enough to render the present claim obvious.

In view of the forgoing, it is clear that Schiraldi and Glass, even in combination, are insufficient to support a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully solicited.

Schiraldi in view of Thakur

Claims 18-21 and 23-24 were rejected under 35 U.S.C. §103(a) as obvious over Schiraldi in view of Thakur et al., U.S. Publication No. 2004/0156901. Applicants respectfully traverse this rejection.

The Examiner acknowledged that Schiraldi fails to teach or suggest that the medicament is coated with a taste-masking water soluble polymer. The Examiner relies on Thakur to fill this gap in Schiraldi.

However, the Examiner conceded that Schiraldi and Thakur, even in combination, do not teach the uniformity limitations of the present claims. Similar to the previous rejections, the Examiner alleged that "Schiraldi and Thakur are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation,…the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient."

Not surprisingly, the Examiner doesn't appear come to any conclusion as to what these observations mean with regard to the present claims. It is not enough for one of skill in the art to desire what the applicant has done. In fact, such a desire coupled with the inability to achieve the desire result is actually evidence of non-obviousness, e.g., failure of others, long felt need.

Unable to make out a *prima facie* case for the obviousness of the claims, the Examiner again attempts to shift the burden to the Applicants to provide evidence that the Schiraldi and Thakur compositions do not meet the express limitations of the claims. However, the Examiner has not met her burden to make out a *prima facie* case for obviousness. And, no amount of unsupported supposition can cure the fatal flaw in the combination of Schiraldi and Thakur – there is simply no disclosure therein of the claimed limitation or any other teaching to arrive at the claimed invention.

As previously discussed, the Examples and Comparative Example in the instant specification illustrate that films having the components recited in the independent claims, but manufactured by two different processes, exhibit different properties. (*See* pages 22-37 of the published specification.) The elements missing from Schiraldi and Thakur are not obvious because the same components can result in vastly different uniformities. Thus, the fact that the cited references similar components and mixing is simply not enough to render the present claim obvious.

In view of the forgoing, it is clear that Schiraldi and Thakur, even in combination, are insufficient to support a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejection are respectfully solicited.

Conclusion

In view of the foregoing, it is respectfully submitted that all of the rejections have been met and this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should any additional fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time pursuant to 37 C.F.R. § 1.136, and includes fees for consideration of any IDS.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
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Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Daniel A. Scola/Ivory Edwards
Attorney Docket Number:	1199-4B CIP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
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Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Extension - 3 months with $0 paid	1253	1	1290	1290

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Miscellaneous:				
			Total in USD ($)	**1290**

Electronic Acknowledgement Receipt

EFS ID:	14516186
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Daniel A. Scola/Ivory Edwards
Filer Authorized By:	Daniel A. Scola
Attorney Docket Number:	1199-4B CIP
Receipt Date:	19-DEC-2012
Filing Date:	10-JUL-2007
Time Stamp:	16:01:00
Application Type:	Utility under 35 USC 111(a)

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1		1199_4B_CIP_RCE_Amendmt_Response_12_19-12.PDF	62007 25771e4e5f7bd70bedc3a6b1fe3f1e879338b9c9	yes	16

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment/Req. Reconsideration-After Non-Final Reject	1	1
	Claims	2	9
	Applicant Arguments/Remarks Made in an Amendment	10	16

Warnings:

Information:

2	Fee Worksheet (SB06)	fee-info.pdf	30934 bf71896c79149a5970c6febe494c99dc493409f8	no	2

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

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

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

PTO/SB/06 (07-06)
Approved for use through 1/31/2007. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number	Filing Date	☐ To be Mailed
11/775,484	07/10/2007	

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	SMALL ENTITY ☒ RATE ($)	SMALL ENTITY ☒ FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A			N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =		OR	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =			X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $250 ($125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	12/19/2012	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 36	Minus	** 37	= 0	X $31 =	0	OR	X $ =	
	Independent (37 CFR 1.16(h))	* 6	Minus	***6	= 0	X $125 =	0	OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE	0	OR	TOTAL ADD'L FEE	

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	SMALL ENTITY RATE ($)	SMALL ENTITY ADDITIONAL FEE ($)	OR	OTHER THAN SMALL ENTITY RATE ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =		OR	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =		OR	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))									
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

Legal Instrument Examiner:
/TERRY MALLOY/

UNITED STATES PATENT AND TRADEMARK OFFICE

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 03/13/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
03/13/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA MERCIER	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12-19-12*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.

4)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

5)☒ Claim(s) *1-8 and 10-37* is/are pending in the application.

5a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

6)☐ Claim(s) _____ is/are allowed.

7)☒ Claim(s) *1-8,10-12, 14-22 and 35-37* is/are rejected.

8)☒ Claim(s) *13,23 and 24* is/are objected to.

9)☐ Claim(s) _____ are subject to restriction and/or election requirement.

* If any claims have been determined allowable, you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov.

Application Papers

10)☐ The specification is objected to by the Examiner.

11)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

3) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

4) ☐ Other: _____.

DETAILED ACTION

Summary

Receipt of Applicants Remarks and Amended Claims filed on December 19, 2012 is acknowledged. Claims 1-8, 10-37 remain pending in this application. Claims 25-34 remain withdrawn from consideration.

Claims 1-8, 10-24, and 35-37 remain under examination. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Objections

Claims 13 and 23-24 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6, 8, 10-12, 14-19, 22, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bess et al. (US Patent 7,067,116).

Bess discloses fast dissolving orally consumable solid film containing a taste masking agent and a pharmaceutically active agent at weight ratio of dissolving 1:3 to 3:1 (Title). The films include a water soluble film forming polymer and a taste masked pharmaceutically active agent (abstract).

Examples of water soluble film forming polymers include pullulan, HPMC, hydroxyethyl cellulose, hydropropyl cellulose, PVP, carboxymethyl cellulose PVA, sodium alginate, PEG, xanthan gum, and mixtures thereof, for example (column 5, lines 1-16).

The active agents include antimicrobial agents, NSAIDS, anti-tussives, decongestants, anti-histamines, expectorants, anti-diarrheals, PPI's, CNS depressants and stimulants (columns 2 and 3).

The taste masking agent is an ion exchange resin includes synthetic polymer of acrylic acid, methacrylic acid, sulfonated styrene, and sulfonated divinylbenzene or partially synthetic polymers of modified celluloses and dextrans, which is water soluble (column 4, lines 1-24). Less preferred embodiments partially taste masking agents of magnesium trisilicate and polymers such as Eudragit E and/or cellulosics, such as ethylcellulose (column 4, lines 60-67).

The active agents adsorbed to the ion exchange resin is in the range from about 25-75% by weight of the pharmaceutically active agent/resin adsorption complex, thereby meeting the limitations of claims 14-15. The recitation of adsorption complex would necessarily result in a thin film coating over portions of the agent.

The pharmaceutically active agent/resin adsorption complex can also be coated in the range from about 40 to about 70% w/w pharmaceutically active agents/resin complex. Variation in the amount of coating and/or the use of coating/uncoated complex mixtures can be employed to selectively modify the dissolution profile (column 11, lines 43-53).

The particle size of the coated and uncoated pharmaceutically active agent/resin adsorption complex is about 60-200 microns (column 11, lines 54-58).

Plasticizers, surfactants, and polyalcohol's are optional ingredients; therefore, they are not required by Bess in order for the film to perform as disclosed.

The films can additionally include polyethylene oxide compound (column 8, line 15-18).

Regarding claim 19, Bess discloses his formulations are cast on a suitable substrate and dried to form a film (column 8, lines 47-48); however, this is considered a product by process limitation. Applicant is directed to MPEP 2112 which discloses "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

Since the methods of preparing the films disclosed in the reference recite numerous mixing steps of the same structural elements as recited in the instant claims, it is the position of the Examiner that absent of showing of evidence to the contrary, the films would possess the same uniformity as recited in instant claims. Applicant is invited to provide evidence that the uniformity of the film does not have a variation of drug content of less than 10% per film unit.

.Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Bess does not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Bess does not disclose the drug content uniformity, Bess does disclose the composition is thoroughly mixed prior to casting into a film. Bess additionally discloses the same components prepared as a film. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. Again, it is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims. Arguments of council do not replace the showing of evidence when evidence is needed to distinguish the instant film from that disclosed in the prior art. Applicant has provided speculative properties of the film of Bess but not any actual measurements or comparisons between the two. Bess does not disclose the difficulty in achieving a uniform film; however, there is nothing of record, with Bess or presented by applicant to show that Bess's film is not uniform.

Applicant appears to be arguing the claims as a process of making and not the final composition. The method in which the composition is made does not hold patentable weight in a composition claims. Applicant has elected the composition and not the method of making the composition in this application.

Claims 1-8, 10-12, 17, and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. (WO 00/42992) in view of Ghana et al (US Patent 5,653,993).

Chen discloses a water soluble hydrocolloid; mucosal surface coated forming film, having an effective dose of an active agent (page 3, lines 30-33).

The hydrocolloid includes a polymer selected from the group consisting of natural, semi-natural and synthetic biopolymers (page 4, lines 1-3).

The active agents is selected from the group consisting of therapeutic agents, dietary supplements, and hygiene aids, for example sildenafil citrate, nicotine, hydromorphone, oxybutynine, or estradiol (page 4, lines 7-10). The active agent can be encapsulated in a material that is different than the hydrocolloid. Encapsulation is additionally utilized to achieve masking of taste of active agents that are bitter (page 9, lines 13-15).

The hydrocolloid is a water soluble non gelling natural polysaccharide, polypeptide or protein (page 14, lines 12-31).

The films can be cast or extruded (page 15-16).

Chen does not disclose the particle size of the encapsulated active agents.

Ghanta discloses the preparation of taste masked microcapsules. The encapsulating material is cellulose acetate phthalate and gelatin (abstract).

The average/mean microcapsule diameter ranges from about 25 to about 600 microns (column 3, lines 59-62).

The gelatin used can be of any origin so long as it is of pharmaceutical grade. The gelatin, for example, can have a number average molecular weight of about 27,000 to 70,000 (column 4, lines 43-47).

It would have been within the skill of the ordinary practitioner to have used the particle size disclosed by Ghanta in order to make the encapsulated active agents utilized by Chen since both references discloses the particles are suitable for taste masking and Ghanta discloses they do not form agglomerates (column 3, lines 33-35), thereby allowing for a more uniform distribution.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have selected the particle size of the microcapsules in Chen since Ghanta discloses in order to make wider use of NSAIDs while substantially eliminating the bitter taste, aftertaste and adverse mouth feel and make these drugs more pleasant upon taking them orally, there has long been desired a way to insure delivery of these drugs in their desired concentrations while avoiding their extremely bitter taste, lingering aftertaste and adverse mouth feel effects referred to above connected with their ingestion orally, thereby encouraging patient compliance.

Response to Arguments

Applicant's arguments have been fully considered but they are not persuasive. Applicant argues:

***Chen and Ghanta do not disclose the active component is uniformly distributed in the film composition; and wherein the uniformity is determined by the composition having a variation of drug content of less than 10% per film unit.**

While it is acknowledged Chen and Ghanta do not disclose the drug content uniformity, Chen and Ghanta are both drawn to the preparation of films, and disclose the solution is mixed to provide a uniform solution prior to film preparation. Furthermore, the skilled artisan would have understood the importance of providing a homogenous film in order to ensure appropriate dosing of active agents to provide correct efficacy of the drug to the patient. Applicant is also reminded that the USPTO does not possess laboratory facilities in order to determine if the compositions possess the same functional properties. It is suggested that Applicant provide evidence that the film does not have a different drug variation than that claims in the instant claims. As discussed above, Arguments of council do not replace the showing of evidence when evidence is needed to distinguish the instant film from that disclosed in the prior art. Applicant has provided speculative properties of the film of Chen and Ghanta but not any actual measurements or comparisons between the two. Chen and Ghanta do not disclose the difficulty in achieving a uniform film, however, there is nothing of record, in the prior art references or presented by applicant to show that the film is not uniform.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
March 11, 2013

Notice of References Cited	Application/Control No. 11/775,484	Applicant(s)/Patent Under Reexamination YANG ET AL.	
	Examiner MELISSA MERCIER	Art Unit 1615	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
*	A	US-7,067,116	06-2006	Bess et al.	424/78.1
*	B	US-5,653,993	08-1997	Ghanta et al.	424/440
*	C	US-4,713,243	12-1987	Schiraldi et al.	424/676
*	D	US-3,237,596	03-1966	GRASS JR GEORGE M et al.	118/62
*	E	US-2004/0156901	08-2004	Thakur et al.	424/471
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

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	N					
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	P					
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	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	May 10, 2013

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: May 10, 2013

Signature: Jane Callahan */Jane Callahan/*

AMENDMENT AND RESPONSE AFTER FINAL OFFICE ACTION

Madam:

In response to the Final Office Action dated March 13, 2013, a response to which is due May 13, 2013, under the 2-month rule, the following amendments and remarks are provided:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 20 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Currently amended) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one ~~two~~ or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active ~~bioeffecting agent~~ substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active ~~bioeffecting agent~~;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active ~~bioeffecting agent~~ therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Currently amended) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said active ~~bioeffecting agent~~.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film dosage unit.

11. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film dosage unit.

12. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

13. (Cancelled).

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Currently amended) The drug delivery composition of claim 1, wherein said active ~~bioeffecting agent~~ is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Currently amended) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23. (Cancelled).

24. (Cancelled).

25. (Withdrawn) A drug delivery vehicle comprising:

a dry mucoadhering film having a thickness defined by opposed surfaces; said film comprising:

(i) a water-soluble polymer;

(ii) a pharmaceutically active particle comprising a pharmaceutically active agent; and a taste-masking agent;

wherein said particle having a particle size of less than about 200 microns and said taste-masking agent being present in amounts of about 15-80% by weight of the particle.

26. (Withdrawn) A method of preparing a thin film drug delivery vehicle comprising:

(a) providing a pharmaceutically active agent / taste-masking agent complex;

(b) combining the complex with a water-soluble polymer and a solvent to form a mixture with uniform distribution of said complex therein;

(c) casting said mixture onto a planar carrier surface to form a thin film on said carrier surface; and

(d) controllably drying said thin film to form a distribution variance of said complex having less than about 10% variance throughout any given area of said thin film.

27. (Withdrawn) The method of claim 26, wherein said drying includes applying heat to the bottom of said carrier surface.

28. (Withdrawn) The method of claim 26, wherein said pharmaceutically active agent / taste-masking agent complex comprises a particulate active agent and a thin film coating of said taste-masking agent over said particulate active agent.

