concentrations to contribute a continuous pleasant smell to the exhalant breath sufficient to mask bad breath odor.

Preferred water soluble adhesives may be permeable to certain mint odorant components; that is, certain of the mint odorant components may by diffusion pass into and through the adhesive layer, to the mucosal surface onto which the adhesive layer is affixed. Because some mint odorant components may be irritating to the mucosa or may cause an unpleasant local numbing effect on the mucosa when present in higher amounts, it may be desirable to avoid delivery of the odorant to the underlying mucosa. This can be accomplished according to the invention by interposing an additional water-soluble layer, poorly permeable to the odorant components, between the odorant-containing layer and the adhesive layer, to substantially prevent movement of the odorant components into the adhesive layer.

Any of a variety of odorants may be delivered according to the invention, and any of various mint odorants, as described below, may be particularly desirable.

Because the device according to the invention remains affixed to a surface of the oral cavity during use, no conscious effort by the user is required to hold the device in place, and the likelihood that it may be swallowed or spit out of the mouth during use is diminished. As the device has a thin profile, and conforms smoothly to the surface of the oral cavity, it is not mechanically annoying and does not interfere with speech or with ingestion of foods or fluids.

Disclosure of the Invention

Water-Soluble Pressure-Sensitive Adhesives

In one general aspect, the invention features a water-soluble pressure-sensitive adhesive including a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer. Suitable

polymers are characterized as being solid at room temperature (that is, as having a glass transition temperature T(g), or melting point T(m), higher than about 25 °C, and more preferably higher than about 30 °C, and lower than about 120 °C, and more preferably lower than about 100 °C); and having a hydrophilicity as measured by water uptake greater than about 25 %. Suitable plasticizers are characterized as being liquid at room temperature and having a boiling point higher than about 80 °C.

Suitable polymers include polysaccharides such as for example cellulose-type materials and natural gums, polypeptides, and water-soluble synthetic polymers. Particular examples of such suitable polymers which are GRAS certified include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934 (B.F. Goodrich), starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In some embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, as well as to human skin.

In other embodiments for oral mucosal contact and for skin contact, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50

weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k.

In another general aspect, the invention features a water-soluble pressure-sensitive adhesive film made up of a water-soluble polymer that is made tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In preferred embodiments the thickness of the film is in the range of about 5 - 20 mils, and is shaped to fit and to conform generally to a mucosal surface-contacting portion of a dental prosthesis such as a dental plate. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Such a film can be used as a denture adhesive, that can adhere to oral mucosal surfaces and to dental prosthesis for an extended period, typically of more than about 5 hours. The film can be used as part of a system for delivery of substances through the oral mucosa (as a buccal transmucosal patch), or for delivery of substances into the oral cavity itself.

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

In another general aspect, the invention features a laminated device for controlled release of one or more substances within a mucosa-lined body cavity, having an adhesive layer by means of which the device can be affixed within the body cavity.

In some embodiments the mucoadhesive layer is water-soluble, constructed in some embodiments of a water-soluble moistenable mucoadhesive, and in some embodiments of a water-soluble pressure-sensitive mucoadhesive; in some embodiments the adhesive adheres to a

variety of materials, such as polymers, that can be used in construction of devices for emplacement on a
mucosal surface or within a body cavity that has a mucosal lining; or it is mucoadhesive and additionally adheres to such materials. Preferably the water-soluble pressure-sensitive adhesive requires no moistening prior to contact with the mucosal or the polymer surface. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments for oral mucosal contact, a water-soluble pressure-sensitive adhesive according to the invention includes PVP (about 95 - 65 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to about 30 weight %) can be made up by water. By way of illustration, such compositions adhere well to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments for oral mucosal contact a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 100 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 5 - 35 weight %). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more

preferably between about 100 k and about 300 k. The water-soluble pressure-sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In preferred embodiments the device includes at least one water-soluble polymer layer in addition to the water-soluble pressure-sensitive adhesive layer. This water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof. In a particular embodiment, sorbitan monostearate (SPAN 60) with hydroxypropyl cellulose (HPC LF) is useful.

The pressure-sensitive adhesive layer and, in some embodiments, one or more of the polymer layers in the device according to the invention are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the pressure-sensitive adhesive layer and the water-soluble polymer layers eventually dissolve completely within the body cavity in which the device is placed, and the material of the dissolved layers is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal.

According to the invention, the adhesive serves to keep the device in place within the body cavity, and release of the substance or substances is controlled by the particular arrangement of layers.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

In a further general aspect, the invention features a device for emplacement within a mucosa-lined body cavity of a subject, the device

including a portion made of a water-soluble pressure sensitive adhesive composition. A surface of the water-soluble pressure sensitive adhesive portion forms a basal surface of the device which, when the device is in use, is affixed to a surface of the body cavity.

The adhesive compositions providing an adhesive surface of the device of the invention are pressure-sensitive; that is, the adhesive surface of the device requires no wetting prior to contacting it with the body cavity surface to which it is to be affixed.

The adhesive compositions are fully water-soluble, and are thus fully soluble in secretions present in mucous-lined body cavities. Consequently, the adhesive eventually dissolves completely within the body cavity in which the device is placed, and is flushed away with the fluid secretions of the cavity or, in the case of use in the oral cavity, passes on to the alimentary canal. For placement within the oral cavity, for example, the adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly they include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the device is emplaced within the body cavity by contacting the adhesive surface with a mucosal surface within the body cavity or with a surface of a prosthesis that is employed within the body cavity, and for such embodiments the water-soluble pressure sensitive adhesive composition preferably includes PVP (about 95 - 40 weight %) and, optionally, HPC (up to about 50 weight %) as a polymer; and glycerin as a plasticizer (about 5 - 35 weight %). Optionally, any balance (up to

about 30 weight %) can be made up by water. By way of illustration, such compositions adhere instantaneously (within less than five seconds) to mucosal surfaces as well as to surfaces of prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type.

In other embodiments, a water-soluble pressure-sensitive adhesive according to the invention includes as a polymer HPC (about 0 - 50 weight %) and, optionally, (up to about 50 weight %) one or more of PVP, PVA, PEO, starch, polysucrose or other polysaccharide, xanthan gum, or karaya gum; and glycerin as a plasticizer (about 11 - 60 weight % and, preferably about 30 - 50 weight % for PVP- or HPC-containing adhesive compositions). In these formulations, the HPC preferably has a molecular weight between about 60 k and about 1,000 k, and more preferably between about 100 k and about 300 k. In some embodiments the device is a device for delivery of one or more substances into the body cavity or across the mucosa. Typically the device has a laminated structure, and the water-soluble pressure sensitive portion is a basal layer of the device. Conveniently, the water-soluble pressure sensitive adhesive portion of such a device is constructed as a film made up of an adhesive composition as described above. In preferred embodiments the film has a thickness in the range about 5 - 20 mils, and is shaped to fit and to conform generally to the surface to which the device is intended to be attached for use. Preferred water-soluble pressure-sensitive adhesive films according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth.

In some embodiments the device when in place within the body cavity provides a protective barrier for the area of the mucosal surface to which it is affixed which is covered by the device. The barrier may protect the underlying mucosal surface from mechanical abrasion or erosion, for example, or, for example, it may serve to protectively isolate the underlying mucosal surface from some substance in the fluid of the milieu of the body cavity.

Where the device is a laminated device for delivery of an active agent, and includes an upper active-containing layer laminated to an adhesive layer, or where the device provides a protective barrier, and includes an upper barrier layer laminated to an adhesive layer, the upper layer is preferably constructed of a hydrophobic polymer material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The material may further be hot water dispersible and may have non-tacky surface properties upon moistening. Examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

The rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component: a given polymer type dissolves or disperses more slowly at higher molecular weights than at lower molecular weights. In some embodiments the active-containing layer includes a polymer such as hydroxypropyl cellulose, and may additionally include a plasticizer such as glycerin. In a particular embodiment, hydroxypropyl cellulose (HPC Klucel LF), having a molecular weight of 80,000, with glycerin as a plasticizer, is useful.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

In yet another general aspect, the invention features a layered composite mucoadhesive device for delivery of an active substance into the oral cavity, having an active-containing layer that includes the active substance dispersed or dissolved in a water soluble polymer, and a water soluble adhesive layer.

In some embodiments the active-containing water soluble polymer layer is a hydrophobic material that will not dissolve in cold water (below about 40 °C) and has little or no tendency to hydrate with water. The

material may further be hot water dispersible and may have non-tacky surface properties upon moistening. As noted above examples of suitable GRAS-certified materials include but are not limited to monoglycerides, triglycerides, waxes such as paraffin, fatty acids, fatty alcohols and mixtures thereof.

Also as noted above, the rate of release of the active substance within the oral cavity depends to at least some extent upon the rate of dissolution or dispersion of the polymer of the active layer *in situ*, which in turn varies substantially according to the molecular weight of the principal polymer component; a desired release rate can be specified by choice of the polymer or polymer combination.

In some embodiments the adhesive for use in the adhesive layer of the invention is a water-soluble pressure-sensitive adhesive according to the invention, as disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and as described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

Additional ingredients, such as, for example, deodorants or reodorants or flavorants, may be delivered along with the active substance as the active-containing layer disperses within the oral cavity. Such additional ingredients include, for example, sweeteners such as aspartame, and breath fresheners such as menthol.

In another general aspect the invention features a method for administering a substance over an extended time period for relief of sore throat or cough. The method involves dissolving or dispersing the substance in a laminated water soluble device that has a water soluble pressure sensitive adhesive layer. The device is affixed to the mucosal surface of the oral cavity.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

In still another general aspect, the invention features a laminated composite device for administering an odorant into the oral cavity over an extended time. The device has at least two layers, including a basal layer constructed of a water soluble pressure sensitive mucoadhesive polymer composition; and an odorant-containing water soluble polymer layer.

In some embodiments the basal adhesive layer is mucoadhesive and additionally adheres to a variety of materials, such as polymers, that can be used in construction of devices for emplacement on an oral mucosal surface or within the oral cavity. The basal adhesive layer preferably is constructed of a water soluble pressure sensitive adhesive that requires no moistening prior to contact with the mucosal or the polymer surface. The adhesive preferably is made from materials generally regarded as safe ("GRAS-certified"), or national formulary ("NF-certified"), and therefore safe for oral use or for ingestion.

Preferred water-soluble pressure-sensitive adhesives for use in the adhesive layer of the invention are those disclosed above under the heading "Water-Soluble Pressure-Sensitive Adhesives", and described in further detail hereafter. Accordingly such adhesives include a water-soluble polymer that is rendered tacky (that is, it is rendered pressure-sensitive) at room temperature by addition of a water-soluble plasticizer that is miscible with the polymer.

In some embodiments the odorant containing layer includes a polymer such as a hydroxypropyl cellulose, and in a particular embodiment may additionally include a plasticizer such as glycerin. The rate of release of the odorant within the oral cavity can be specified by selection of particular polymer or polymer combinations, as noted generally above under the heading "Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity". In a particular embodiment, a hydroxypropyl cellulose (HPC Klucel GF), having a molecular weight of 300,000, is useful.

The water soluble odorant containing layer may take the form of a film which preferably is about 20 - 30 mils thick. Suitable slow-dissolving polymers such as HPC are typically not sufficiently flexible to conform with the irregularly curved surfaces of the oral cavity or of oral or dental prostheses, and addition of a plasticizer to the polymer or polymer mixture of films would be required for these applications. Suitable plasticizers can include glycerin, for example.

In some embodiments the odorant is an essential oil of a plant material, or a refined fraction of an essential oil, or a combination of the chief aromatic constituents of an essential oil. Preferably the odorant is a mint odorant. We have discovered that, surprisingly, the essential oils that are commonly used as flavorings, particularly oil of wintergreen, oil of peppermint, and oil of spearmint, are themselves effective as plasticizers. For breath freshener devices for delivering a mint odorant, therefore, the odorant containing layer therefore can consist of the polymer and the mint odorant (and, optionally, a sweetener and a preservative), without any requirement for a plasticizer other than the mint odorant.

Accordingly, in another aspect the invention features a laminated composite device for administering a mint odorant into the oral cavity over an extended time, comprising a basal layer constructed of a water soluble pressure sensitive mucoadhesive composition and an upper layer containing a water soluble polymer, such as a HPC, and a mint oil.

Extended delivery of odorant can be obtained according to the invention from devices whose composite thickness is 35 mils or less. The devices according to the invention are very flexible, and are therefore capable of conforming to and adhering to contoured surfaces such as the gum or the roof of the mouth. Breath freshening devices according to the invention can deliver a mint odorant such as a peppermint continuously over a period of up to two hours or longer from a single device, and can provide breath freshening for even greater periods of time.

Description of Preferred Embodiments

Preferred embodiments of the invention will now be described, beginning with a brief description of the drawings.

Brief Description of the Drawings

Fig. 1 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances at two different rates.

Fig. 2 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances.

Fig. 3 is a sketch in sectional view showing a device of the invention configured to provide delivery of one or more substances in a sequence of pulses.

Fig. 4 is a sketch in sectional view showing a device of the invention configured to provide delayed-onset delivery of one or more substances while minimizing diffusion of the substance(s) at the edges of the device.

Figs. 5 through 7 are rough hypothetical plots showing quantity of an active substance released by devices of the invention configured on the plans shown in Figs. 1 through 3, respectively.

Fig. 8 is a sketch in transverse sectional view showing a bilaminate device according to the invention.

Fig. 9 is a sketch in transverse sectional view showing a trilaminate device according to the invention.

Fig. 10 is a plot of data showing the cumulative release of Dyclonine HCl into water from a mucoadhesive disc according to the invention, and from a Sucrets® lozenge.

Fig. 11 is a plot of data comparing release of benzocaine into distilled water from mucoadhesive discs according to the invention, having different molecular weight polymers in the active-containing layer.

Fig. 12 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 13 is a sketch in sectional view showing another embodiment of a device according to the invention.

Fig. 14 is a graph comparing tack characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with tack characteristics of conventional films.

Fig. 15 is a graph comparing adhesion characteristics, on a PMMA surface, of dry and of moistened adhesive films according to the invention with adhesion characteristics of conventional films.

Fig. 16 is a graph comparing elastic moduli of HPC films, illustrating the plasticizing effect of mint odorants.

Fig. 17 is a graph comparing menthol release over time from a breath freshening device according to the invention and from a conventional commercially marketed "breath mint" (Certs®).

As will be appreciated, the drawings are not made to scale, and, in particular, no attempt has been made to represent relative thicknesses of the layers proportionately, and the thicknesses of the various layers are exaggerated for clarity of presentation.

Modes of Carrying out the invention

Water-Soluble Pressure-Sensitive Adhesives

1. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software

package (Stable Micro Systems, Ltd.), as follows. A sample of the film on a release liner is mounted upon a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by submersion of a sample of the film in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes. 2. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

3. Preparation of dental prosthesis adhesive film.

A water-soluble pressure-sensitive adhesive film made as described above can be die-cut in a shape that conforms to that portion of the dental prosthesis that closely fits the mucosal surface of the mouth, such as the part of the dental plate that fits against the palate. The shaped film pieces can be packaged dry. For use, the dry film is pressed onto the appropriate surface

of the dental prosthesis so that it adheres. Then the dental prosthesis with the adhesive affixed is inserted into the correct position in the mouth and pressed against the mucosal surface until adhesion is achieved.