29. (Withdrawn) A method of preparing a thin film drug delivery vehicle having a substantially uniform distribution of components comprising:

(a) forming a masterbatch pre-mix of an edible water-soluble polymer component and water;

(b) feeding a predetermined amount of the premix to at least one mixer;

(c) adding to the at least one mixer a predetermined amount of a taste-masked active component comprising a particulate active component and a taste masking agent coating the particulate active component;

(d) mixing the premix and the taste-masked active component in the at least one mixer to form a uniform matrix;

(e) forming a wet film from the matrix;

(f) rapidly forming a visco-elastic film by applying hot air currents to the bottom side of the wet film with substantially no top air flow; and

(g) drying the visco-elastic film to form a self-supporting edible film.

30. (Withdrawn) The method of claim 29, wherein the wet film is fed onto a substrate having a top and a bottom side, and the wet film forms a visco-elastic film by applying hot air currents to the bottom side of the substrate while minimizing air flow on the top side of the film.

31. (Withdrawn) The method of claim 29, wherein the taste-masked active component is stable for a sufficient time prior to drying for the visco-elastic film to form a self-supporting edible film.

32. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 100° C.

33. (Withdrawn) The method of claim 29, wherein the temperature at which the film is dried does not exceed 80° C.

34. (Withdrawn) A process for making a self-supporting, edible film having a substantially uniform distribution of components comprising:

(a) forming a premix of an edible water-soluble polymer component containing polyethylene oxide and optionally one or more additional polymers;

(b) blending into the premix a taste-masked active component comprising a particulate active component coated with a taste masking agent, to form a uniform matrix;

(c) extruding a film from the matrix; and

(d) cooling the film to form a self-supporting edible film.

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Currently amended) The drug delivery composition of claim 1, wherein said active ~~bioeffecting agent~~ is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and

hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (Previously presented) The drug delivery composition of claim 1, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

38. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

39. (New) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative.

40. (New) The drug delivery composition of claim 18, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

41. (New) The drug delivery composition of claim 18, wherein said active is an opiate or opiate derivative.

42. (New) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the coated particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

43. (New) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

44. (New) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

45. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said active.

46. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

47. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

48. (New) The drug delivery composition of claim 47, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

49. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

50. (New) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film dosage unit.

51. (New) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film dosage unit.

52. (New) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

53. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

54. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

55. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

56. (New) The drug delivery composition of claim 1, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

57. (New) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

58. (New) The drug delivery composition of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory

agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

59. (New) The drug delivery composition of claim 1, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

60. (New) The drug delivery composition of claim 1, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

61. (New) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative.

62. (New) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

63. (New) The drug delivery composition of claim 62, wherein said thin film drug delivery composition is extruded.

64. (New) The drug delivery composition of claim 62, wherein the taste-masking agent is a thin film coating over the particulate active component.

65. (New) The drug delivery composition of claim 62, wherein the taste-masking agent is a water-soluble polymer.

66. (New) The drug delivery composition of claim 62, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

67. (New) The drug delivery composition of claim 62, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

68. (New) The drug delivery composition of claim 62, wherein said active is an opiate or opiate derivative.

69. (New) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

70. (New) The drug delivery composition of claim 69, wherein said thin film drug delivery composition is extruded.

71. (New) The drug delivery composition of claim 69, wherein the taste-masking agent is a thin film coating over the particulate active component.

72. (New) The drug delivery composition of claim 69, wherein the taste-masking agent is a water-soluble polymer.

73. (New) The drug delivery composition of claim 69, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

74. (New) The drug delivery composition of claim 69, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

75. (New) The drug delivery composition of claim 69, wherein said active is an opiate or opiate derivative.

76. (New) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof to provide taste-masking of the active;

wherein the particulate active has a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

77. (New) The drug delivery composition of claim 76, wherein the particulate active has a particle size of 150 microns or less.

78. (New) The drug delivery composition of claim 76, wherein the particulate active has a particle size of 100 microns or less.

79. (New) The drug delivery composition of claim 76, wherein said variation of drug content is less than 5% by weight per film dosage unit.

80. (New) The drug delivery composition of claim 76, wherein said variation of drug content is less than 2% by weight per film dosage unit.

81. (New) The drug delivery composition of claim 76, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

82. (New) The drug delivery composition of claim 76, wherein the particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

83. (New) The drug delivery composition of claim 76, wherein said taste-masking agent is present in the amount of about 0.1-30% by weight of the drug delivery composition.

84. (New) The drug delivery composition of claim 76, wherein said taste-masking agent is present in the amount of about 0.01-10% by weight of the drug delivery composition.

85. (New) The drug delivery composition of claim 1, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

86. (New) The drug delivery composition of claim 1, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

87. (New) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative.

88. (New) The drug delivery composition of claim 87, wherein said taste masking agent is peppermint oil.

89. (New) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative and said taste masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof

90. (New) The drug delivery composition of claim 87, wherein said taste masking agent is peppermint oil.

REMARKS

In view of the agreement reached in the interview and the claims amendments above, it is respectfully submitted that all objections and rejections have been overcome. Accordingly, it is believed that with entry of the amendments this Application is in condition for allowance.

As discussed in the interview, should the Examiner Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is urged to contact the undersigned by phone at (973) 331-1700.

Interview Summary

Examiner Mercier is thanked for the courtesies extended during the in-person interview conducted on May 1, 2013.

During the interview an agreement was reached that both the Chen reference and Bess reference were overcome. During the Interview 2 exhibits were discussed: 1) the Declaration under 35 U.S.C. § 1.132 of B. Arlie Bogue dated March 13, 2013 demonstrating the uniformity of the Applicants' drug delivery compositions both within single lots and across lots and 2) a sheet based on Figure 5 of the Chen reference demonstrating that Chen's compositions vary by greater than 10% from a desired amount of active. The Examiner agreed in the Interview that recitation of "the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active" in the claims overcomes the Bess and Chen references.

The Bogue declaration was submitted in Reexamination No. 95/002,170. Reexamination Nos. 90/012,097; 90/012,098; 95/001,753; and 95/002,171.

As agreed in the Examiner Interview, both of these exhibits are being submitted for entry into the record, as Exhibits 1 and 2, respectively.

Review of Claim Amendments

Claim 1 has been amended to replace "bioeffecting agent" with "active" as agree in the interview. Claims 1 has also been amended to recite "one or more substantially water soluble or water swellable polymers…." In addition, claim 1 has been amended for consistency to recite "substantially uniformly…" and "substantial uniformity …." Finally, claim 1 has been amended to recite casting and drying of the matrix…" merely for clarity. Support for these amendments can be found throughout the specification at, for example, ¶¶ 0017, 0025, 0036, 0044, 0089-0090, 0095, 0148-0149, 0181-0238, and 291; and in original claims 29 and 34.

Claims 4, 17, and 36 have also been amended to replace "bioeffecting agent" with "active" as agree in the interview. Support for these amendments can be found throughout the specification at, for example, ¶ 0090.

Claim 18 has been amended for consistency to recite "substantially uniformly…." Support for these amendments can be found throughout the specification at, for example, ¶¶ 0036, 0044, and 291; and in original claims 29 and 34.

Claims 38 and 40, depending from claims 1 and 18, respectively, recite that the "taste-masking agent is a flavor, sweetener, flavor enhancer, or combination thereof." Support for these

claims can be found throughout the specification at, for example, ¶¶ 0117, 0121, 0162, and 0165-0176.

Claims 39 and 41, depending from claims 1 and 18, respectively, recite that the "active is an opiate or opiate-derivative." Support for these claims can be found throughout the specification at, for example, ¶ 153.

Claims 89 depends from claim 1 and recites that the "taste-masking agent is a flavor, sweetener, flavor enhancer, or combination thereof" and the "active is an opiate or opiate-derivative." Claim 90 depends from claim 89 and further recites that the taste-masking agent is peppermint oil. Support for these claims can be found throughout the specification at, for example, ¶¶ 0117, 0121, 0153, 0162, and 0165-0176.

Claims 39 and 41, depending from claims 1 and 18, respectively, recite that Support for these claims can be found throughout the specification at, for example, ¶ 153.

In the Final Office Action, the Examiner indicated that claims 13, 23, and 24 would be allowable if rewritten in independent form. (Paper No. 20130225 at 2.) Accordingly, claims 42, 62, and 69 have been added and present claims 13, 23, and 24 rewritten in independent form. In view of addition of these claims, claims 13, 23, and 24 have been deleted as redundant.

Claims 43-61, dependent from claim 42, have been added to mirror the claims dependent from claim 1, while omitting any that are inconsistent with claim 42.

Claims 63-68, dependent from claim 62, have been added to mirror the claims dependent from claim 18, while omitting any that are inconsistent with claim 62.

Claims 70-75, dependent from claim 69, have been added to mirror the claims dependent from claim 1, while omitting any that are inconsistent with claim 69.

Claim 76 has been added and defines the taste-masking agent as a flavor, sweetener, flavor enhancer, or combination thereof. Claim 76 substantially mirrors claim 1, inclusive of the recitation of "the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active." Support for these amendments can be found throughout the specification at, for example, ¶¶ 0017, 0025, 0036, 0044, 0089-0090, 0095, 0148-0149, 0181-0238, and 291; and in original claims 1, 29, and 34. Claims 77-88 mirror the claims dependent from claim 1, while omitting any that are inconsistent with claim 76.

In view of the foregoing, Applicants submit that not new matter has been added by the claim amendments and additions. Entry of the amendment and allowance of all the claims are respectfully solicited.

35 U.S.C. § 103 Rejections

Claims 1-5, 8-12, 14-19, 22, and 35-36 have been rejected under 35 U.S.C. § 103 as obvious over Bess et al., U.S. Patent No. 7,067,116. Applicants respectfully traverse the rejection.

Claims 1–8, 10-12, 17, and 35-36 were rejected under 35 U.S.C. §103(a) as obvious over Chen et al., WO 00/42992 in view of Ghanta et al., U.S. Patent No. 5,653,993. Applicants respectfully traverse the rejection.

As was demonstrated to the Examiner in the Interview, neither Chen nor Bess teach or suggest the claimed uniformity of active. In fact, Chen's own Figure 5 shows that the films produced by Chen lack the claimed uniformity. (Exhibit 2). Bess is completely silent as to the uniformity of its films.

Accordingly, neither Bess, nor Chen (even combined with Ghanta), is capable of supporting a *prima facie* case for the obviousness of the claimed invention. Reconsideration and withdrawal of the rejections are respectfully solicited.

Conclusion

In view of the agreement reached during the interview and the foregoing, it is respectfully submitted that all of the rejections have been met and this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should any additional fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time pursuant to 37 C.F.R. § 1.136, and includes fees for consideration of any IDS.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is urged to contact the undersigned at the telephone number set forth below.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
Registration No. 43,519
Attorney for Applicant

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6900 Jericho Turnpike
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Electronic Acknowledgement Receipt

EFS ID:	15747427
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Stephen J. Brown/Jane Callahan
Filer Authorized By:	Stephen J. Brown
Attorney Docket Number:	1199-4B CIP
Receipt Date:	10-MAY-2013
Filing Date:	10-JUL-2007
Time Stamp:	15:59:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1199-4_B-CIP-RCE_-_Amendment.PDF	79896 134d41e401e120051a0050dc25ee36da69b89011	yes	25

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Amendment After Final	1	1
	Claims	2	19
	Applicant Arguments/Remarks Made in an Amendment	20	25
Warnings:			
Information:			
	Total Files Size (in bytes):	79896	

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Stephen J. Brown
Attorney Docket Number:	1199-4B CIP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Claims in Excess of 20	1202	49	80	3920
Independent claims in excess of 3	1201	6	420	2520
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**6440**

Electronic Acknowledgement Receipt

EFS ID:	15748253
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	1199-4B CIP
Receipt Date:	10-MAY-2013
Filing Date:	10-JUL-2007
Time Stamp:	16:33:46
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$6440
RAM confirmation Number	3493
Deposit Account	082461
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

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Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Fee Worksheet (SB06)	fee-info.pdf	32364 5978820154 21f5d8c324e92c1a4d411cfc0fecf7	no	2

Warnings:

Information:

Total Files Size (in bytes):	32364

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

PTO/SB/06 (09-11)
Approved for use through 1/31/2014. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875	Application or Docket Number 11/775,484	Filing Date 07/10/2007	☐ To be Mailed

ENTITY: ☐ LARGE ☒ SMALL ☐ MICRO

APPLICATION AS FILED – PART I

FOR	(Column 1) NUMBER FILED	(Column 2) NUMBER EXTRA	RATE ($)	FEE ($)
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A	
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	minus 20 =	*	X $ =	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	minus 3 =	*	X $ =	
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is $310 ($155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).			
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))				
* If the difference in column 1 is less than zero, enter "0" in column 2.			TOTAL	

APPLICATION AS AMENDED – PART II

AMENDMENT	05/10/2013	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	* 86	Minus	** 37	= 49	X $40 =	1960
	Independent (37 CFR 1.16(h))	* 10	Minus	***6	= 4	X $210 =	840
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	**2800**

AMENDMENT		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)
	Total (37 CFR 1.16(i))	*	Minus	**	=	X $ =	
	Independent (37 CFR 1.16(h))	*	Minus	***	=	X $ =	
	☐ Application Size Fee (37 CFR 1.16(s))						
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))						
						TOTAL ADD'L FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

LIE
/KIM DOWNING/

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

23869 7590 06/14/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER
MERCIER, MELISSA S

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/14/2013

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

TITLE OF INVENTION: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	09/16/2013

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23869 7590 06/14/2013
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

TITLE OF INVENTION: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	09/16/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
MERCIER, MELISSA S	1615	424-435000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,

(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ❑ Individual ❑ Corporation or other private group entity ❑ Government

4a. The following fee(s) are submitted:

❑ Issue Fee

❑ Publication Fee (No small entity discount permitted)

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**

❑ A check is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

❑ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
❑ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
❑ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature _____ Date _____

Typed or printed name _____ Registration No. _____

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
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www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 06/14/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
MERCIER, MELISSA S	

ART UNIT	PAPER NUMBER
1615	

DATE MAILED: 06/14/2013

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 503 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 503 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 11/775,484	Applicant(s) YANG ET AL.	
	Examiner MELISSA MERCIER	Art Unit 1615	AIA (First Inventor to File) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *Applicants after final remarks and amended claims filed on May 10, 2013*.
   ☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on_____.
2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on _____; the restriction requirement and election have been incorporated into this action.
3. ☒ The allowed claim(s) is/are *1-8,10-12,14-22 and 35-90*. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to PPHfeedback@uspto.gov .
4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

   Certified copies:

   a) ☐ All b) ☐ Some *c) ☐ None of the:
   1. ☐ Certified copies of the priority documents have been received.
   2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
   3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

   Interim copies:

   a) ☐ All b) ☐ Some c) ☐ None of the: Interim copies of the priority documents have been received.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

   Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892)
2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date _____
3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
5. ☒ Examiner's Amendment/Comment
6. ☐ Examiner's Statement of Reasons for Allowance
7. ☐ Other _____.