The following Example is intended to illustrate but not to limit the invention.

Example I

Breath Freshening Device

A dissolvable mucoadhesive device capable of releasing a flavor into the oral cavity was constructed as follows: A solution was made up by co-dissolving 15.4 grams of polyvinyl pyrrolidone PVP (K90) and 6.0 grams of glycerin in 80 grams of isopropanol (IPA). The resulting solution was coated at a thickness of 30 mils onto a polyester release liner and allowed to dry for 15 hours at room temperature. The resulting dry film was tacky at room temperature and had a final thickness of about 5 mils. A second solution containing 43 grams of IPA, 42 grams of water, 15 grams of HPC EF, 2.5 grams of peppermint oil and 3.0 grams of Nutrasweet™ brand sweetener containing aspartame was prepared by mixing all the components until fully dissolved. The solution was then coated at a thickness of 50 mils onto a polyester release liner. The film was allowed to dry at room temperature for 15 hours to a final thickness of about 5 mils.

The two dry films were laminated together. Discs having a diameter of about 1.2 cm were cut from the laminate. The discs were tested *in vivo* by adhering a single disc to the upper palate of three volunteers. The discs adhered well to the mucosal surface and upon hydration with saliva immediately began releasing peppermint oil and aspartame as noticed by taste. The total time of dissolution in the mouth was about 10 minutes, during which time a pleasant, refreshing mint flavor was perceived.

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

1. Water-soluble pressure-sensitive adhesive layer.

The preferred water-soluble pressure-sensitive adhesive layer of the device according to the invention provides the foundation upon which the device operates. There follows first a description, by way of examples, of protocols for making exemplary water-soluble pressure-sensitive adhesives and films suitable for use in the adhesive layer.

a. Preparation of a water-soluble pressure-sensitive adhesive composition made up of PVP and glycerin.

A solution of poly(vinyl pyrrolidone) ("PVP": Kollidon®, obtained from BASF) and glycerin was first prepared in isopropyl alcohol ("IPA"), in the following proportion by weight: 15 parts PVP, 6 parts glycerin, and 79 parts IPA. The solution was coated on a polyester release liner and allowed to dry at room temperature for 15 hours to permit evaporation of the IPA. The resulting dry film is both pressure-sensitive and water-soluble.

Measurements of tack were made using a TA.XT2 Texture Analyzer (Texture Technologies Corp.) together with an XT.RA Dimension software package (Stable Micro Systems, Ltd.), as follows. A sample of the film is first mounted onto a block, and a probe is moved at a fixed speed against the adhesive surface of the film, distorting the film to a fixed penetration depth, where the probe is permitted to dwell for a fixed time. The probe is then withdrawn from the film, at a fixed speed, and the peak force required to detach the probe from the film surface is measured as a measure of tack.

Measured tack of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was 1820 g/cm^2, using a probe diameter of 0.80 cm, a penetration depth of 0.1 mm, a penetration rate of 1.0 mm/sec, a dwell time of 10 sec, and a withdrawal rate of 5.0 mm/sec. Typical tack values for adhesives used in transdermal devices, for example, are about 1000 - 2000 g/cm^2.

Measurements of water solubility were made by immersing a sample in water at 21 °C, stirring the water, and determining the time required for apparent complete dissolution of the film.

The total measured dissolution time of samples of a PVP-glycerin film prepared as described above and having 5 mils thickness was about 10 minutes.

b. Preparation of a water-soluble pressure-sensitive adhesive composition made up of HPC, PVP and glycerin.

Hydroxy propyl cellulose ("HPC"), PVP and glycerin were first blended in the proportion, by weight, of 4 parts HPC, 2 parts PVP, and 2 parts glycerin. The resulting mixture was pressed in a heated Carver laboratory press at 200 °F to a thickness about 35 mils. The resulting film was flexible, translucent and tacky at room temperature.

2. Device configurations.

a. Device having two substance-containing layers:

Referring to Fig. 1, there is shown by way of example a device **10** having a basal adhesive layer **12** which in use adheres to mucosal surface **M** and an upper polymer layer **14**, in which a substance or substances to be delivered are contained in both layers. As the upper layer is bathed by the fluids in the body cavity (for example by saliva and ingested fluids in the mouth), dissolution of the upper layer begins first and is substantially complete when dissolution of the basal layer begins. Where a different substance is contained in each layer, the substances are released sequentially. The two layers can be made to have different dissolution rates or swelling rates, resulting in one release rate for the substance or substances in the basal adhesive layer, and another release rate for the substance or substances in the upper polymer layer. If, for instance, the dissolution rate of the upper layer is slower than that of the lower layer, the resulting release regime is of a slow release of the substance in the upper layer, followed by a relatively rapid release of the substance in the basal layer. Or, alternatively, the two layers can have approximately the same dissolution

rates, but be loaded with the substance at different concentrations, resulting in a higher rate of delivery from that layer having the substance present in higher concentration.

Fig. 5 shows a rough diagrammatic plot of the release of active over time from a device made on the plan in Fig. 1. As will be appreciated, the different rates need not be linear, nor need the break between the rates be abrupt as shown.

Such a configuration can be useful in a breath freshener for oral use, by way of example, in which the basal layer can have a relatively slow dissolution rate and can be loaded with an antimicrobial, while the upper layer can have a relatively fast dissolution rate and can be loaded with a flavor or a reodorant. Such can result in a rapid release of flavorant or reodorant after emplacement in the mouth, followed by a slower release of the antimicrobial. Or, both layers can be loaded with a microbial, resulting release in an early burst followed by a more sustained delivery.

In one embodiment of this configuration, the basal layer is made of a polymer that becomes sticky on moistening, such as, *e.g.*, HPC or PAA.

In a modification of this configuration, the two layers described above can constitute middle and upper layers, respectively, of a three-layer device that is provided with a basal layer that is a water-soluble pressure-sensitive adhesive, so that the device need not be moistened prior to placement within the body cavity. As is described above, suitable compositions for such an adhesive layer include PVP as a polymer (95 - 65 weight %) and glycerine as plasticizer (5 - 35 weight %).

b. Device providing delayed-onset delivery:

Referring now to Fig. 2, there is shown a device **20** having a basal adhesive layer **22** which in use adheres to the mucosal surface **M**, a middle substance-containing water-soluble layer **26**, and an upper layer **28**, not containing the substance, that dissolves relatively slowly in the fluid environment of the body cavity. As in the device shown in Fig. 1, the adhesive layer is a water-soluble adhesive, which may be a mucoadhesive

that becomes tacky when moistened. More preferably, the basal adhesive layer is a water-soluble pressure-sensitive adhesive as described above; and in some embodiments the middle layer is eliminated and the substance to be delivered in loaded into the adhesive layer. However, where loading is so high (upwards of 25 % by weight, for example) that it would compromise the adhesive capacity of the adhesive layer, a system having the substance to be delivered loaded in a middle layer can be preferred.

Fig. 6 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 2. Here, as in Fig. 5, the rate need not be linear, nor need the onset be abrupt as shown.

Such a delayed-onset release configuration can be useful, by way of example, in a breath freshener that can be emplaced in the mouth before retiring for sleep, and which provides for release several hours later, so that the breath is fresh upon waking.

c. Device providing pulsed delivery:

A more complex release pattern can be achieved using several layers, in which altering layers contain the active, as shown by way of example in Fig. 3. The basal adhesive layer **34** of device **32** can be made, as in the devices of Figs. 1 and 2, either as a moistenable adhesive, or as a water-soluble pressure-sensitive adhesive. A moistenable adhesive may be preferred for reasons of greater stability. Basal layer **34** adheres to mucosal surface **M** when the device is in use and contains a substance to be delivered. Layers **36, 38** contain a substance to be delivered, while alternating layers **35, 37** are slowly dissolving layers not containing the substance.

Fig. 7 shows a rough plot of the amount of active released over time from a device made on the plan of Fig. 3. Here, as in Figs. 5 and 6, the rates for each delivery phase need not be linear, nor need the onset be abrupt as shown.

Such a configuration can be useful, for example, in an oral after-meals breath freshener, which provides for release of a flavor or reodorant

or deodorant at intervals corresponding with post-mealtimes, with no release during mealtimes or at other times.

Such a configuration can be useful, to cite another example, for pulsed delivery of actives that can be toxic if administered continuously. Such actives include, by way of example, anti-bacterials such as Cetyl Pyridinium Chloride ("CPC"); pulsed release can give adequate antibacterial protection without raising toxicity concerns.

d. Device having suppressed marginal release.

In any of the devices described above, dissolution at the edges or margins of the device, as well as from the upper surface, can be expected to result in release of the substance or substances within the layers whose edges are exposed. Loss of the desired release pattern can result, particularly where, as in Fig. 2, delayed onset is desired, or where, as in Fig. 3, pulsed release is desired. To minimize loss from the margins, a peripheral adhesive can be provided, as shown in Fig. 4, by way of example of a delayed onset release device having a marginal adhesive. The device **40** includes a moistenable mucoadhesive layer **44** containing the substance or substances to be delivered, which in use adheres to the mucosal surface **M**, and which is overlain by a water-soluble pressure-sensitive adhesive layer **46** whose edges extend beyond the edges of the mucoadhesive layer **44** on all sides and there adhere to the mucosal surface, forming a seal to prevent escape of the substance from the edges of the mucoadhesive layer **44** until the water-soluble pressure-sensitive adhesive layer has dissolved. The water-soluble pressure-sensitive adhesive layer is in turn covered by a slowly dissolving layer **48** not containing the substance. The slowly dissolving layer **48** provides a delay before the water-soluble pressure-sensitive adhesive begins to dissolve, which in turn prevents release of the substance until the upper surface of the substance-containing mucoadhesive layer is exposed.

Examples of substances that can be delivered within the oral cavity include: reodorants such as peppermint oil and other flavors, deodorants

such as for example the odor-preventive antimicrobial CPC, anti-bacterials such as chlorhexidine, sore-throat medicants such as Hexylresorcinol/Phenol derivatives/Menthol, cough suppressants such as Dextrathomorphan Hydochloride, agents to prevent mouth dryness, benzocaine for treatment of rhinitis, *etc.*

3. Particular devices.

Example II

Two-layer device having a water-soluble pressure-sensitive adhesive layer

A two-layer device according to the invention was made according to the following protocol. First the necessary components (polymers, additives, *etc.*) for each layer were dissolved or dispersed in an appropriate solvent. For an upper layer, the casting solution in one prototype consisted of 41 parts isopropyl alcohol ("IPA"), 40 parts water, 14 parts hydroxypropyl cellulose ("HPC") EF (MW ~ 80,000), 2.4 parts peppermint oil and 2.8 parts Aspartame. The casting solution for the basal layer consisted of 79 parts IPA, 15 parts poly(vinyl pyrrolidone) ("PVP") (Kollidon 90), and 6 parts glycerin. Each of these two casting solutions was coated onto a polyester release liner, to provide a substratum for forming the layer, at the desired thicknesses of 50 mils for the upper layer and 25 mils for the basal layer. The layers were then allowed to dry on the respective release liners overnight (at least 15 hours) at room temperature inside a hood). The dry films were then carefully hand-laminated together to provide a two-layer system consisting of a non-tacky upper layer containing the substances to be released, and an adjacent tacky pressure-sensitive-adhesive soluble basal layer.

Alternatively, manufacture of the pressure sensitive adhesive device can be carried out by extruding a blend of the components for each layer through a slit die to form a thin film. The upper and basal films can then be laminated together through rollers, with the tacky layer protected by a release liner from contact with the rollers.

Alternately, the substances to be delivered (*e.g.*, peppermint oil or other printable material or materials) can be printed onto an extruded pure HPC EF or other similar extruded film, as described in Miranda *et al.* U.S. Patent No. 4,915,950, which is hereby incorporated by reference.

Example III

Two-layer device having a moistenable mucoadhesive layer, and capable of delivering at two different constant rates

An alternative two-layer device according to the invention was made as follows. The upper layer was made by first co-dissolving HPC HF and CPC in IPA in the following proportions: 10 parts HPC EF, 0.135 parts CPC, and 90 parts IPA. The solution was then coated at a thickness of 15 mils onto a polyester release liner, and allowed to dry at room temperature overnight (at least 15 hours). This film formed an upper layer having a dry thickness of 1.5 mils. The basal layer was made by first co-dissolving HPC EF, CPC and IPA in the following proportions: 2 parts HPC HF, 0.0054 parts CPC, and 98 parts IPA. The solution was then coated at a thickness of 50 mils onto a polyester release liner, and dried in an oven at 70 °C for 6 hours. The dry film was then collected and ground to a coarse powder using a mortar and pestle. This powder was then pressed in a heated Carver laboratory press to form a film having a thickness about 2 mils. Then the upper (EF) and basal (HF) films were laminated together and then bonded by compressing in a heated (275 °F) Carver press.

Example IV

Multilayer device providing pulsed release

A multilayer device was made by first co-dissolving poly(vinyl propylene) ("PVP") (K 90), glycerine, methylene blue and IPA in the following proportions: 7.2 parts PVP (90), 2.8 parts glycerine, 90 parts IPA and 0.030 parts methylene blue. The solution was coated onto a polyester release liner at a thickness about 25 mils wet, and then dried at room temperature for 15 hours. The resulting dry film constituted the active

layer material. A second film was prepared by pressing HPC EF powder to a thickness of about 4 mils, using the heated Carver press.

The PVP/glycerin/methylene blue film and the HPC EF film were then arranged in alternating fashion to produce a laminate of six layers, three containing and three not containing the substance to be delivered. The PVP/glycerin/methylene blue layers served as an adhesive to bond the laminate composite, and served as a reservoir for the substance (methylene blue, in this illustrative example) to be released from each layer as it dissolved. The HPC EF layers provided for periods of time between releases, providing the pulsed release profile.

Example V

Delayed-Onset device

A delayed-onset device was made by first blending hydroxypropyl cellulose (HPC LF) and sorbitan monostearate (SPAN 60) as dry powders in a 1:1 ratio by weight. This blend was pressed using a heated Carver press at

200 °F to a thickness of 15 mils. The resulting polymer film was flexible having a waxy, hydrophobic surface.

An adhesive film was made by blending the following components:

HPC MF	1.0 gram
Kollidon PVP (K90)	2.0 grams
Glycerin	2.0 grams

After blending at room temperature, the resulting mixture was pressed in a heated Carver press at 200 °F to a thickness of 10 mils. This adhesive layer was used to adhere the HPC LF:SPAN 60 film to the top layer of the 25 min. breath disc described above in Example II.

The multilayer disc was tested over-night by adhering the disc to the upper palate just prior to going to sleep for the night. There was no noticeable mint flavor initially and during the several minutes thereafter before actually falling asleep. Approximately 5.5 hours later, however, the

disc released a burst of peppermint oil into the mouth strong enough to stimulate and awaken the wearer.

Device for Controlled Release of Substance within a Mucosa-Lined Body Cavity

Any of a variety of devices, in any configuration and for any intended use when emplaced within a body cavity of a subject, are within the scope of the claims. The invention is illustrated below by way of example only; the examples are not intended as limiting the scope of applicants' contribution to the art, and other types and arrangements of devices are within the scope of the invention.