/ANAND U DESAI/	/Melissa S Mercier/
Primary Examiner, Art Unit 1656	Examiner, Art Unit 1615

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

The application has been amended as follows:

Claims 25-34: cancelled

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MELISSA MERCIER whose telephone number is (571)272-9039. The examiner can normally be reached on 8:00am-4:30pm Mon through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on (571) 272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Melissa S Mercier/
Examiner, Art Unit 1615

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
May 31, 2013

OK TO ENTER: /MM/ (06/12/2013)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	May 10, 2013

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: May 10, 2013

Signature: Jane Callahan */Jane Callahan/*

AMENDMENT AND RESPONSE AFTER FINAL OFFICE ACTION

Madam:

In response to the Final Office Action dated March 13, 2013, a response to which is due May 13, 2013, under the 2-month rule, the following amendments and remarks are provided:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 20 of this submission.

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	**Art Unit**
	MELISSA MERCIER	1615

CPC

Symbol					Type	Version
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CPC Combination Sets

Symbol					Type	Set	Ranking	Version
			/					
			/					

US ORIGINAL CLASSIFICATION	
CLASS	**SUBCLASS**
424	435

CROSS REFERENCE(S)

CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)				
424	484				

INTERNATIONAL CLASSIFICATION

CLAIMED					NON-CLAIMED				
A	6	1	F	13 / 00 (2006.01.01)					
A	6	1	K	9 / 00 (2006.01.01)					
A	6	1	K	9 / 70 (2006.01.01)					

/MELISSA MERCIER/ Examiner.Art Unit 1615 (Assistant Examiner)	5-31-13 (Date)	**Total Claims Allowed:** 76	
/ANAND DESAI/ Primary Examiner.Art Unit 1656 (Primary Examiner)	05/31/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	**Art Unit**
	MELISSA MERCIER	1615

/MELISSA MERCIER/ Examiner.Art Unit 1615	5-31-13	**Total Claims Allowed:**	
(Assistant Examiner)	(Date)	76	
/ANAND DESAI/ Primary Examiner.Art Unit 1656	05/31/2013	O.G. Print Claim(s)	O.G. Print Figure
(Primary Examiner)	(Date)	1	1

Issue Classification	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	**Art Unit**
	MELISSA MERCIER	1615

☒ **Claims renumbered in the same order as presented by applicant** ☐ **CPA** ☐ **T.D.** ☐ **R.1.47**

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
1	1	15	17		33	35	49	51	65	67	81				
2	2	16	18		34	36	50	52	66	68	82				
3	3	17	19	21	35	37	51	53	67	69	83				
4	4	18	20	22	36	38	52	54	68	70	84				
5	5	19	21	23	37	39	53	55	69	71	85				
6	6	20	22	24	38	40	54	56	70	72	86				
7	7		23	25	39	41	55	57	71	73	87				
8	8		24	26	40	42	56	58	72	74	88				
	9		25	27	41	43	57	59	73	75	89				
9	10		26	28	42	44	58	60	74	76	90				
10	11		27	29	43	45	59	61	75						
11	12		28	30	44	46	60	62	76						
	13		29	31	45	47	61	63	77						
12	14		30	32	46	48	62	64	78						
13	15		31	33	47	49	63	65	79						
14	16		32	34	48	50	64	66	80						

/MELISSA MERCIER/ Examiner.Art Unit 1615 (Assistant Examiner)	5-31-13 (Date)	**Total Claims Allowed:** 76	
/ANAND DESAI/ Primary Examiner.Art Unit 1656 (Primary Examiner)	05/31/2013 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure 1

Search Notes	Application/Control No.	Applicant(s)/Patent Under Reexamination
	11775484	YANG ET AL.
	Examiner	Art Unit
	MELISSA S MERCIER	1615

CPC- SEARCHED		
Symbol	Date	Examiner

CPC COMBINATION SETS - SEARCHED		
Symbol	Date	Examiner

US CLASSIFICATION SEARCHED			
Class	Subclass	Date	Examiner

SEARCH NOTES		
Search Notes	Date	Examiner
East-see attached	5-14-13	MMercier

INTERFERENCE SEARCH			
US Class/ CPC Symbol	US Subclass / CPC Group	Date	Examiner
424	film SAME cast SAME ("Water swellable" OR "water soluble") AND "taste masking" AND active	5-14-13	MMercier

UNITED STATES PATENT AND TRADEMARK OFFICE

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BIB DATA SHEET

CONFIRMATION NO. 5059

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
11/775,484	07/10/2007 RULE	424	1615	1199-4B CIP

APPLICANTS

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

**** CONTINUING DATA ****************************

This application is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and claims benefit of 60/386,937 06/07/2002
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and claims benefit of 60/371,940 04/11/2002
This application 11/775,484 07/10/2007
is a CIP of 10/856,176 05/28/2004 PAT 7666337
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891

**** FOREIGN APPLICATIONS ****************************

**** IF REQUIRED, FOREIGN FILING LICENSE GRANTED **** ** SMALL ENTITY **
09/12/2007

Foreign Priority claimed ☐ Yes ☐ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and Acknowledged _____ Examiner's Signature	☐ Met after Allowance _____ Initials	STATE OR COUNTRY	SHEETS DRAWINGS	TOTAL CLAIMS	INDEPENDENT CLAIMS
		NY	34	34	6

ADDRESS

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791
UNITED STATES

TITLE

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

	FEES: Authority has been given in Paper	☐ All Fees ☐ 1.16 Fees (Filing)

BIB (Rev. 05/07).

FILING FEE RECEIVED 7783	No._____ to charge/credit DEPOSIT ACCOUNT No._____ for following:	❑ 1.17 Fees (Processing Ext. of time) ❑ 1.18 Fees (Issue) ❑ Other _____ ❑ Credit

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
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or Fax (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

23869 7590 06/14/2013
Hoffmann & Baron LLP
6900 Jericho Turnpike
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I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO (571) 273-2885, on the date indicated below.

(Depositor's name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

TITLE OF INVENTION: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	SMALL	$890	$300	$0	$1190	09/16/2013

EXAMINER	ART UNIT	CLASS-SUBCLASS
MERCIER, MELISSA S	1615	424-435000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).
☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.
☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list
(1) the names of up to 3 registered patent attorneys or agents OR, alternatively,
(2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.
1 Hoffmann & Baron, LLP
2
3

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE: MonoSol RX, LLC
(B) RESIDENCE: (CITY and STATE OR COUNTRY): Warren , New Jersey

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☒ Corporation or other private group entity ☐ Government

4a. The following fee(s) are submitted:
☒ Issue Fee
☒ Publication Fee (No small entity discount permitted)
☐ Advance Order - # of Copies _____

4b. Payment of Fee(s): **(Please first reapply any previously paid issue fee shown above)**
☐ A check is enclosed.
☐ Payment by credit card. Form PTO-2038 is attached.
☒ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment, to Deposit Account Number 08-2461 (enclose an extra copy of this form).

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29	NOTE: Absent a valid certification of Micro Entity Status (see form PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.
☐ Applicant asserting small entity status. See 37 CFR 1.27	NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.
☒ Applicant changing to regular undiscounted fee status.	NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

Authorized Signature /Stephen J. Brown/ Date June 18, 2013

Typed or printed name Stephen J. Brown Registration No. 43,519

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

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Electronic Patent Application Fee Transmittal

Application Number:	11775484
Filing Date:	10-Jul-2007
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Daniel A. Scola/Ivory Edwards
Attorney Docket Number:	1199-4B CIP

Filed as Large Entity

Utility under 35 USC 111(a) Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Utility Appl Issue Fee	1501	1	1780	1780
Publ. Fee- Early, Voluntary, or Normal	1504	1	300	300

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Extension-of-Time:				
Miscellaneous:				
			Total in USD ($)	**2080**

Electronic Acknowledgement Receipt

EFS ID:	16073442
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Daniel A. Scola/Ivory Edwards
Filer Authorized By:	Daniel A. Scola
Attorney Docket Number:	1199-4B CIP
Receipt Date:	18-JUN-2013
Filing Date:	10-JUL-2007
Time Stamp:	15:55:31
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$2080
RAM confirmation Number	2923
Deposit Account	082461
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

Charge any Additional Fees required under 37 C.F.R. Section 1.16 (National application filing, search, and examination fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.17 (Patent application and reexamination processing fees)

Charge any Additional Fees required under 37 C.F.R. Section 1.19 (Document supply fees)	
Charge any Additional Fees required under 37 C.F.R. Section 1.20 (Post Issuance fees)	
Charge any Additional Fees required under 37 C.F.R. Section 1.21 (Miscellaneous fees and charges)	

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		1199_4B_CIP_RCE_312_Amendment.PDF	111179 7627189b6facd783f9f9e4c3bc546b75d06d9207	yes	21

Multipart Description/PDF files in .zip description

Document Description	Start	End
Amendment after Notice of Allowance (Rule 312)	1	1
Claims	2	16
Applicant Arguments/Remarks Made in an Amendment	17	21

Warnings:

Information:

2	Issue Fee Payment (PTO-85B)	1199_4B_CIP_RCE_Issue_Fee.PDF	120822 ebcda210f8f1b5a2f073b5b1823b2c5bc0f650ab	no	2

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	32187 9fcd082e48485995922caf6276cc216ff8f0a7ff	no	2

Warnings:

Information:

Total Files Size (in bytes):	264188

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New Applications Under 35 U.S.C. 111

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National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	June 18, 2013

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

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Dated: June 18, 2013

Signature: Ivory Edwards */Ivory Edwards/*

AMENDMENT AFTER ALLOWANCE PURSUANT TO 37 C.F.R. § 1.312

Madam:

Pursuant to 37 C.F.R. § 1.312, the following amendments and remarks are provided:

Amendments to the Claims begin on page 2 of this submission.

Remarks begin on page 17 of this submission.

Amendments to the Claims

This listing of claims shall replace all previous listings of claims:

1. (Previously presented) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

2. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

3. (Original) The drug delivery composition of claim 1, wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

4. (Previously presented) The drug delivery composition of claim 1, wherein said taste-masking agent is a thin film coating over portions of said active.

5. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a polymer.

6. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is a water-soluble polymer.

7. (Original) The drug delivery composition of claim 6, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

8. (Original) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

9. (Cancelled)

10. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 5% by weight per film dosage unit.

11. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 2% by weight per film dosage unit.

12. (Previously presented) The drug delivery composition of claim 1, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

13. (Cancelled).

14. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

15. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

16. (Original) The drug delivery composition of claim 1, wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

17. (Previously presented) The drug delivery composition of claim 1, wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

18. (Previously presented) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

19. (Original) The drug delivery composition of claim 18, wherein said thin film drug delivery composition is extruded.

20. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a thin film coating over the particulate active component.

21. (Previously presented) The drug delivery composition of claim 18, wherein the taste-masking agent is a water-soluble polymer.

22. (Original) The drug delivery composition of claim 18, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

23-34. (Cancelled).

35. (Previously presented) The drug delivery composition of claim 1, wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

36. (Previously presented) The drug delivery composition of claim 1, wherein said active is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

37. (Previously presented) The drug delivery composition of claim 1, wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

38. (Previously presented) The drug delivery composition of claim 1, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

39. (Previously presented) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative.

40. (Previously presented) The drug delivery composition of claim 18, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

41. (Previously presented) The drug delivery composition of claim 18, wherein said active is an opiate or opiate derivative.

42. (Previously presented) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent coated or intimately associated with said particulate to provide taste-masking of the active;

wherein the combined particulate and taste-masking agent have a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the coated particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

43. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the size of said combined particulate and taste-masking agent have a particle size of 150 microns or less.

44. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the size of said combined particulate and taste-masking agent have a particle size of 100 microns or less.

45. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said taste-masking agent is a thin film coating over portions of said active.

46. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the taste-masking agent is a polymer.

47. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the taste-masking agent is a water-soluble polymer.

48. (Previously presented) The drug delivery composition of claim 47, wherein said water-soluble polymer has an average molecular weight of equal to or greater than about 40,000.

49. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the taste-masking agent is selected from the group consisting of acrylic polymers, cellulosic polymers, vinyl polymers, crown ethers, hydrogenated oils and waxes, and combinations thereof.

50. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said variation of drug content is less than 5% by weight per film dosage unit.

51. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said variation of drug content is less than 2% by weight per film dosage unit.

52. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

53. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said taste-masking agent is present in the amount of about 15-80% by weight of the particle.

54. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said taste-masking agent is present in the amount of about 20-60% by weight of the particle.

55. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said taste-masking agent is present in the amount of about 25-35% by weight of the particle.

56. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs,

narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

57. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the taste-masking agent is selected from the group consisting of carboxymethyl cellulose; methyl cellulose; ethyl cellulose; hydroxyl methyl cellulose; hydroxyethyl cellulose; hydroxypropyl cellulose; hydroxypropylmethyl cellulose; hydroxymethylpropyl cellulose; gum arabic; xanthan gum; tragacanth; acacia; carageenan; guar gum; locust bean gum; pectin; alginates; gelatinized, modified or unmodified starch; polyvinyl alcohol; polyacrylic acid; polyvinyl pyrrolidone; poly(meth)acrylate; poly(meth)copolymers; dextrin; dextran; proteins; whey protein isolate; casein; levin; collagen; chitin; chitosin; polydextrose and combinations thereof.

58. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said active is selected from the group consisting of ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations,

urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

59. (Currently amended) The drug delivery composition of claim 42[[1]], wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

60. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

61. (Currently amended) The drug delivery composition of claim 42[[1]], wherein said active is an opiate or opiate derivative.

62. (Previously presented) A thin film drug delivery composition comprising:
(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;
wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent, and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises about 20% to about 100% by weight polyethylene oxide.

63. (Previously presented) The drug delivery composition of claim 62, wherein said thin film drug delivery composition is extruded.

64. (Previously presented) The drug delivery composition of claim 62, wherein the taste-masking agent is a thin film coating over the particulate active component.

65. (Previously presented) The drug delivery composition of claim 62, wherein the taste-masking agent is a water-soluble polymer.

66. (Previously presented) The drug delivery composition of claim 62, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

67. (Previously presented) The drug delivery composition of claim 62, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

68. (Previously presented) The drug delivery composition of claim 62, wherein said active is an opiate or opiate derivative.

69. (Previously presented) A thin film drug delivery composition comprising:

(a) a cast film comprising an edible water-soluble or water swellable film-forming matrix comprising at least one water-soluble or water swellable polymer comprising polyethylene oxide alone or in combination with a hydrophilic cellulosic polymer; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

and

(b) a coated particulate active component substantially uniformly stationed in the matrix;

wherein the coating on the particulate active component is a taste-masking agent,

and

wherein the active component is substantially uniformly distributed in the film composition;

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active; and

wherein the at least one water-soluble polymer comprises a hydrophilic cellulosic polymer in a ratio of up to about 4:1 with polyethylene oxide.

70. (Previously presented) The drug delivery composition of claim 69, wherein said thin film drug delivery composition is extruded.

71. (Previously presented) The drug delivery composition of claim 69, wherein the taste-masking agent is a thin film coating over the particulate active component.

72. (Previously presented) The drug delivery composition of claim 69, wherein the taste-masking agent is a water-soluble polymer.

73. (Previously presented) The drug delivery composition of claim 69, wherein the composition is free of added plasticizers, surfactants, or polyalcohols.

74. (Previously presented) The drug delivery composition of claim 69, wherein said taste-masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

75. (Previously presented) The drug delivery composition of claim 69, wherein said active is an opiate or opiate derivative.

76. (Previously presented) A drug delivery composition comprising:

(i) a cast film comprising a flowable water-soluble or water swellable film-forming matrix comprising one or more substantially water soluble or water swellable polymers; and a desired amount of at least one active;

wherein said matrix has a viscosity sufficient to aid in substantially maintaining non-self-aggregating uniformity of the active in the matrix;

(ii) a particulate active substantially uniformly stationed in the matrix; and

(iii) a taste-masking agent selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof to provide taste-masking of the active;

wherein the particulate active has a particle size of 200 microns or less and said flowable water-soluble or water swellable film-forming matrix is capable of being dried without loss of substantial uniformity in the stationing of said particulate active therein; and

wherein the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active.

77. (Previously presented) The drug delivery composition of claim 76, wherein the particulate active has a particle size of 150 microns or less.

78. (Previously presented) The drug delivery composition of claim 76, wherein the particulate active has a particle size of 100 microns or less.

79. (Previously presented) The drug delivery composition of claim 76, wherein said variation of drug content is less than 5% by weight per film dosage unit.

80. (Previously presented) The drug delivery composition of claim 76, wherein said variation of drug content is less than 2% by weight per film dosage unit.

81. (Previously presented) The drug delivery composition of claim 76, wherein said variation of drug content is less than 0.5% by weight per film dosage unit.

82. (Previously presented) The drug delivery composition of claim 76, wherein the particulate active has a shape selected from the group consisting of spherically shaped particles, ellipsoidally shaped particles, irregularly shaped particles, and combinations thereof.

83. (Previously presented) The drug delivery composition of claim 76, wherein said taste-masking agent is present in the amount of about 0.1-30% by weight of the drug delivery composition.

84. (Previously presented) The drug delivery composition of claim 76, wherein said taste-masking agent is present in the amount of about 0.01-10% by weight of the drug delivery composition.

85. (Currently amended) The drug delivery composition of claim 76[[1]], wherein said active is selected from the group consisting of antimicrobial agents, non-steroidal anti-inflammatory drugs, anti-tussives, decongestants, antihistamines, expectorants, anti-diarrheals, H_2 antagonists, proton pump inhibitors, general non-selective CNS depressants, general non-selective CNS stimulants, selective CNS functional modifiers, anti-parkinsonism drugs, narcotics, analgesics, erectile dysfunction therapies, anti-pyretics, psychopharmacological drugs and combinations thereof.

86. (Currently amended) The drug delivery composition of claim 76[[1]], wherein the film forming matrix has the viscosity in an amount sufficient to substantially prevent an active from settling out during mixing or coating.

87. (Currently amended) The drug delivery composition of claim 76[[1]], wherein said active is an opiate or opiate derivative.

88. (Previously presented) The drug delivery composition of claim 87, wherein said taste masking agent is peppermint oil.

89. (Previously presented) The drug delivery composition of claim 1, wherein said active is an opiate or opiate derivative and said taste masking agent is selected from the group consisting of flavors, sweeteners, flavor enhancers, and combinations thereof.

90. (Currently amended) The drug delivery composition of claim 89[[87]], wherein said taste masking agent is peppermint oil.

REMARKS

The amendments above correct only obvious typographical errors in dependencies. In particular, claims 43-47 and 49-61 have been amended to depend from claim 42, claims 85-87 have been amended to depend from claim 76, and claim 90 has been amended to depend from claim 89.

These errors were pointed out in voicemail messages left with the Examiner on or about May 14, 2013, and correction was requested.

The obvious nature of these errors is apparent when the Remarks in the Amendment and Response After Final filed May 10, 2013, are considered:

> **Claims 43-61, dependent from claim 42**, have been added to mirror the claims dependent from claim 1, while omitting any that are inconsistent with claim 42.

(Emphasis added.)

> Claim 76 has been added and defines the taste-masking agent as a flavor, sweetener, flavor enhancer, or combination thereof. Claim 76 substantially mirrors claim 1, inclusive of the recitation of "the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active." Support for these amendments can be found throughout the specification at, for example, ¶¶ 0017, 0025, 0036, 0044, 0089-0090, 0095, 0148-0149, 0181-0238, and 291; and in original claims 1, 29, and 34. **Claims 77-88 mirror the claims dependent from claim 1, while omitting any that are inconsistent with claim 76**.

(Emphasis added.)

> Claim 89 depends from claim 1 and recites that the "taste-masking agent is a flavor, sweetener, flavor enhancer, or combination thereof" and the "active is an opiate or opiate-derivative." **Claim 90 depends from claim 89** and further recites that the taste-masking agent is peppermint oil. Support for these claims can be found throughout the specification at, for example, ¶¶ 0117, 0121, 0153, 0162, and 0165-0176.

(Emphasis added.)

In view of the foregoing, Applicants submit that no new matter has been added by the claim amendments and entry pursuant to 37 C.F.R. § 1.312 is appropriate. Entry of the amendments is respectfully solicited.

Detailed Interview Summary

The Applicants note that the Notice of Allowance mailed June 14, 2013, was not accompanied by a summary of the in-person interview conducted on May 1, 2013, by the Examiner as was expected. Accordingly, to complete the record the Applicants offer the following detailed interview summary to supplement the brief interview summary supplied in the Amendment and Remarks After Final dated May 10, 2013.

Agreement was reached that both the Chen reference (WO 00/42992) and Bess reference (U.S. Patent No. 7,067,116) were overcome. During the interview, Mr. Mark Schobel, Mr. Daniel Scola, and the undersigned explained at length the disclosure of the present application, which teaches that achieving uniformity of content of the active in unit doses requires much more than simply producing a homogenous mixture of ingredients prior to casting and drying. For example, the Chen reference teaches a homogeneous mixture of ingredients (*i.e.*, "a coating solution") that is then cast and dried to form a film. (*See* p. 15, ll.19-30.) However, the films of Chen do not achieve the uniformity of active claimed. As shown in Figure 5 of Chen, which shows the release profiles of four actives from exemplary films, in many instances the amount of active released from Chen's films is greater than 110% of the expected amount.

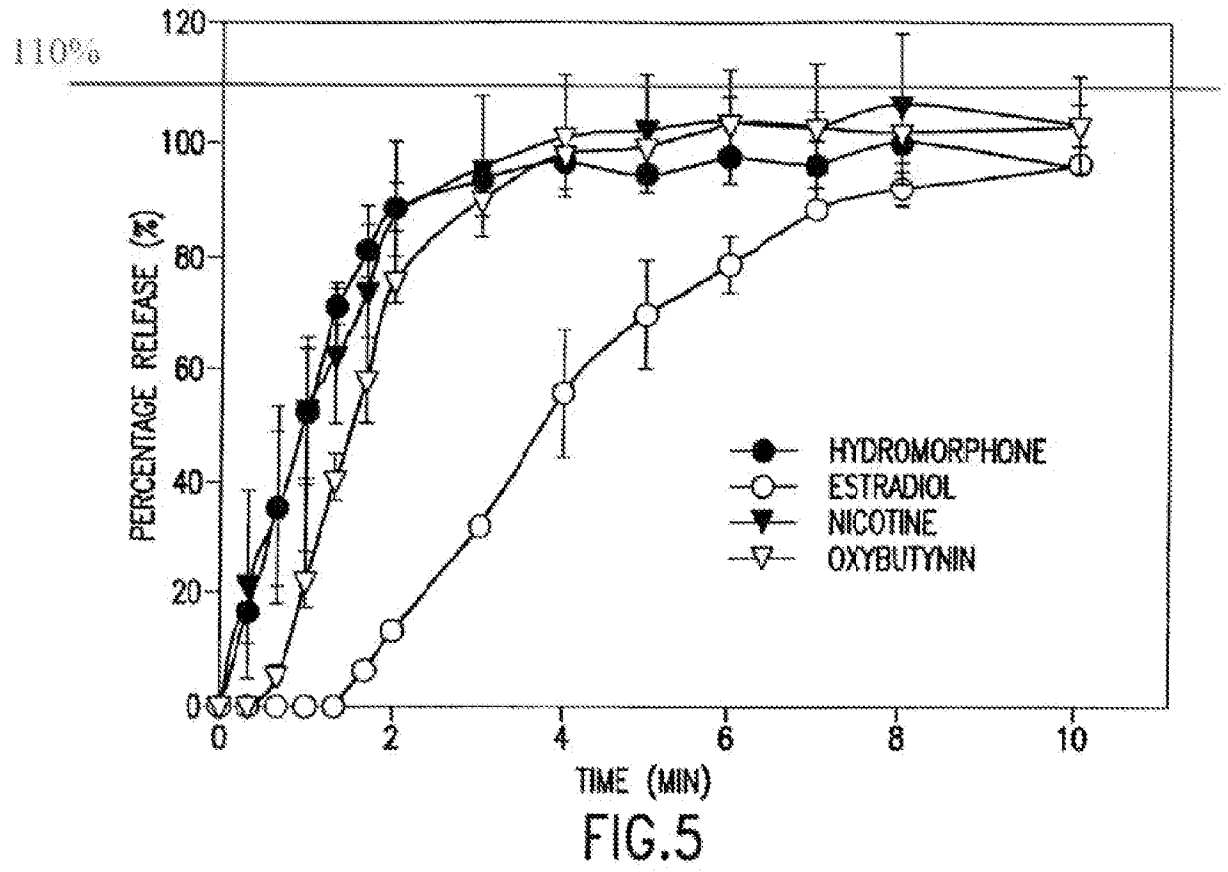

FIG.5

(Chen, Figure 5 (red line added by Applicants for clarity).)

In sum, the Applicants demonstrated that Chen teaches that even with a homogeneous mixture of starting materials, one of skill in the art would not have expected to produce "substantially equally sized unit doses which do not vary by more than 10% of said desired amount of said at least one active." (*See e.g.*, claim 1.) The Examiner agreed that Chen does not inherently teach any film composition or method of making a film composition having unit doses that do not vary by more than 10% of a desired amount of an active. Applicants also pointed out that Bess is devoid of any teaching of the active content uniformity of its compositions.

Based on this discussion, the Examiner agreed in the Interview that recitation of "the uniformity subsequent to casting and drying of the matrix is measured by substantially equally sized individual unit doses which do not vary by more than 10% of said desired amount of said at least one active" in combination with the other related elements in the claims overcomes the Bess and Chen references.

Conclusion

Entry of the amendments is respectfully solicited. Should the Examiner have any questions regarding this communication, the Examiner is urged to contact the undersigned at the telephone number set forth below.

Should any additional fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a constructive petition for an extension of time pursuant to 37 C.F.R. § 1.136, and includes fees for consideration of any IDS.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
Registration No. 43,519
Attorney for Applicant

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 07/24/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
07/24/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Response to Rule 312 Communication	Application No.	Applicant(s)
	11/775,484	YANG ET AL.
	Examiner	Art Unit
	MELISSA MERCIER	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

1. ☒ The amendment filed on *18 June 2013* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

/Melissa S Mercier/ Examiner, Art Unit 1615	/ANAND U DESAI/ Primary Examiner, Art Unit 1656

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 08/01/2013

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EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
08/01/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Applicant-Initiated Interview Summary	Application No.	Applicant(s)	
	11/775,484	YANG ET AL.	
	Examiner	Art Unit	
	MELISSA MERCIER	1615	

All participants (applicant, applicant's representative, PTO personnel):

(1) *MELISSA MERCIER*.

(3) *Daniel Scola*.

(2) *Stephen Brown*.

(4) *N/A*.

Date of Interview: *01 May 2013*.

Type: ☐ Telephonic ☐ Video Conference
☒ Personal [copy given to: ☐ applicant ☐ applicant's representative]

Exhibit shown or demonstration conducted: ☐ Yes ☐ No.
If Yes, brief description: _____.

Issues Discussed ☐101 ☐112 ☐102 ☒103 ☐Others
(For each of the checked box(es) above, please describe below the issue and detailed description of the discussion)

Claim(s) discussed: *all*.

Identification of prior art discussed: *Chen (WO00/42992) and Bess (US 7,067,116)*.

Substance of Interview
(For each issue discussed, provide a detailed description and indicate if agreement was reached. Some topics may include: identification or clarification of a reference or a portion thereof, claim interpretation, proposed amendments, arguments of any applied references etc...)

Applicants presented arguments regarding the teachings of Bess and Chen. After reviewing Figure 5 of Chen and the Declaration, it was determined that neither Bess nor Chen inherently result in a film having a uniformity in which the individual dosage unit does not vary by more than 10% of the desired amount of the active. All pending claims appear allowable over the prior art. .

Applicant recordation instructions: The formal written reply to the last Office action must include the substance of the interview. (See MPEP section 713.04). If a reply to the last Office action has already been filed, applicant is given a non-extendable period of the longer of one month or thirty days from this interview date, or the mailing date of this interview summary form, whichever is later, to file a statement of the substance of the interview

Examiner recordation instructions: Examiners must summarize the substance of any interview of record. A complete and proper recordation of the substance of an interview should include the items listed in MPEP 713.04 for complete and proper recordation including the identification of the general thrust of each argument or issue discussed, a general indication of any other pertinent matters discussed regarding patentability and the general results or outcome of the interview, to include an indication as to whether or not agreement was reached on the issues raised.