Example VI

Laminated Composite Device for Delivery of Antimicrobial

By way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide delivery of an active substance into the body cavity, Fig. 12 shows generally at **70** a device having a basal water-soluble pressure-sensitive adhesive layer **72**, and an overlying polymer layer **74** containing the active substance **78**. The device is shown removably affixed by the adhesive surface to a release liner **76**.

The adhesive layer can be constructed as follows. An HPC polymer is thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture is formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described below, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams.

The active containing layer can be constructed as follows. Using 85 grams of ethyl alcohol as the solvent, 13.5 grams of hydrohypropyl cellulose (HPC EF) was dissolved with stirring with 1.5 g CPC. The mixture was blended until uniform, at which time the thickened solution was cast as a film onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a heated Carver press to form an active containing layer of 25 mils thickness.

The tack and work of adhesion of the adhesive surface of the device as described in this example, as an indication of its adhesive properties, was measured for three samples as follows.

Sample 1 peak: -0.561 kg; area:-0.0177 kg

Sample 2 peak: -0.420 kg; area:-0.0097 kg

Sample 3 peak: -1.306 kg; area:-0.0352 kg

Example VII

Protective Barrier Device

Additionally by way of example of a device according to the invention that can be affixed to a mucosal surface of a body cavity to provide a protective barrier for the underlying mucosal surface, Fig. 13 shows generally at **80** a device having a basal water-soluble pressure-

sensitive adhesive layer **82**, and an overlying protective layer **84** constructed of a relatively abrasion-resistant water soluble polymer. The device is shown removably affixed by the adhesive surface to a release liner **86**.

In this example, the adhesive layer can have the composition, and can be constructed, as described generally above and particularly, for example, as described for the adhesive layer of Example VI.

The overlying protective layer can be constructed, for example, of a water soluble polymer as would be suitable for an active containing layer for delivery into the body cavity; and the protective layer can be constructed as described generally and particularly above. Particularly suitable polymers include for example HPC HF, polyvinyl alcohol ("PVA"), and hydroxymethyl cellulose.

A device made according to this example can be used, for example, as a temporary covering for an area of injury to the mucosal surface, such as an area of cheek of lip that has been abraded or cut. Or, the device can provide an abrasion preventive for areas of mouth tissue that are subject to abrasion by, for example, orthodontural devices.

Long-Lasting Mucoadhesive Device for Temporary Relief of Sore Throat and Cough

1. Construction of the device

Preparation of a mucoadhesive disc for containing a sore throat medication.

A medication-containing mucoadhesive laminated disc according to the invention can be made by forming and then laminating an adhesive film and an active substance-containing polymer film generally as follows.

a. The adhesive layer. A water-soluble adhesive layer can be formed from an adhesive polymer film, according to the following general protocol. First, the polymer (or polymers) and the plasticizer are thoroughly mixed, using where necessary a suitable solvent such as ethyl alcohol. Where a solvent is used, the resulting mixture is then coated on a release liner, and the solvent is allowed to evaporate to produce a dry film.

Dry film samples are then collected and pressed to the desired final film thickness. Where no solvent is used, the mixture can be pressed to a film of the desired thickness.

b. The active substance-containing layer. First, the polymers and one or more desired active agents and one or more desired flavorants are dissolved, for example by stirring, in an appropriate solvent. Then the resulting thickened solution is formed into a thin (wet) film, for example by casting onto a release liner, and then the solvent is permitted to evaporate to a dry film. Then the dry film is pressed to a desired thickness and is affixed, for example by pressing, onto an adhesive layer prepared as described above.

Hydroxypropyl cellulose (HPC) can be a particularly suitable polymer for construction of the active-containing layer. HPC dissolves completely in aqueous fluids such as the fluids of the oral cavity, and within a selected range of molecular weights, HPC dissolves (or disperses) in the oral cavity sufficiently slowly to provide substantially continuous delivery of the active substance over an extended period. HPC is flexible, so that it conforms well to irregular curved surfaces of the oral cavity; HPC is not tacky when moistened, and has a pleasant texture in the mouth. It is thus comfortable and unobtrusive for the user. HPC blends well with a variety of active substances.

Glycerol, which may be added as a plasticizer in the active-containing layer, may additionally (or alternatively) act to inhibit crystallization of some active substances that might otherwise occur at the loading concentrations employed (for example, menthol).

c. Laminated devices are then cut from the laminated film by, for example, die-cutting, to the desired size and shape. Typically, circular or oval shapes may be preferred. The devices can be stored on a release liner affixed to the adhesive surface, and removed from the liner as needed by the user.

A laminated device according to the invention may be bilaminate, having an adhesive layer and an active-containing layer, as shown for example in transverse sectional view in Fig. 8. Or, the device may be trilaminate, having a third water soluble layer, poorly permeable to the active substance, interposed between the adhesive layer and the active-containing layer, as shown for example in transverse sectional view in Fig 9. This layer may be made of a material such as for example polvinyl acetate ("PVAc") or ethyl cellulose, or such, for example, one of the Eudragit family of polymethacrylic copolymers commercially available from Rohm (*e.g.*, Eudragit S100, L100, E100, L100-55). The Eudragit polymethacrylic copolymers are characterized by being variously soluble at various pH; Eudragit S100 has a suitably low solubility at the typical pH of the normal human saliva. The interposed third layer may where desired be made more flexible by addition of a plasticiser such as, for example, glycerine, in amount up to, for example, about 20 %.

Referring now to Fig. 8, a bilaminate device **50** includes a polymer layer **52** containing the active substance **54**, laminated onto an adhesive layer **56**. The device is shown removably affixed to a release liner **58**.

Referring to Fig. 9, a trilaminate device **60** includes a third polymer layer **72**, poorly permeable to the active substance, laminated between polymer layer **62** containing the active substance **64**, laminated onto an adhesive layer **66**. The device is shown removably affixed to a release liner **68**.

2. Use of the device

As the need for relief of sore throat or cough arises, the user simply peels a laminated device away from the release liner, and affixes it to a surface within the oral cavity. It can be preferred to affix the device to the mucosal surface at the roof of the mouth, as that provides for direct flow of the active substance toward the rear of the mouth and the throat.

The following examples, are intended for illustration only, and are not intended to limit the scope of the invention.

Example VIII

Disc for Delivery of Cineole

The active containing layer was constructed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	1.0 grams
Cineole	1.0 grams
Aspartame	0.3 grams
Menthol	1.7 grams
HPC Klucel LF	16 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in a hood overnight to allow the solvent to evaporate, forming a dried film. The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to form an active containing layer of 25 mils thickness.

The adhesive layer was constructed as follows. An HPC polymer was thoroughly mixed with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and the resulting mixture was formed and pressed to a thickness of 5 mils. For this particular example, the components were mixed in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

This resulting adhesive film was then laminated to the active containing film, described above, to form a bilaminate composite 30 mils thick. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 8.5 milligrams of menthol and 5 milligrams of cineole.

Example IX

Disc for Delivery of Dyclonine HCl

The active containing layer was formed as follows. Using 80 grams of ethyl alcohol as the solvent, the following materials were dissolved with stirring in order of appearance:

Glycerin	2.0 grams
Dyclonine HCl	0.6 grams
Menthol	1.0 grams
Aspartame	0.3 grams
HPC Klucel LF	16.1 grams

The mixture was blended until uniform, at which time the thickened solution was coated to a thickness of 50 mils wet onto a release liner and left in the hood overnight to allow the solvent to evaporate, forming a dried film.