☐ Attachment

/ANAND U DESAI/ Primary Examiner, Art Unit 1656	/Melissa S Mercier/ Examiner, Art Unit 1615

Summary of Record of Interview Requirements

Manual of Patent Examining Procedure (MPEP), Section 713.04, Substance of Interview Must be Made of Record
A complete written statement as to the substance of any face-to-face, video conference, or telephone interview with regard to an application must be made of record in the application whether or not an agreement with the examiner was reached at the interview.

Title 37 Code of Federal Regulations (CFR) § 1.133 Interviews
Paragraph (b)

In every instance where reconsideration is requested in view of an interview with an examiner, a complete written statement of the reasons presented at the interview as warranting favorable action must be filed by the applicant. An interview does not remove the necessity for reply to Office action as specified in §§ 1.111, 1.135. (35 U.S.C. 132)

37 CFR §1.2 Business to be transacted in writing.
All business with the Patent or Trademark Office should be transacted in writing. The personal attendance of applicants or their attorneys or agents at the Patent and Trademark Office is unnecessary. The action of the Patent and Trademark Office will be based exclusively on the written record in the Office. No attention will be paid to any alleged oral promise, stipulation, or understanding in relation to which there is disagreement or doubt.

The action of the Patent and Trademark Office cannot be based exclusively on the written record in the Office if that record is itself incomplete through the failure to record the substance of interviews.

It is the responsibility of the applicant or the attorney or agent to make the substance of an interview of record in the application file, unless the examiner indicates he or she will do so. It is the examiner's responsibility to see that such a record is made and to correct material inaccuracies which bear directly on the question of patentability.

Examiners must complete an Interview Summary Form for each interview held where a matter of substance has been discussed during the interview by checking the appropriate boxes and filling in the blanks. Discussions regarding only procedural matters, directed solely to restriction requirements for which interview recordation is otherwise provided for in Section 812.01 of the Manual of Patent Examining Procedure, or pointing out typographical errors or unreadable script in Office actions or the like, are excluded from the interview recordation procedures below. Where the substance of an interview is completely recorded in an Examiners Amendment, no separate Interview Summary Record is required.

The Interview Summary Form shall be given an appropriate Paper No., placed in the right hand portion of the file, and listed on the "Contents" section of the file wrapper. In a personal interview, a duplicate of the Form is given to the applicant (or attorney or agent) at the conclusion of the interview. In the case of a telephone or video-conference interview, the copy is mailed to the applicant's correspondence address either with or prior to the next official communication. If additional correspondence from the examiner is not likely before an allowance or if other circumstances dictate, the Form should be mailed promptly after the interview rather than with the next official communication.

The Form provides for recordation of the following information:
- Application Number (Series Code and Serial Number)
- Name of applicant
- Name of examiner
- Date of interview
- Type of interview (telephonic, video-conference, or personal)
- Name of participant(s) (applicant, attorney or agent, examiner, other PTO personnel, etc.)
- An indication whether or not an exhibit was shown or a demonstration conducted
- An identification of the specific prior art discussed
- An indication whether an agreement was reached and if so, a description of the general nature of the agreement (may be by attachment of a copy of amendments or claims agreed as being allowable). Note: Agreement as to allowability is tentative and does not restrict further action by the examiner to the contrary.
- The signature of the examiner who conducted the interview (if Form is not an attachment to a signed Office action)

It is desirable that the examiner orally remind the applicant of his or her obligation to record the substance of the interview of each case. It should be noted, however, that the Interview Summary Form will not normally be considered a complete and proper recordation of the interview unless it includes, or is supplemented by the applicant or the examiner to include, all of the applicable items required below concerning the substance of the interview.

A complete and proper recordation of the substance of any interview should include at least the following applicable items:
1) A brief description of the nature of any exhibit shown or any demonstration conducted,
2) an identification of the claims discussed,
3) an identification of the specific prior art discussed,
4) an identification of the principal proposed amendments of a substantive nature discussed, unless these are already described on the Interview Summary Form completed by the Examiner,
5) a brief identification of the general thrust of the principal arguments presented to the examiner,
   (The identification of arguments need not be lengthy or elaborate. A verbatim or highly detailed description of the arguments is not required. The identification of the arguments is sufficient if the general nature or thrust of the principal arguments made to the examiner can be understood in the context of the application file. Of course, the applicant may desire to emphasize and fully describe those arguments which he or she feels were or might be persuasive to the examiner.)
6) a general indication of any other pertinent matters discussed, and
7) if appropriate, the general results or outcome of the interview unless already described in the Interview Summary Form completed by the examiner.

Examiners are expected to carefully review the applicant's record of the substance of an interview. If the record is not complete and accurate, the examiner will give the applicant an extendable one month time period to correct the record.

Examiner to Check for Accuracy

If the claims are allowable for other reasons of record, the examiner should send a letter setting forth the examiner's version of the statement attributed to him or her. If the record is complete and accurate, the examiner should place the indication, "Interview Record OK" on the paper recording the substance of the interview along with the date and the examiner's initials.

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 10/04/2013

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EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
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10/04/2013	PAPER

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United States Patent and Trademark Office
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www.uspto.gov

Application No. : 11775484
Applicant : Yang
Filing Date : 07/10/2007
Date Mailed : 10/04/2013

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given 1 month from the mail date of this Notice, or the time remaining from the Notice of Allowance and Fee(s) Due, whichever is longer, within which to respond.

The application is not in compliance with 37 CFR 1.78, as indicated in the attachment. The consequences of failure to respond within the above-identified time period are set forth in the attachment.

Even if the Office has recognized a benefit claim and has entered it into the Office's database and included it on applicant's filing receipt, the benefit claim is not a proper benefit claim unless the reference in compliance with 37 CFR 1.78 is included, depending upon the application's filing date and as indicated in the attachment, in an application data sheet or in the first sentence(s) of the specification and all other requirements are met.

This period for reply is NOT extendable under 37 CFR 1.136(a).

See attachment.

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Doug Gemmill/
Publication Branch
Office of Data Management
(571) 272-4200

Application No. 11775484

APPLICATION FILED PRIOR TO SEPTEMBER 16, 2012, NOT IN COMPLIANCE WITH 37 CFR 1.78

[X] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification does not indicate the relationship (continuation, division, continuation-in-part) to the prior U.S. nonprovisional application or international application designating the U.S. See document coded ADS dated 07/10/2007, listing application number(s) 10/074,272.

[ ] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title does not provide the U.S. nonprovisional application number (series code and serial number) or, with respect to an international PCT application designating the U.S., it provides the international application number or international filing date but not both. See document coded dated , in which the following is missing: .

[ ] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. nonprovisional application number, international PCT application number, or international PCT filing date. See document coded dated , in which the following error was made: .

[ ] The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title, thus removing the validating link under 35 U.S.C. 119(a)-(d) to a prior foreign application or under 35 U.S.C. 119(e) to a prior U.S. provisional application.

[ ] The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title.

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application is not present on an application data sheet or in first sentence(s) of the specification following the title.

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title does not provide the provisional application number (series code and serial number). See document coded dated , in which the following is missing: .

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. provisional application number. See document coded dated , in which the following error was made: .

[ ] Other: .

HOW TO RESPOND

A proper response to this notice would include any one of: (1) a supplemental Application Data Sheet (ADS) pursuant to 37 CFR 1.76(c) which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); (2) an amendment to the first sentence(s) of the specification which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); or (3) a petition filed pursuant to the provisions of 37 CFR 1.78(a)(3) or 37 CFR 1.78(a)(6) if the benefit information from the document identified above by code and date does not accurately reflect the benefits under 35 U.S.C. 119(e), 120, 121 or 365(c) as claimed by applicant (a grantable petition would include either a supplemental ADS or an amendment to the first sentence(s) of the specification as required by 37 CFR 1.78(a)(3)(i) or 37 CFR 1.78(a)(6)(i)). Such amendments to the specification or supplemental ADS submission may be filed after payment of the issue fee if limited to informalities noted herein. See Waiver of 37 CFR 1.312 for Document Required by Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004).

WARNING: If Applicant fails to timely submit a proper response, the benefit information will be deleted and the patent will be printed without the benefit information present.

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	October 6, 2013

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: October 6, 2013

Signature: Stephen J. Brown */Stephen J. Brown/*

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS AND AMENDMENT AFTER ALLOWANCE

Madam:

In response to the Notice to File Corrected Application Papers ("the Notice") dated October 4, 2013, a response to which is due by November 4, 2013, the following amendments and remarks are provided:

Amendments to the Specification begin on page 2 of this submission.

Remarks begin on page 3 of this submission.

Amendments to the Specification

Please replace paragraph 0001 with the following:

[0001] This application is a continuation-in-part of U.S. Application No. 10/768,809, filed January 30, 2004, which claims benefit to U.S. Provisional Application No. 60/443,741 filed January 30, 2003; U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32575, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed June 7, 2002, and is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32594, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/414,276, filed September 27, 2002, and U.S. Provisional Application No. 60/386,937, filed June 7, 2002, and is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; and U.S. Application No. 10/768,809 is also a continuation-in-part of PCT/US02/32542, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/386,937, filed June 7, 2002, and U.S. Provisional Application No. 60/371,940, filed April 11, 2002, and is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002, which claims priority to U.S. Provisional Application No. 60/328,868, filed October 12, 2001; this application is also a continuation-in-part of U.S. Application No. 10/856,176, filed May 28, 2004, which claims priority to U.S. Provisional Application No. 60/473,902, filed May 28, 2003; U.S. Application No. 10/856,176 is also a continuation-in-part of U.S. Application No. 10/768,809; the contents all of which are incorporated herein by reference.

REMARKS

The Cross-Reference to Related Applications section of the present application has been amended (as shown above) only to provide the benefit relationship of U.S. Patent Application 10/074,272 to the 3 International Applications recited in the Cross-Reference to Related Applications section of the present application. In particular, the Cross-Reference to Related Applications section has been amended to recite:

1) "PCT/US02/32575, filed October 11, 2002 … is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002…";

2) "PCT/US02/32594, filed October 11, 2002 … is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002…"; and

3) "PCT/US02/32542, filed October 11, 2002 … is a continuation-in-part of U.S. Application No. 10/074,272, filed February 14, 2002…."

No new matter has been added.

The Notice to File Corrected Application Papers dated October 4, 2013, indicates that:

> The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification does not indicate the relationship (continuation, division, continuation-in-part) to the prior U.S. nonprovisional application or international application designating the U.S. See document coded ADS dated 07/10/2007, listing application number(s) 10/074,272.

(Emphasis original.) As required, a copy of the Notice is attached hereto.

The Notice further indicates that:

> A proper response to this notice would include … an amendment to the first sentence(s) of the specification which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5) ….

As noted above, the Cross-Reference to Related Applications section of the present application has been amended to recite that each of International Applications PCT/US02/32542, PCT/US02/32575, and PCT/US02/32594 is a Continuation-In-Part of U.S. Patent Application 10/074,272. In view of the amendment, it is believed that the Cross-Reference to Related Applications section of the present application fully complies with 37 C.F.R. 1.78(a) (pre-AIA), as required.

In view of the foregoing, Applicants respectfully submit that all formalities have been met and that the present application in condition for issue.

Conclusion

Entry of the amendment and issue of the application as a patent is respectfully solicited. Should the Examiner have any questions regarding this communication, the Examiner is urged to contact the undersigned at the telephone number set forth below.

No fees are believed to be due with this communication. Should any additional fees be due, the Commissioner is hereby authorized to charge payment of any required fees associated with this communication to Deposit Account No. 08-2461. This includes authorization to charge fees for extensions of time, if any, under 37 C.F.R § 1.17 and also should be treated as a

constructive petition for an extension of time pursuant to 37 C.F.R. § 1.136, and includes fees for consideration of any IDS.

Respectfully submitted,

/Stephen J. Brown/
Stephen J. Brown
Registration No. 43,519
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, NY 11791
(973) 331-1700

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 10/04/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	

MAIL DATE	DELIVERY MODE
10/04/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Application No. : 11775484
Applicant : Yang
Filing Date : 07/10/2007
Date Mailed : 10/04/2013

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Notice of Allowance Mailed

This application has been accorded an Allowance Date and is being prepared for issuance. The application, however, is incomplete for the reasons below.

Applicant is given 1 month from the mail date of this Notice, or the time remaining from the Notice of Allowance and Fee(s) Due, whichever is longer, within which to respond.

The application is not in compliance with 37 CFR 1.78, as indicated in the attachment. The consequences of failure to respond within the above-identified time period are set forth in the attachment.

Even if the Office has recognized a benefit claim and has entered it into the Office's database and included it on applicant's filing receipt, the benefit claim is not a proper benefit claim unless the reference in compliance with 37 CFR 1.78 is included, depending upon the application's filing date and as indicated in the attachment, in an application data sheet or in the first sentence(s) of the specification and all other requirements are met.

This period for reply is NOT extendable under 37 CFR 1.136(a).

See attachment.

A copy of this notice MUST be returned with the reply. Please address response to "Mail Stop Issue Fee, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450".

/Doug Gemmill/
Publication Branch
Office of Data Management
(571) 272-4200

APPLICATION FILED PRIOR TO SEPTEMBER 16, 2012, NOT IN COMPLIANCE WITH 37 CFR 1.78

[X] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification does not indicate the relationship (continuation, division, continuation-in-part) to the prior U.S. nonprovisional application or international application designating the U.S. See document coded ADS dated 07/10/2007, listing application number(s) 10/074,272.

[ ] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title does not provide the U.S. nonprovisional application number (series code and serial number) or, with respect to an international PCT application designating the U.S., it provides the international application number or international filing date but not both. See document coded dated , in which the following is missing: .

[ ] The 37 CFR 1.78(a)(2) reference on the application data sheet or in the first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. nonprovisional application number, international PCT application number, or international PCT filing date. See document coded dated , in which the following error was made: .

[ ] The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title, thus removing the validating link under 35 U.S.C. 119(a)-(d) to a prior foreign application or under 35 U.S.C. 119(e) to a prior U.S. provisional application.

[ ] The 37 CFR 1.78(a)(2) reference to the prior U.S. nonprovisional application or international application designating the U.S. is not present on an application data sheet or in the first sentence(s) of the specification following the title.

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application is not present on an application data sheet or in first sentence(s) of the specification following the title.

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title does not provide the provisional application number (series code and serial number). See document coded dated , in which the following is missing: .

[ ] The 37 CFR 1.78(a)(5) reference to the prior U.S. provisional application on an application data sheet or in first sentence(s) of the specification following the title shows an incorrect, incomplete, or illegible U.S. provisional application number. See document coded dated , in which the following error was made: .

[ ] Other: .

HOW TO RESPOND

A proper response to this notice would include any one of: (1) a supplemental Application Data Sheet (ADS) pursuant to 37 CFR 1.76(c) which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); (2) an amendment to the first sentence(s) of the specification which provides benefit information that complies with 37 CFR 1.78(a)(2) or 37 CFR 1.78(a)(5); or (3) a petition filed pursuant to the provisions of 37 CFR 1.78(a)(3) or 37 CFR 1.78(a)(6) if the benefit information from the document identified above by code and date does not accurately reflect the benefits under 35 U.S.C. 119(e), 120, 121 or 365(c) as claimed by applicant (a grantable petition would include either a supplemental ADS or an amendment to the first sentence(s) of the specification as required by 37 CFR 1.78(a)(3)(i) or 37 CFR 1.78(a)(6)(i)). Such amendments to the specification or supplemental ADS submission may be filed after payment of the issue fee if limited to informalities noted herein. See Waiver of 37 CFR 1.312 for Document Required by Office of Patent Publication, 1280 Off. Gaz. Patent Office 918 (March 23, 2004).

WARNING: If Applicant fails to timely submit a proper response, the benefit information will be deleted and the patent will be printed without the benefit information present.

Electronic Acknowledgement Receipt

EFS ID:	17049667
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	1199-4B CIP
Receipt Date:	06-OCT-2013
Filing Date:	10-JUL-2007
Time Stamp:	15:36:33
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Post Allowance Communication - Incoming	1199-4B_CIP_RCE_Response_to_Notice_to_File_Corrected_Application_Papers.PDF	157332 d86e4b026080e595f62bdecbf15dc4b89491900d	no	8

Warnings:	
Information:	

Total Files Size (in bytes):	157332

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

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

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

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

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/775,484	07/10/2007	1615	8083	1199-4B CIP	34	6

CONFIRMATION NO. 5059

CORRECTED FILING RECEIPT

23869
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

Date Mailed: 10/30/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOLRX LLC, Portage, IN

Power of Attorney: The patent practitioners associated with Customer Number 23869

Domestic Priority data as claimed by applicant

This application is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001

and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/328,868 10/12/2001
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
This application 11/775,484
is a CIP of 10/856,176 05/28/2004 PAT 7666337
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/12/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/775,484**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application

serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

LICENSE FOR FOREIGN FILING UNDER

Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

SelectUSA

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The U.S. offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to promote and facilitate business investment. SelectUSA provides information assistance to the international investor community; serves as an ombudsman for existing and potential investors; advocates on behalf of U.S. cities, states, and regions competing for global investment; and counsels U.S. economic development organizations on investment attraction best practices. To learn more about why the United States is the best country in the world to develop technology, manufacture products, deliver services, and grow your business, visit http://www.SelectUSA.gov or call +1-202-482-6800.

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	07/10/2007	Robert K. Yang	1199-4B CIP	5059

23869 7590 10/30/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

EXAMINER	
MERCIER, MELISSA S	
ART UNIT	PAPER NUMBER
1615	
MAIL DATE	DELIVERY MODE
10/30/2013	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Response to Rule 312 Communication	Application No.	Applicant(s)
	11/775,484	YANG
	Examiner	Art Unit
	MERCIER	1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

1. ☒ The amendment filed on *06 October 2013* under 37 CFR 1.312 has been considered, and has been:

   a) ☒ entered.

   b) ☐ entered as directed to matters of form not affecting the scope of the invention.

   c) ☐ disapproved because the amendment was filed after the payment of the issue fee.
   Any amendment filed after the date the issue fee is paid must be accompanied by a petition under 37 CFR 1.313(c)(1) and the required fee to withdraw the application from issue.

   d) ☐ disapproved. See explanation below.

   e) ☐ entered in part. See explanation below.

N.Y. Horne

PUBLISHING DIVISION

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Yang et al.	Examiner:	Melissa S. Mercier
Application No.:	11/775,484	Group Art Unit:	1615
Filed:	July 10, 2007	Docket:	1199-4B CIP/RCE
Confirmation No.	5059	Dated:	November 1, 2013

For: UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Certificate of EFS-Web Transmission
I hereby certify that this correspondence is being transmitted to the U.S. Patent and Trademark Office via the Office's electronic filing system.

Dated: November 1, 2013

Signature: Stephen J. Brown */Stephen J. Brown/*

REQUEST FOR CORRECTION OF APPLICATION FILING RECEIPT

Madam:

In reviewing the Corrected Filing Receipt mailed October 30, 2013, for the above-identified application, we uncovered errors in the section entitled "Domestic Priority data as claimed by applicant." In particular, the domestic priority listed on the Corrected Filing Receipt does not match that recited in Cross-Reference to Related Applications as amended in the Amendment After Allowance filed October 6, 2013. (*See* Amendments to the Specification, p. 2.)

The Patent Office appears to be responsible for these errors. Accordingly, we ask that corrections be made to the Filing Receipt as indicated below.

The requested corrections are shown below – deletions are shown as a strikethrough and additions are underlined (for clarity the corrected lines are in boldface).

This application is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001
and said 10/768,809 01/30/2004
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which claims benefit of 60/414,276 09/27/2002
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which claims benefit of 60/328,868 10/12/2001
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
~~**which claims benefit of 60/328,868 10/12/2001**~~
which claims benefit of 60/386,937 06/07/2002
and claims benefit of 60/371,940 04/11/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001
This application 11/775,484
is a CIP of 10/856,176 05/28/2004 PAT 7666337
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891

Attached is a copy of the original filing receipt with the above referenced corrections noted therein.

To aid the Office, a clean version of the Domestic Priority data as claimed by the applicant is presented below:

This application is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
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which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891

In view of the above, correction of the Filing Receipt is respectfully requested. If any fees are required, please charge to Deposit Account No. 08-2461.

If there are any questions with respect to this matter, please direct them to the undersigned.

Respectfully submitted,
/Stephen J. Brown/
Stephen J. Brown
Registration No.: 43,519
Attorney for Applicants

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/775,484	07/10/2007	1615	8083	1199-4B CIP	34	6

CONFIRMATION NO. 5059

CORRECTED FILING RECEIPT

23869
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

OC000000064711675

Date Mailed: 10/30/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOLRX LLC, Portage, IN

Power of Attorney: The patent practitioners associated with Customer Number 23869

Domestic Priority data as claimed by applicant

This application is a CIP of 10/768,809 01/30/2004 PAT 7357891
which claims benefit of 60/443,741 01/30/2003
and is a CIP of PCT/US02/32575 10/11/2002
which claims benefit of 60/386,937 06/07/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001
and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002 ← and claims benefit of 60/386,937 06/07/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292
which claims benefit of 60/328,868 10/12/2001

and said 10/768,809 01/30/2004
is a CIP of PCT/US02/32542 10/11/2002
~~which claims benefit of 60/328,868 10/12/2001~~ which claims benefit of 60/386,937 06/07/2002 and claims benefit of 60/371,940 04/11/2002
and is a CIP of 10/074,272 02/14/2002 PAT 7425292 which claims benefit of 60/328,868 10/12/2001
This application 11/775,484
is a CIP of 10/856,176 05/28/2004 PAT 7666337
which claims benefit of 60/473,902 05/28/2003
and is a CIP of 10/768,809 01/30/2004 PAT 7357891

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/12/2007

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/775,484**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

Almost every country has its own patent law, and a person desiring a patent in a particular country must make an application for patent in that country in accordance with its particular laws. Since the laws of many countries differ in various respects from the patent law of the United States, applicants are advised to seek guidance from specific foreign countries to ensure that patent rights are not lost prematurely.

Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application

serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

Applicants may wish to consult the USPTO booklet, "General Information Concerning Patents" (specifically, the section entitled "Treaties and Foreign Patents") for more information on timeframes and deadlines for filing foreign patent applications. The guide is available either by contacting the USPTO Contact Center at 800-786-9199, or it can be viewed on the USPTO website at http://www.uspto.gov/web/offices/pac/doc/general/index.html.

For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

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Electronic Acknowledgement Receipt

EFS ID:	17296286
Application Number:	11775484
International Application Number:	
Confirmation Number:	5059
Title of Invention:	UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Stephen J. Brown
Filer Authorized By:	
Attorney Docket Number:	1199-4B CIP
Receipt Date:	01-NOV-2013
Filing Date:	10-JUL-2007
Time Stamp:	17:22:23
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Corrected Filing Receipt	1199-4B_CIP_RCE_Request_for_Correction_of_Application_Filing_Receipt.PDF	12656 6befc2b088cd4b9e1271b25538ce05102462b861	no	4

Warnings:	
Information:	

2	Request for Corrected Filing Receipt	1199-4B_CIP_RCE_MARKED-UP_FILING_RECEIPT.PDF	500728 b8ad740c5c86218631cb2dc48c4554fcaa8e0649	no	4

Warnings:	
Information:	
Total Files Size (in bytes):	513384

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

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

National Stage of an International Application under 35 U.S.C. 371

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

New International Application Filed with the USPTO as a Receiving Office

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

UNITED STATES PATENT AND TRADEMARK OFFICE

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United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
11/775,484	07/10/2007	1615	8083	1199-4B CIP	34	6

CONFIRMATION NO. 5059

CORRECTED FILING RECEIPT

23869
Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

OC000000064797519

Date Mailed: 11/04/2013

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Applicant(s)

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Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOLRX LLC, Portage, IN

Power of Attorney: The patent practitioners associated with Customer Number 23869

Domestic Priority data as claimed by applicant

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Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see http://www.uspto.gov for more information.) - None.
Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

If Required, Foreign Filing License Granted: 09/12/2007
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 11/775,484**
Projected Publication Date: Not Applicable
Non-Publication Request: No
Early Publication Request: No
Title

UNIFORM FILMS FOR RAPID DISSOLVE DOSAGE FORM INCORPORATING TASTE-MASKING COMPOSITIONS

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications:

PROTECTING YOUR INVENTION OUTSIDE THE UNITED STATES

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For information on preventing theft of your intellectual property (patents, trademarks and copyrights), you may wish to consult the U.S. Government website, http://www.stopfakes.gov. Part of a Department of Commerce initiative, this website includes self-help "toolkits" giving innovators guidance on how to protect intellectual property in specific countries such as China, Korea and Mexico. For questions regarding patent enforcement issues, applicants may call the U.S. Government hotline at 1-866-999-HALT (1-866-999-4258).

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Bureau of Industry and Security, Department of Commerce (15 CFR parts 730-774); the Office of Foreign AssetsControl, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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Receipt date: 12/15/2010	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT (**Not for submission under 37 CFR 1.99)**	Filing Date	2007-07-10	
	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Mercier, Melissa S.	
	Attorney Docket Number	1199-4 B CIP	

/MM/	9	6660292	B2	2003-12-09	Zerbe et al.	
/MM/	10	6,800,329 ~~6800239~~	B2	2004-10-05	Horstmann et al.	
/MM/ Change(s) applied to document, /P.A.P./ 11/7/2013	11	6824829	B2	2004-11-30	Berry et al.	
/MM/	12	7005142	B2	2006-02-28	Leon et al.	
/MM/	13	7579019	B2	2009-08-25	Tapolsky et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
/MM/	1	20050048102	A1	2005-03-03	Tapolsky et al.	
/MM/	2	20070148097	A1	2007-06-28	Finn et al.	

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Examiner Initial*	Cite No	Foreign Document Number[3]	Country Code[2] i	Kind Code[4]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear	T[5]

/Melissa Mercier/ (01/21/2011)

Receipt date: 01/29/2008

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	11775484 11775484 - GAU: 1615
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	1199-4B CIP

	9	5455043		1995-10-03	Fischel-Ghodsian	
	10	5462749		1995-10-31	Rencher	
	11	5472704		1995-12-05	Santus, et al. ~~Giancarlo et al.~~	
	12	5518902		1996-05-12	Ozaki et al.	
	13	5567431		1996-10-22	Vert et al.	
	14	5620757		1997-04-15	Ninomiya et al.	
	15	5629003		1997-05-13	Horstmann et al.	
	16	5700478		1997-12-23	Biegajski et al.	
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	18	5766620		1998-06-16	Herber et al.	
	19	5948430		1999-09-07	Zerbe et al.	

Change(s) applied to document, /P.A.P./ 11/7/2013

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

Receipt date: 01/29/2008	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2007-07-10	
(Not for submission under 37 CFR 1.99)	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

	42	4438258		1984-03-20	Graham	
	43	4460562		1984-07-17	Keith et al.	
	44	4466973		1984-08-21	Rennie	
	45	4503070		1985-03-05	Eby	
	46	4515162		1985-05-07	Yamamoto , et al. ~~Katsuhiro~~	
Change(s) applied to document, /P.A.P./ 11/7/2013	47	4517173		1985-05-14	Kizawa et al.	
	48	4529601		1985-07-16	Broberg et al.	
	49	4529748		1985-07-16	Wienecke	
	50	4562020		1985-12-31	Hijiya et al.	

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Examiner Initial*	Cite No	Publication Number	Kind Code[1]	Publication Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

Receipt date: 01/29/2008	Application Number	11775484	11775484 - GAU: 1615
INFORMATION DISCLOSURE STATEMENT BY APPLICANT	Filing Date	2007-07-10	
(Not for submission under 37 CFR 1.99)	First Named Inventor	Robert K. Yang	
	Art Unit	1615	
	Examiner Name	Unassigned	
	Attorney Docket Number	1199-4B CIP	

	31	4925670		1990-05-15	Schmidt	
	32	4927634		1990-05-22	Sorrentino et al.	
	33	4927636		1990-05-22	Hijiya et al.	
	34	4937078		1990-06-26	Mezei et al.	
	35	4940587		1990-07-10	Jenkens et al.	
	36	4948580		1990-08-14	Browning	
	37	4958580		1990-09-25	Asaba et al.	
	38	4978531		1990-12-18	Yamazaki, et al. ~~Koike et al.~~	
	39	4981693		1991-01-01	Higashi et al.	
	40	4981875		1991-01-01	Leusner et al.	
	41	5023082		1991-06-11	Friedman et al.	