The dried film was pressed using a Carver press under 20,000 p.s.i. at 200 °F for 1 - 2 min., to 25 mils thickness. This pressed film was then laminated to an adhesive film, 5 mils thick, made as described in Example 1, to form a bilaminate composite. Disks having diameter 1/2 inch were then die cut from the bilaminate composite.

Disks formed as described above, 1/2 inch in diameter and 30 mils thick have an active substance-containing layer weighing approximately 100 milligrams. Such a layer (and the disc) therefore contains 5 mg of menthol and 3 mg of Dyclonine HCl.

Example X

Comparison of release of Dyclonine HCl from a mucoadhesive disc and from a Sucrets® lozenge: disc affixed to glass.

The release profile of Dyclonine HCl into water from a prototype mucoadhesive disc according to the invention and from Sucrets® lozenge were compared as follows.

A Sucrets® lozenge containing 3.0 mg Dyclonine HCl was placed in a Pyrex® flask. A laminated disc made as described in Example 2 above, and containing 3.0 mg Dyclonine HCl, was removed from the release liner and affixed to the inner surface of a second Pyrex® flask by pressing the adhesive surface onto the flask wall. 100 ml deionized water at 25 °C were added to the flasks and the contents of the flasks were stirred priodically.

Thereafter sample aliquots of the aqueous phase were removed from each flask at intervals, and analyzed using UV spectroscopy to determine the amount of Dyclonine HCl released.

The resulting release profiles for both the prototype mucoadhesive disc and the Sucrets lozenge are shown in Fig. 10. Fig. 10 shows the cumulative release of Dyclonine HCl into the water. Although both dosage forms initially contained equivalent amounts of Dyclonine HCl (3.0 mg), the disc gives an appreciably extended and more uniform delivery of the Dyclonine HCl.

Example XI

Release of Dyclonine HCl from a mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as follows.

A laminated disc was made generally as described in Example IX above, except that it was die cut to 3/8 inch diameter so that it contained 1.11 mg Dyclonine HCl. The disc was removed from the release liner and affixed to a piece of palate tissue (porcine palate) by pressing the adhesive

surface of the disc onto a surface of the palate tissue. Then the palate tissue with the disc affixed was immersed in deionized water at 25 °C in a flask the contents of the flask were stirred prior to removing the sample.

After 2 hours, the disc was removed from the palate tissue and the disc was returned to the flask and allowed to dissolve completely (with stirring). Then the amount of Dyclonine HCl in the water was measured. The Dyclonine HCl not accounted for was taken to be an amount that had been delivered to the palate tissue. That is, the difference between the amount of Dyclonine HCl initially present in the disc and the amount that was released into the water is the amount released into the mucous tissue. The results are shown in Table I.

Table I

Dyclonine HCl initially in the disc	1.11 mg
Dyclonine HCl released to water	1.04 mg
Dyclonine HCl not accounted for	.07 mg

As Table I shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.07 mg of Dyclonine HCl (5.8 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue.

Example XII

Inhibition of release of Dyclonine HCl from a trilaminate mucoadhesive disc into a mucous surface to which the disc is affixed.

In this Example, a prototype mucoadhesive disc containing Dyclonine HCl according to the invention was constructed with a third layer interposed between the adhesive layer and the active substance-containing layer, for limiting the rate of movement of the active substance into and through the adhesive layer. The trilaminate disc was affixed to mucous tissue and the quantity of Dyclonine HCl released into the mucous tissue over an extended time was determined as described in Example XI.

A laminated disc was made generally as described in Example IX above, except that a thin film (5 mil thickness) of a polymethacrylic copolymer (Eudragit S100) was laminated between the adhesive later and the active substance-containing layer, and the disc was die cut to 3/8 inch diameter so that it contained 1.02 mg Dyclonine HCl. The trilaminate disc was removed from the release liner and affixed to porcine palate tissue, and the release to the palate tissue was determined as described in Example XI. The results are shown in Table II.

Table II

Dyclonine HCl initially in the disc	1.02 mg
Dyclonine HCl released to water	0.98 mg
Dyclonine HCl not accounted for	.04 mg

As Table II shows, after the disc had been affixed to the mucous tissue and suspended in water for 2 hours, only 0.04 mg of Dyclonine HCl (3.9 % of the total amount initially contained in the disc) was unaccounted for in the water, and presumably had diffused into the palate tissue. The interposition of the limiting layer between the Dyclonine HCl-containing layer and the adhesive layer reduced the amount of Dyclonine HCl diffused into the palate tissue from 5.8% to 3.9%.

Example XIII

Comparison of release of Dyclonine HCl through a semipermeable membrane from a trilaminate mucoadhesive disc and from a bilaminate mucoadhesive disc to which the disc is affixed.

In this Example, bilaminate and trilaminate mucoadhesive discs containing Dyclonine HCl according to the invention were constructed generally as described in examples XI and XII. The discs were affixed to a semipermeable membrane, and the quantity of Dyclonine HCl released through the membrane over an extended time was determined as described in Example 4. Briefly, the disc (1/2 inch diameter) was placed in a horizontal Franz cell (7.5 ml capacity) separated by a mesh barrier (70 μm Teflon), by

affixing an adhesive surface of the disc onto the mesh barrier. Both sides of the cell were filled with nano-filtered water; water in the "donor" side of the cell bathed the surface of the active layer, and water in the "receiver" side of the cell bathed the mesh barrier. The results are shown in Table III.

Table III

	Sample	Dyclonine Release
Bilaminate disc	1	9.65 %
Bilaminate disc	2	10.91 %
Bilaminate disc	3	8.82 %
	Mean	9.79 ± 1.05 %
Trilaminate disc	1	1.45 %
Trilaminate disc	2	1.43 %
Trilaminate disc	3	0.30 %
	Mean, Samples 1 & 2	1.44 ± 0.014 %

As Table III shows, the total quantity of Dyclonine passing from the active-containing layer into and through the adhesive layer and then through the semipermeable membrane was greatly reduced by interposition of the occlusive layer between the adhesive layer and the active-containing layer. Particularly, in three experiments for each disc type (bilaminate and trilaminate) shows an average decrease in the release of Dyclonine HCl into the receiver side, from 9.79 ± 1.05 % to 1.44 ± 0.014 %, after a period of two hours.

Example XIV

Release of benzocaine into distilled water from a mucoadhesive disc according to the invention: effect of different molecular weight of polymer in the benzocaine-containing layer.

In this Example, bilaminate mucoadhesive discs containing benzocaine were constructed generally as described in Example IX, substituting benzocaine for Dyclonine. Discs were made using HPC both at the same molecular weight as described in Example 2 (80 k), and at a higher molecular weight (300 k), and the release into distilled water was tested as described in Example X. The results are shown in Fig. 11. These results show a decrease in release rate of benzocaine with increasing molecular weight of HPC in the active-containing layer.

Example XV

Transport of Dyclonine HCl and of benzocaine through pig mucosa.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to porcine buccal mucosa and mounted on Franz diffusion cells as described in Example XIII. Average amounts of active substance was measured using HPLC, and percents were expressed as a percent of the total initially in the disc.

Particularly, the donor side of the cell was filled with pH 6 buffer and the receiver side was filled with phosphate buffered saline ("PBS"). Samples were taken from the receiver side every thirty minutes for three hours, and the samples were analyzed by HPLC. The average amount and the average percent of active substance appearing in the receiver side after three hours are shown in Table IV.

Table IV

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	284.63	3.29
15 % Dyclonine HCl	282.77	3.94

The average amount delivered reflects the cumulative amount of drug transported through the mucosa over the three hour period. The average percent delivered represents the cumulative amount of drug transported, in terms of percent of drug contained in the device at the outset. The data show that very low values of benzocaine or Dyclonine HCl were transported through the tissue, and demonstrate that such devices, placed within a mucosa-lined body cavity, such as the oral cavity, can be expected to deliver relatively little of such active substances through the mucosa during the period that the active substance is administered into the body cavity itself.

Example XVI

Transport of Dyclonine HCl and of benzocaine through human stratum corneum.

In this example, bilaminate mucoadhesive discs, containing as an active substance benzocaine or Dyclonine HCl, were affixed to human stratum corneum and mounted on Franz diffusion cells. The donor side of the cell was filled with pH 6 buffer and the receiver side was filled with PBS. Samples were taken from the receiver side and analyzed using HPLC, and the average amount and percentage of active substance appearing in the receiver cell were determined. The average amount and the average percent of active substance appearing in the receiver side are shown in Table V.

For both benzocaine and Dyclonine HCl the amount of active substance delivered through the human stratum corneum (Example XVI) is lower than the amount of active substance delivered through the pig buccal mucosa (Example XV). For administration of Dyclonine HCl or benzocaine

into the oral cavity of a human subject, so that the active substance is carried by the saliva to the irritated tissues of the mouth and throat, it is desirable to limit the amount of active substance delivered through the oral mucosal surface to which the device is affixed. Preferably a device for delivery of active substances for relief of cough and sore throat is affixed to the palate. The transfer coefficient for human palate tissue is lower than that for pig buccal mucosa and higher than that for human stratum corneum, and Examples XV and XVI thus provide an approximate range within which the extent to which delivery of active substances across the underlying human palate mucosa can be expected to fall. For a device according to the invention, affixed to the palate, the great majority of benzocaine or Dyclonine HCl can be expected to be delivered into the oral cavity.

Table V

	Average Amount Delivered ($\mu g/cm^2$)	Average % Transported
15 % Benzocaine	255.56	2.42
15 % Dyclonine HCl	14.60	0.18

Interposition of a third layer, relatively impermeable to the active agent, between the active agent-containing layer and the adhesive layer, as described for example in Example XII, can reduce further the quantity of active agent passing through the mucosa. As the results in Examples XV and XVI show, however, a bilaminate system can be suitable for delivery.

Long-Lasting Mucoadhesive Device for Administration of Breath-Freshening Agent

Generally, the breath freshening device according to the invention is constructed as a laminated composite including a basal adhesive layer constructed of a water soluble pressure sensitive mucoadhesive composition; and an odorant containing layer constructed of a water soluble polymer

mixed with the odorant. Optionally the device may include a third layer, interposed between the adhesive layer and the odorant containing layer, constructed of a water soluble polymer that is substantially impermeable or is poorly permeable to the constituents of the odorant.

The device may be made by forming the respective layers as films and then laminating the films, and finally cutting (as, for example, by die cutting) the device from the laminate.

The films may be made from polymer mixtures by any of a variety of techniques known in the polymer film-forming art, including casting, calendaring, coating, and extrusion. Batch processing techniques may be employed, but for large scale production, continuous processing can be preferred. Die extrusion through a slit is a particularly suitable continuous processing technique for making the films for use in the devices according to the invention.

Lamination may be carried out by contacting the films and applying pressure. Laminated films may be made in small quantities by use of a press, but for continuous processing the films can be pressed together using one or more rollers. Heat may be applied to the films as they are brought together, for example by heating the press or by heating the roller or rollers.

Referring again now to Fig. 8, a bilaminate device configuration according to the invention suitable for a breath freshening device is shown generally at **50**. The device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**.

A trilaminate device configuration suitable for a breath freshening device is shown generally at **60** in Fig. 9. The trilaminate device includes a basal adhesive layer **56** constructed of a water soluble pressure sensitive mucoadhesive composition, and an upper odorant containing layer **52** constructed of a water soluble polymer mixed with the odorant **54**, generally

as in the bilaminate device shown in Fig. 8. The trilaminate device additionally includes a third layer **62**, interposed between layer **52** and layer **56**, constructed of a water soluble polymer that is substantially impermeable or poorly permeable to the constituents of the odorant.

The devices as shown in the Figs. are provided with a release liner **58**, which is peeled away from the device just prior to use.

The content of the layers is described in greater detail below.

1. The adhesive layer.

Suitable GRAS certified polymers for use in the water soluble pressure sensitive mucoadhesives include poly(vinyl pyrrolidone) ("PVP"), poly(vinyl alcohol) ("PVA"), hydroxy propyl cellulose ("HPC"), poly(ethylene oxide) ("PEO"), poly(acrylic acid) ("PAA"), polyacrylates such as Carbopol 934, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose ("Na-CMC"), xanthan gum, karaya gum, and gelatin, among others. Suitable plasticizers include, for example and particularly for oral-mucosal contact and other use in the oral cavity, glycerin, sorbitol, any of the glycols, polysorbate 80, triethyl citrate, acetyl triethyl citrate, and tributyl citrate.

In particular embodiments the water soluble pressure sensitive mucoadhesive includes as a polymer PVP (about 30 - 60 weight %), HPC (about 10 - 30 weight %); and glycerin as a plasticizer (about 10 - 60 weight %). In these formulations, the molecular weight of the PVP is in the range about 30,000 - 1,000,000; and the molecular weight of the HPC is in the range about 60,000 - 1,000,000. Such compositions adhere quickly on contact and without moistening to oral mucosal surfaces and to oral cavity prostheses or other devices of the poly(methyl methacrylate) ("PMMA") type, and continue to adhere well to such surfaces for extended times in the milieu of the oral cavity.

The water soluble pressure sensitive adhesive layer may take the form of a film which preferably is about 5-10 mils thick.

Preferably the adhesive layer additionally includes a preservative, such as for example BHA or BHT, in a suitable small quantity. The adhesive additionally may include a certified colorant.

2. The odorant-containing layer.

Suitable GRAS certified polymers for use in the odorant containing layer include, particularly, hydroxypropyl cellulose ("HPC").

The term "odorant", as used herein, refers to a substance or combination of substances which, when present in the fluids of a subject's oral cavity, impart a pleasing smell to the person's exhalant breath. A breath freshening substance may work in part by addition of a desirable odor to the breath, and in part as a "reodorant", that is, by masking an unpleasant odor in the subject's breath, and the term "odorant" herein includes such reodorant effects.

As is well recognized in the flavorist's art, the appreciation of flavor is a complex response, principally, to the senses of aroma and taste. *See generally, e.g.*, G. Reiniccius, ed. (1994), *Source Book of Flavors*, 2d Ed., Chapman & Hall (herein, the "*Source Book of Flavors*"). The various tastes (sweet, salt, sour, bitter) are due to nonvolatile components of the flavor, while the aroma or odor is due to volatile components. The chemical makeup of a flavor, and particularly of the volatile components of a flavor, may be exceedingly complex, with a number of volatile components contributing significantly to the distinctive aroma. On the other hand, certain chemical compounds are by themselves when smelled reminiscent of a particular flavor, even where the flavor that is recalled is in fact complex. Such character impact compounds include, for example, Menthol (having the character impact of peppermint); L-Carvone (spearmint); Methyl salicylate (wintergreen); and Citral (lemon).

A straightforward way to provide desired odorant in the odorant-containing layer of a breath freshening device according to the invention is to add to the polymer of the layer an essential oil (*i.e.*, a volatile oil) of a plant material. The *Source Book of Flavors* describes essential oils that are

in common use in the flavoring industry, including descriptions of methods for their industrial production and an account of their chemistry.

Any of a variety of breath freshening odorants may be delivered to the oral cavity by adding into the polymer of the odorant-containing layer a flavoring that includes the odorant. In at least some cultures, mint-like odorants are acceptable and even desireable on the breath, and accordingly the odorant containing layer of a suitable breath freshening device can include a mint flavoring, as described more fully below.