Change(s) applied to document, /P.A.P./ 11/7/2013

/Melissa Mercier/ (09/03/2010)

INFORMATION DISCLOSURE STATEMENT BY APPLICANT
(Not for submission under 37 CFR 1.99)

Application Number	11775484
Filing Date	2007-07-10
First Named Inventor	Robert K. Yang
Art Unit	1615
Examiner Name	Unassigned
Attorney Docket Number	1199-4B CIP

U.S.PATENTS Remove

Examiner Initial*	Cite No	Patent Number	Kind Code[1]	Issue Date	Name of Patentee or Applicant of cited Document	Pages,Columns,Lines where Relevant Passages or Relevant Figures Appear
	1	4569837		1986-02-11	Suzuki et al.	
	2	4593053		1986-06-03	Jevne	
	3	4608249		1986-08-26	Otsuka et al.	
	4	4615697		1986-10-07	Robinson	
	5	4623394		1986-11-18	Nakamura et al.	
	6	4652060		1987-03-24	Miyake	
	7	4659714		1987-04-21	Watt-Smith	
	8	4675009		June 23, 1987 ~~1987-07-23~~	Hymes et al.	

Change(s) applied to document,
/P.A.P./
11/7/2013

/Melissa Mercier/ (09/03/2010)

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /MM/

UNITED STATES PATENT AND TRADEMARK OFFICE

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P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/775,484	12/10/2013	8603514	1199-4B CIP	5059

23869 7590 11/20/2013

Hoffmann & Baron LLP
6900 Jericho Turnpike
Syosset, NY 11791

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment is 779 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site http://pair.uspto.gov for additional applicants):

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Garry L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-cv-1461-RGA	8/20/2013	of Delaware

PLAINTIFF	DEFENDANT
RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC,	PAR PHARMACEUTICAL, INC., INTELGENX TECHNOLOGIES CORP., and LTS LOHMANN THERAPY SYSTEMS CORP.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	U.S. 8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	U.S. 8,017,150	9/13/2011	MonoSol Rx, LLC
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
2/18/2014		
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 U.S. 8,603,514	12/10/2013	MonoSol RX, LLC
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13-cv-1674-RGA	10/8/2013	of Delaware

PLAINTIFF	DEFENDANT
RECKITT BENCKISER PHARMACEUTICALS, INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC,	WATSON LABORATORIES, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	U.S. 8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	U.S. 8,017,150	9/13/2011	MonoSol Rx, LLC
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY
2/18/2014	☑ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	U.S. 8,603,514	12/10/2013	MonoSol RX, LLC
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

TO:	Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court DELAWARE on the following

☐ Trademarks or ☐ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	4/4/2014	DELAWARE

PLAINTIFF	DEFENDANT
RECKITT BENCKISER PHARMACEUTICALS INC., RB PHARMACEUTICALS LIMITED, and MONOSOL RX LLC	PAR PHARMACEUTICAL, INC. and INTELGENX TECHNOLOGIES CORP.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	8,017,150	9/13/2011	MonoSol RX, LLC
3	8,603,514	12/10/2013	MonoSol RX, LLC
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13cv2003-RGA	12/6/2013	DISTRICT OF DELAWARE
PLAINTIFF		DEFENDANT
Reckitt Benckiser Pharmaceuticals Inc., et al.		Alvogen Pine Brook Inc., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	8,017,150	9/13/2011	MonoSol RX LLC
3	8,603,514	12/10/2013	MonoSol RX LLC
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
See attached Order

CLERK	(BY) DEPUTY CLERK	DATE
JOHN A. CERINO, CLERK OF COURT		5/9/2014

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**

AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
13cv1461-RGA	8/20/2013	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
Reckitt Benckiser Pharmaceuticals Inc., et al.	Par Pharmaceutical Inc., et al.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	8,017,150	9/13/2011	Mo noSol RX LLC
3	8,603,514	12/10/2013	MonoSol RX LLC
4			
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
See attached Order

CLERK	(BY) DEPUTY CLERK	DATE
JOHN A. CERINO, CLERK OF COURT		5/28/2014

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court DELAWARE on the following

☐ Trademarks or ☐ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	12/2/2014	DELAWARE

PLAINTIFF	DEFENDANT
RECKITT BENCKISER PHARMACEUTICALS INC., RB PHARMACEUTICALS LIMITED, and MONOSOL RX LLC	TEVA PHARMACEUTICALS USA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	8,017,150	9/13/2011	MonoSol RX, LLC
3	8,603,514	12/10/2013	MonoSol RX, LLC
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In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court DELAWARE on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	6/10/2015	DELAWARE

PLAINTIFF	DEFENDANT
RECKITT BENCKISER PHARMACEUTICALS INC., RB PHARMACEUTICALS LIMITED and MONOSOL RX, LLC	ALVOGEN PINE BROOK, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	RB Pharmaceuticals Limited
2	8,017,150	9/13/2011	MonoSol Rx, LLC
3	8,603,514	12/10/2013	MonoSol Rx, LLC
4	8,900,497	12/2/2014	MonoSol Rx, LLC
5	8,906,277	12/9/2014	MonoSol Rx, LLC

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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AO 120 (Rev. 08/10)

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Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court District of Delaware on the following

☐ Trademarks or ☑ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	7/17/2014	District of Delaware

PLAINTIFF	DEFENDANT
Antennatech, LLC	Volkswagen Group of America, Inc. dba Audi of America

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	US 8,180,279 B2	6/16/2012	Antennatech, LLC
2			
3			
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
Closed per Stay - See Attached

CLERK	(BY) DEPUTY CLERK	DATE
John A Cerino, Clerk United States District Court 844 N. King Street, Unit 18 Wilmington, DE 19801		6/11/15

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ANTENNATECH, LLC Plaintiff, v. VOLKSWAGEN GROUP OF AMERICA, INC., dba AUDI OF AMERICA, Defendant.	)	C.A. No. 14-cv-948 (GMS)

ORDER

At Wilmington this 9th day of June, 2015, this matter having been stayed pending the conclusion of the United States Patent and Trademark Office's reexamination of the patent-in-suit, including any appeals (D.I. 41);

IT IS ORDERED that the above-captioned case is **stayed** and **administratively closed** until further order of the court. The parties shall promptly notify the court when the IPR proceedings have been resolved so that the case may be reopened and other appropriate action may be taken.

UNITED STATES DISTRICT JUDGE

AO 120 (Rev. 08/10)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court DELAWARE on the following

☐ Trademarks or ☐ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
	3/21/2016	DELAWARE

PLAINTIFF	DEFENDANT
INDIVIOR INC., INDIVIOR UK LIMITED, and MONOSOL RX LLC	TEVA PHARMACEUTICALS USA, INC.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	Indivior UK Limited
2	8,017,150	9/13/2011	MonoSol RX, LLC
3	8,603,514	12/10/2013	MonoSol RX, LLC
4	8,900,497	12/2/2014	MonoSol RX, LLC
5	8,906,277	12/9/2014	MonoSol RX, LLC

In the above---entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
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In the above---entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK	(BY) DEPUTY CLERK	DATE

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Copy 2---Upon filing document adding patent(s), mail this copy to Director Copy 4---Case file copy

Trials@uspto.gov
571-272-7822

Paper 21 (IPR2016-00281)
Paper 19 (IPR2016-00282)
Entered: May 23, 2016

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

TEVA PHARMACEUTICALS USA, INC.,
Petitioner,

v.

MONOSOL RX, LLC,

Patent Owner.

Case IPR2016-00281 (Patent 8,603,514 B2)
Case IPR2016-00282 (Patent 8,017,150 B2)[1]

Before ERICA A. FRANKLIN, TINA E. HULSE, and
CHRISTOPHER G. PAULRAJ, *Administrative Patent Judges.*

FRANKLIN, *Administrative Patent Judge.*

DECISION
Denying Petitioner's Motions to Change the Filing Date Accorded and
Denying Institution of *Inter Partes* Reviews
37 C.F.R. §§ 42.71 and 42.108

---

[1] This Decision relates to and shall be filed in each referenced case.

I. INTRODUCTION

Teva Pharmaceuticals USA, Inc. ("Petitioner") filed a petition to institute an *inter partes* review of claims 1–3, 9, 15, 62–65, 69–73, and 75 of U.S. Patent No. 8,603,514 B2 (Ex. 1001, "the '514 patent"). Case IPR2016-00281 ("IPR281"), Paper 1. Petitioner also filed a petition to institute an *inter partes* review of claims 1, 4–10, and 13–18 of U.S. Patent No. 8,017,150 B2 (Ex. 1001, "the '150 patent"). Case IPR2016-00282 ("IPR282"), Paper 1. Each petition was accorded a filing date of December 4, 2015. IPR281, Paper 3; IPR282, Paper 3.

By Order dated February 18, 2016, we authorized Petitioner to file a motion requesting the filing date accorded to each petition to be changed from December 4, 2015, to December 3, 2015. IPR281, Paper 8, 3; IPR282, Paper 7, 3. On February 29, 2016, Petitioner filed in each case a "Motion to Correct Filing Date"[2] (collectively, "Motions"). IPR281, Paper 10 ("Mot."); IPR282, Paper 9. As authorized, Patent Owner filed Oppositions to the Motions (IPR281, Paper 12 ("Opp."); IPR282, Paper, 11), and Petitioner filed Replies to those Oppositions to the Motions (IPR281, Paper 14

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[2] We note that it is undisputed that the petitions were each accorded a filing date that reflects the date that the petition filings, payment, and service, albeit defective, were completed. Thus, the issue is not simply whether to "correct" any error. Rather, the issue is whether Petitioner is entitled to the benefit of a filing date that is earlier than our regulations describe. Therefore, although Petitioner styled the Motions as requests to "Correct" the filing date accorded to the petitions, we treat them as requests to "Change" that date.

("Reply"); IPR282, Paper 13).[3] Patent Owner subsequently filed a timely Preliminary Response in each case. IPR281, Paper 16; IPR282, Paper 15.

II. MOTIONS TO CHANGE FILING DATES ACCORDED

The parties agree that because Petitioner was served with a complaint on December 3, 2014, asserting infringement of the patents at issue, the statutory bar date for IPR281 and IPR282 is December 3, 2015. *See* 35 U.S.C. § 315(b) ("An inter partes review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent."); 37 C.F.R. § 42.101(b); Mot. 1–2, 6; Opp. 1. Petitioner acknowledges that the December 4, 2015 filing date accorded to the petitions reflects the date that the Petitioner completed filing the petitions, including paying the fees and attempting service on the Patent Owner. Mot. 4–5.

Nevertheless, Petitioner requests that we change the filing date accorded in each case from December 4, 2015, to December 3, 2015, because the petitions and exhibits were uploaded on December 3, 2015, and payment was attempted, but not completed on that date due to "technical issues." *Id.* at 1. In support of its contentions, Petitioner relies upon the declarations of Ms. Eleanor Yost, an attorney at the law firm of Goodwin

---

[3] With respect to the Motions, Oppositions, and Replies, Petitioner and Patent Owner certify that "word-for-word identical" papers and declaratory exhibits were filed in IPR281 and IPR282, although the paper and exhibit numbers may differ. In the remaining portions of this Decision, we include citation only to paper and exhibit numbers in IPR281.

Procter LLP, and Ms. Linda Rogers, a legal assistant supervised by Ms. Yost. Mot. 1–2; Ex. 1041 ¶ 1; Ex. 1042 ¶ 1. Patent Owner opposes Petitioner's request and relies upon the declarations of Mr. Daniel Doran, the Docketing Manager for Hoffmann & Baron, LLP, and Mr. Michael I. Chakansky, a partner at that law firm. Opp. 2, n.3; Ex. 2006 ¶ 1; Ex, 2007 ¶ 1.

PRPS filing

Petitioner asserts that at approximately 9:45 p.m. EST on December 3, 2015, Ms. Rogers logged into the Patent Review Proccssing System ("PRPS") and began uploading documents for a petition in another case, Case IPR2015-00280 ("IPR280"). Mot. 2. The Motions explain that, based on their experience, Ms. Yost and Ms. Rogers believed that they would be able to complete the filings in that case, as well as start and complete the filings in IPR281 and IPR282, prior to midnight. *Id.*

According to Petitioner, however, Ms. Rogers found that the PRPS system "repeatedly froze" during the upload process for IPR280. *Id.* Petitioner asserts that during the upload process, Ms. Rogers observed that the "spinning wheel" that normally appears during the upload process did so "for an unusual length of time (sometimes several minutes), and then eventually stop[ped] spinning, resulting in a 'frozen' screen that prevented her from taking any action (including closing the browser window or opening new windows)." *Id.* at 3. To remedy that issue, Ms. Rogers and Ms. Yost decided to "force-close the browser, re-open the browser, re-login to PRPS and attempt to resume the filing." *Id.* Upon doing so, Petitioner asserts that Ms. Rogers was "met with a 'padlock' graphic and an error message," requiring her to select a menu option to "unlock" the session and

begin uploading the documents again. *Id.* According to Petitioner, the alleged "'freezing,' re-starting, and unlocking process added a significant amount of time to the filing" process for IPR280. *Id.*

Petitioner asserts that at approximately 11:00 p.m., Ms. Yost initiated "a separate, parallel PRPS session" on a different computer and began filing the petition in IPR281. *Id.* at 3–4. Petitioner asserts that she "experienced the same freezing errors in connection with several different documents (sometimes more than once for the same document)." *Id.* at 4. According to Petitioner, Ms. Rogers began filing the petition in IPR282 after completing the petition filing in IPR280 at approximately 11:11 p.m. *Id.*

Petitioner asserts that the petitions and exhibits in both IPR281 and IPR282 were successfully uploaded to the PRPS server on December 3, 2015. *Id.* Petitioner asserts that, prior to midnight, Ms. Yost and Ms. Rogers attempted to submit payments for those IPRs, but that the "PRPS system rejected the payments without explanation." *Id.* at 4 (citing Ex. 1041 ¶¶ 27–29; Ex. 1042 ¶ 18; Exs. 1044–45, 1047–1051 (PRPS failed payment receipts)). According to Petitioner, at midnight, i.e., on December 4, 2015, payment was accepted for IPR281 and Ms. Yost clicked "submit" and received a filing notification at 12:01 a.m. *Id.* at 4–5. Petitioner asserts that the payment was accepted for IPR282 at 12:04 a.m., and after clicking "submit," Ms. Rogers received a filing notification at 12:09 a.m. *Id.* at 5.

Service

Petitioner acknowledges that "[t]he petitions and supporting documents were tendered to FedEx® at 3:02 am on Friday, December 4, 2015." Mot. 5. Petitioner acknowledges also that "Ms. Yost neglected to appreciate that the Certificates of Service . . . still said December 3, and

needed to be updated to reflect that the documents were not tendered to FedEx® until December 4th." *Id.* at 6. Petitioner asserts that there was a delay in printing hard-copy versions of the petitions and relevant documents for service because "[g]iven the slow upload times experienced by Ms. Rogers and Ms. Yost, Office Services was directed to exit all of the PDFs until the filings were complete, as a troubleshooting measure in the event that their accessing the PDFs was exacerbating the upload times." *Id.* at 5. According to Petitioner, "[o]nce the filings were complete, printing resumed." *Id.*

Patent Owner asserts that Petitioner "made no effort to effect service" on December 3, 2015, but instead did not provide any service documents to FedEx® until 3:02 a.m. on December 4, 2015. Opp. 3–4. Additionally, Patent Owner asserts that Petitioner served an incomplete set of documents on December 4, 2015. *Id.* Specifically, Patent Owner asserts that for IPR281, Petitioner failed to include a copy of the declaration of Jayanth Panyam referenced in the petition (Ex. 1003), and for IPR282, Petitioner failed to include a copy of the petition itself and the declaration of Nandita Das referenced therein (Ex. 1003). *Id.* at 2. Further, Patent Owner asserts that Petitioner "misrepresented" in an *ex parte* email to the Board and in both the original and amended Certificates of Service that the documents were served on December 3, 2015. *Id.* at 4.

In the Reply, Petitioner asserts that it subsequently provided to Patent Owner a copy of the IPR282 Petition, the Nandita Das declaration, and the Jayanth Panyam declaration, referring to those items as "allegedly missing documents." Reply 3. Petitioner asserts that "to the extent the service copy was incomplete, it was due to clerical errors." *Id.* With respect to Patent

Owner's assertion that Petitioner misrepresented the date of service on the original and amended Certificates of Service, Petitioner responds that Ms. Yost only made corrections identified by the Board's Trial Paralegal "because she believed that she needed the Board's authorization to make changes to the record other than those requested by the Board, and a panel had not been appointed from which she could seek authorization." *Id.* at 4 (citing Ex. 1041 ¶ 41).

Relief Requested

According to Petitioner, it has satisfied the statutory requirements for consideration of petitions for *inter partes* review by, at some point, paying the required fee and providing copies of the petitions and supporting evidence to Patent Owner. Mot. 7. Acknowledging that the timing of both of those requirements, set forth by regulation, were not met, Petitioner requests the Board to exercise its discretion to waive the regulatory requirements for electronic filing and change the filing date accorded to the petitions to December 3, 2015. *Id.* at 1, 8 (citing 37 C.F.R. § 42.5(b) ("The Board may waive or suspend a requirement of parts 1, 41, and 42 . . . ")). Petitioner cites a number of cases that allegedly support its assertion that the Board should exercise its discretion to waive the regulatory requirements for electronic filing. Mot. 8–10. According to Petitioner, we should waive those requirements for the petitions in IPR281 and IPR282 because "[b]ut for the compromised PRPS system that unexpectedly delayed them, the filings would have been completed prior to midnight on December 3." *Id.* at 10. Further, Petitioner asserts that Teva will be greatly prejudiced if the filing dates are not changed, "as its petition would be barred under 35 U.S.C. § 315(b)." *Id.* at 6.

Patent Owner asserts that changing the filing date accorded to the petitions would prejudice Patent Owner because "[l]osing the benefit of the one year statutory bar of 35 U.S.C. § 315(b) will result in [Patent Owner] having to expend significant amounts of time and money to defend the two patents of the 281 [and] 282 IPRs." Opp. 6. Patent Owner asserts further that the cases cited by Petitioner in support of its request to change the filing date accorded to the petitions are distinguishable from the present situation "because none of them addressed the combination of a failure to file, serve and pay the required fee as set out in our Rules and governing statute." *Id.* at 7 (quoting *Terremark N. Am. LLC v. Joao Control & Monitoring Sys., LLC*, Case IPR2015-01482, slip op. at 10 (PTAB Dec. 28, 2015) (Paper 10)). According to Patent Owner, in each case cited by Petitioner, "service on patent owner's counsel was accomplished or attempted before the statutory bar." *Id.* at 7–8. Additionally, Patent Owner asserts that Petitioner has not established that it is entitled to a December 3, 2015 filing date because Petitioner has (a) admitted to failing to file the petitions on that date, (b) repeatedly misrepresented the date that it served the papers on Patent Owner, and (c) offered only an unsupported reason for its delay in filing the "last minute" petitions. *Id.* at 3, 8–10.

Analysis

The patent statute sets forth requirements that must be satisfied for an *inter partes* review petition to be considered, such as inclusion of certain documents, payment of fees, and providing copies of documents to the designated representative of the patent owner. 35 U.S.C. § 312(a). The applicable regulations clarify that a petition will not be accorded a filing date until the petition satisfies the following: (1) the content of the petition

complies with 37 C.F.R. § 42.104, (2) the fee to institute has been paid, *see* 37 C.F.R. §§ 42.15(a), 42.103(b), and (3) the petition and relevant documents have been served on the patent owner. 37 C.F.R. § 42.106(a).

As discussed *supra*, Petitioner acknowledges that the petitions in IPR281 and IPR282 did not satisfy the latter two requirements by the filing date that it now requests. Petitioner, however, asserts that we should exercise our discretion to waive those regulatory requirements because technical difficulties caused by PRPS prevented Petitioner from satisfying those requirements on December 3, 2015. As the moving party, Petitioner has the burden of proof to establish that it is entitled to the requested relief. *See* 37 C.F.R. § 42.20(c).

Having considered the arguments and evidence, we agree with Patent Owner that Petitioner has not established that it is entitled to a waiver of the regulatory requirements for according a filing date to a petition. In particular, we do not find that Petitioner has established persuasively that a "compromised PRPS system" caused Petitioner's delay in uploading the petition documents, or prevented Petitioner from paying the petition fees, and serving Patent Owner with the petitions on December 3, 2015. *See* Mot. 10. Rather, based upon our review, Petitioner has not shown that such delays are attributable to the system rather than to the users.

As an initial matter, we note that, by their own admission, Petitioner's counsel, Ms. Yost, and her legal assistant, Ms. Rogers, began to serially upload the first of three petitions and corresponding exhibits at approximately 9:45 p.m. on the critical date for those petitions to be filed. Ex. 1041 ¶ 5; Ex. 1042 ¶ 4. Petitioner does not, however, persuasively explain why it waited to upload and file, serially, *three* petitions and

numerous exhibits (based on our calculation, the three petitions and accompanying exhibits total approximately 12,000 pages and nearly 500 MB) with little more than two hours remaining before the statutory bar date. Ms. Yost and Ms. Rogers both attest that, "[i]n [their] experience, a complete filing with a similar number of exhibits to that of the '280 and '281 petitions typically takes 20 minutes or less each." Ex. 1041 ¶ 24; Ex. 1042 ¶ 13. Even if 20 minutes were typical for filing a petition, that would only leave about an hour before the bar date to complete all three filings. Waiting until the last minute—without explanation—is ill advised and had Petitioner not done so, any alleged delays caused by "technical issues" would have been moot.

In any event, according to Ms. Yost and Ms. Rogers, they experienced technical issues while using PRPS, including the system "crashing," and "freezing" inexplicably. Ex. 1041 ¶¶ 4, 8, 15, 19, 22, 25; Ex. 1042 ¶¶ 13, 11, 14. Neither Petitioner nor its declarants, however, have provided any objective evidence to support that testimony. In particular, Petitioner has not provided any objective evidence that technical issues occurred with the PRPS system during the evening of December 3, 2015. Nor are we aware of any technical issues during that time. Moreover, Petitioner has not established persuasively that any delays or issues it allegedly experienced were not the result of processes unrelated to PRPS.

Ms. Yost and Ms. Rogers declare that they received an "error message," but neither declarant described that message or provided a screenshot of such message. Ex. 1041 ¶ 13; Ex. 1042 ¶ 9.

Further, with respect to the December 4, 2015 fee payments, we remain unpersuaded that a PRPS error was the cause. Contrary to the

assertion of Petitioner and the declaration testimony of Ms. Yost and Ms. Rogers, the payment history in PRPS reveals that their initial payment attempts were not rejected "without explanation." *See* Mot. 4. That payment history, for each petition, was immediately available to the PRPS users during the payment process when viewing the "Payment" tab. The payment history provides information relating to each attempted payment, including the credit card or deposit account applied, the transaction date, the status as "Fail" or "Cleared," and the reason for any failed payment. For example, in IPR281, the payment history identifies an initial attempt to pay the petition fee on December 3, 2015, using a credit card. That payment attempt has a "Fail" status and an explanation that "[y]our transaction exceeds the maximum daily limit for credit card transactions. The transaction will not be processed." On December 4, 2015, a payment was made using a different credit card, and the status for that approved payment was noted as "Cleared."

Similarly, in IPR282, the payment history indicates two attempts to pay using a deposit account wherein each attempt resulted in a "Fail" status with an explanation that the "Deposit Account has insufficient funds to complete the sale." The payment history indicates also that two subsequent attempts to pay using a credit card each resulted in a "Fail" status with an explanation that the "[c]ard account number is invalid." A payment was eventually approved after another deposit account having sufficient funds was applied on December 4, 2015. Thus, we remain unpersuaded by the declaration testimony of Ms. Yost and Ms. Rogers that their payment attempts were rejected "without explanation" or that any "technical issues" attributable to PRPS delayed the successful fee payments for IPR281 and

IPR282. *See* Mot. 1, 4–5.

Additionally, Petitioner has not provided a reasonable explanation for failing to timely serve Patent Owner. *See* Mot. 5–6, 10; Reply 4. As discussed, we do not find that Petitioner established that PRPS was not functioning properly on December 3, 2015. Nor has Petitioner provided any other persuasive argument or evidence that it even attempted to serve the petitions on December 3, 2015. Moreover, we are troubled by the fact that Petitioner did not acknowledge that both the original and amended certificates in both cases recorded the wrong date of service until after Patent Owner raised the issue. Further, Petitioner's failure to acknowledge that error when amending the certificates of service, or in any of its e-mail communications to the Board requesting to change the filing date accorded is not well taken.[4]

With respect to the cases cited by Petitioner to support its request that we waive the regulatory requirements to pay petition fees and serve the petition on the Patent Owner prior to according filing dates, we remain unpersuaded. We begin by noting that those cited cases are non-precedential and reflect the Board's exercise of discretion based on the particular facts presented therein. Further, as Patent Owner has argued, each of those cited cases are distinguishable from the circumstances present here because none of the cited cases address the combination of a failure to complete filing, including paying fees, along with a failure to timely serve the petition. *See*

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[4] We note also, that Petitioner has at no time sought to correct its certification in the petitions regarding grounds for standing under 37 C.F.R. § 42.104(a) or its statement that the petitions were "timely filed on December 3, 2015." IPR281, Paper 1, 8; IPR282, Paper 1, 4.

Opp. 7–8; *see also Terremark N. Am. LLC*, Case IPR2015-01482, slip op. at 10–13 (Paper 10) (distinguishing a number of cases cited by Petitioner as not including the combination of deficiencies regarding requirements to have a filing date accorded, including petition filing, payment, and service). Moreover, here, as discussed *supra*, Petitioner has failed to establish persuasively that PRPS functioned improperly during the time that Petitioner endeavored to file the petitions.

Thus, considering the totality of circumstances present in these cases, we determine that Petitioner has not met its burden of establishing that it is entitled to have the filing dates accorded to the petitions in IPR281 and IPR282 changed. That determination is unchanged by Petitioner's assertion that it will be prejudiced if the filings dates accorded remain December 4, 2015, because the petitions will be time-barred. Mot. 6. Any prejudice to Petitioner was created by Petitioner's own delay. Accordingly, Petitioner's Motions are *denied*.

III. STATUTORY BAR TO *INTER PARTES* REVIEW

Whether Petitioner is barred from pursuing an *inter partes* review under 35 U.S.C. § 315(b) is a threshold issue. 35 U.S.C. § 315(b) provides:

> An inter partes review may not be instituted if the petition requesting the proceeding is filed more than 1 year after the date on which the petitioner, real party in interest, or privy of the petitioner is served with a complaint alleging infringement of the patent.

As discussed in Section I *supra*, the parties agree that because Petitioner was served with complaints asserting the patents at issue on December 3, 2014, and that the statutory bar date for IPR281 and IPR282 is

December 3, 2015.[5] Mot. 1–2, 6; Opp. 1. The petitions in IPR281 and IPR282 each were accorded a filing date of December 4, 2015, one day after the statutory bar date. Paper 3, 1. We have declined to change that date. As Petitioner acknowledges, if the filing dates accorded to the petitions are not changed, each "petition would be barred under 35 U.S.C. § 315(b)." Mot. 6. Accordingly, the petitions are barred under 35 U.S.C. § 315(b).

ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner's Motions are *denied*;

FURTHER ORDERED that institution of an *inter partes* review of any challenged claim of the '514 patent in IPR281 is *denied*; and

FURTHER ORDERED that institution of an *inter partes* review of any challenged claim of the '150 patent in IPR282 is *denied*.

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[5] Petitioner explains that the complaints were served in *Reckitt Benckiser Pharmaceuticals, Inc., RB Pharmaceuticals Limited, et al v. Teva Pharmaceuticals USA, Inc.*, Civil Action 14-1451 (D. Del.). IPR281, Paper 1, 8; IPR282, Paper 1, 4. The real parties-in-interest for Patent Owner in IPR281 and IPR282 are identified as MonoSol Rx, LLC, and the exclusive licensee of the patents at issue, Indivior Inc., formerly known as Reckitt Benckiser Pharmaceuticals Inc. IPR281, Paper 7, 1; IPR282, Paper 6, 1.

IPR2016-00281 (Patent 8,603,514 B2)
IPR2016-00282 (Patent 8,017,150 B2)

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AO 120 (Rev. 3/04)

TO:	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been filed in the U.S. District Court Delaware on the following X Patents or Trademarks:

DOCKET NO.	DATE FILED	U.S. DISTRICT COURT
15cv1051-RGA	11/13/2015	DISTRICT OF DELAWARE

PLAINTIFF	DEFENDANT
Indivior, Inc., et al.	Sandoz, Inc.

	PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1	8,475,832	7/2/2013	Indivior UK Limited
2	8,017,150	9/13/2011	Mo noSol Rx, LLC
3	8,603,514	12/10/2013	MonoSol Rx, LLC
4			
5			

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT
See attached Order

CLERK	(BY) DEPUTY CLERK	DATE
JOHN A. CERINO, CLERK OF COURT		8/22/2016

Copy 1—Upon initiation of action, mail this copy to Director **Copy 3—Upon termination of action, mail this copy to Director**
Copy 2—Upon filing document adding patent(s), mail this copy to Director **Copy 4—Case file copy**