Preferably the odorant containing layer additionally includes a preservative, such as for example BHA or BHT in a suitable small quantity. Optionally the odorant containing layer additionally includes a sweetener, most preferably a non-sugar sweetener, such as aspartame in a suitable small quantity.

3. Mint odorants.

Mint odorants can be provided by essential oils derived by extraction and distillation from leaves and/or flowering parts of any of various plants. The composition of such distillates depends, among other things, upon the species and variety of plant, as well as its geographical origin, and upon the method of extraction and degree of distillation. A variety of mint flavorings are described, for example in the *Source Book of Flavors*. They include, particularly for example, oil of peppermint, the chief aromatic constituents of which are menthol, menthone, and menthyl acetate; oil of spearmint, the chief aromatic constituent of which is L-Carvone; and oil of wintergreen, the chief aromatic constituent of which is Methyl salicylate.

4. Device fabrication.

As pointed out generally above, the layers can be produced using techniques known in the art of polymer film fabrication, by conventional batch process or by continuous process, as for example by conventional die extrusion through a slit. Typically, for example, batch processing can be carried out as follows. The components making up each layer (*e.g.*, the

adhesive layer, or the odorant containing layer, or an intermediate layer) are blended together either with a suitable solvent to aid in mixing or, as may be more preferable, without a solvent. The blending may be carried out at an elevated temperature (particularly where no solvent is employed), to aid in homogeneous mixing of the components. The blended components of each layer are thereafter pressed to a film having the desired final layer thickness using a heated Carver press. The resulting films are then laminated, for example by contacting them and applying pressure.

Generally, for example, a conventional continuous die extrusion process entails feeding the components of the layer to an extruder, such as a twin screw extruder. The extruder melt blends the components of the layer and then forces the blended mixture continuously through a slit whose thickness is selected to provide the desired thickness in the resulting film. The individual films may be rolled for temporary storage before lamination, or the lamination may be carried out immediately following extrusion. The films are containuously laminated by bringing the films into contact and pressing them together over a roller or between rollers, which may as appropriate be heated to facilitate the lamination process.

Individual devices are then cut from the completed laminate, for example by punching or die cutting, and stored for use.

The examples that follow are presented by way of illustration only, and are not meant as limiting the invention.

Example XVII

Construction of Device for Delivery of Peppermint

This example illustrates the construction of a device for delivery of a refined (reduced) oil of peppermint. The oil of peppermint used in this example is a "Reduced Oil of Peppermint FCC/NF "Rose Mitcham" ", which is commercially available from the A.M. Todd Company of Kalamazoo, MI. It contains the following mint flavor components:

menthofuran (GLC)	02.6 %
menthol	57.0
menthone	24.8
menthyl acetate	07.4

As provided from the commercial source, this reduced oil of peppermint has a specific gravity .903, an optical rotation -28.2, and a refractive index 1.4600. It is soluble in three volumes of 70 % ethanol.

1. Construction of the odorant containing layer.

In this example, the odorant containing layer is constructed by thoroughly mixing the peppermint oil (as described above), a non-sugar sweetener (Aspartame), and a preservative (BHA) with a hydroxypropyl cellulose ("HPC") polymer, and then extruding the odorant containing polymer mixture through a slit to form a film. Preferably a twin screw extruder is employed, and the components are continuously fed into the extruder, in which the blending is effected. In this particular example, the odorant containing layer has these ingredients in the following proportions.

Klucel HPC GF	83.5 %
Peppermint oil	15.0
Aspartame	1.50
BHA	0.0083

2. Construction of the adhesive layer.

In this example, the adhesive layer is constructed by thoroughly mixing an HPC polymer with a poly vinylpyrrolidone ("PVP") polymer, with glycerol as a plasticizer, with a food colorant, and with a preservative (BHA), and then extruding the adhesive polymer mixture through a slit to form a film. In this particular example, the adhesive layer has these ingredients in the following proportions.

PVP (K90)	47.0 %
Glycerin	37.0
Klucel HPC GF	16.0
FD & C #40	0.024
BHA	0.0020

The formed adhesive film and odorant containing film are then laminated by passing the films together between rollers under pressure, and the individual devices are die cut from the resulting laminated composite.

Example XVIII

Tack and Adhesion Properties of the Adhesive Layer

The properties of tack and adhesion of the water soluble pressure sensitive mucoadhesive employed in the breath freshening device of the invention were tested as follows.

An adhesive film was made generally as described in Example XVII.

Tack and work of adhesion were measured using a Texture Technologies TXA.XT2 Texture Analyzer in which a PMMA probe was used in place of the usual SS probe. A 5 mil thick adhesive film made as described in Example XVII was tested under the following conditions.

Probe speed (penetration):	1.0 mm/sec
Penetration depth:	0.10 mm
Dwell time:	10 sec
Probe speed (withdrawal)	5.0 mm/sec
Probe diameter:	0.80 cm

All measurements were made at room tepmerature (20 - 25 °C).

The resulting trace of the force during withdrawal versus time allowed for a determination for each sample of both the tack (the peak maximum, in Kg) as well as the work of adhesion (area under the peak curve, in Kg-sec). Films were tested dry as well as after moistening by

spraying the dry film surface with a fine mist of distilled water, followed by a resting time of 60 seconds to allow for hydration of the sample.

In this example, the above test protocol was applied to films according to the invention (indicated as "BFD" in the Figs.), and to constructed with the following compositions.

"279-190": 60 % PEO 301; 30 % HPC MF; 5 % PE; 3 % PG; 2 % PEG 400 (described in Schiraldi U.S. 4,731,243).

"279-191": 55.3 % NaPAA; 37.5 % HPC HF; 6.3 % Glycerin (described in Chang U.S. 4,373,036).

"310-30B#2": 40 % HPC HF; 35.5 % PVP 90 F; 20 % HPC LF; 2 % Mentha Oil; 2 % Menthol; 0.5 % Fennel Oil (described in Hisahige JP 63-209797).

"310-44" 44.5 % PVP 90 F; 30 % HPC LF; 10 % HPC HF; 10 % PEG 400; 2.5 % Menthol; 2.0 % Mentha Oil; 1.0 % Fennel Oil (described in Hisahige JP 63-209797).

The results are shown in Figs. 14 and 15. In these tests the adhesive film according to the invention is significantly more adhesive toward the PMMA probe in the dry state (*i.e.*, before moistening) than did four other formulations tested. Following moistening the adhesive film according to the invention was comparably adhesive or was more adhesive toward the PMMA probe than were the other tested formulations.

Example XIX

Flexibility of Odorant Containing Layer

As noted above, water soluble polymers such a hydroxypropyl cellulose that dissolve suitably slowly in the milieu of the oral cavity may not themselves be sufficiently flexible for use in an odorant containing layer in a device according to the invention. Conventionally, the layer would be rendered more flexible by addition of a suitable plasticizer such as glycerol. We have discovered that the essential oils of Spearmint, or Peppermint, and

of Wintergreen can provide substantial and sufficient plasticizing effect when mixed with HPC in quantities suitable for extended delivery of mint odorant to the oral cavity at breath freshening rates.

In this example, the elastic moduli (as a measure of flexibility) are compared for film preparations of HPC containing no additional components, and of film preparations containing 15 weight % of oil of peppermint, oil of spearmint, oil of wintergreen, and oil of lemon. This conventional measurement entails measuring the tensile force per unit cross sectional area (stress) of a sample of the film during elongation of the sample at a fixed rate (strain). The elastic modulus is derived from the stress/strain curve. In this example, the test was carried out on bone-shaped film samples 5 mils thick and 0.25 inch wide, gage length 1.0 inch, at an elongation rate of 0.2 inch/min. All samples were tested at room temperature (20 - 25 °C).

The results are shown in Fig. 16. As the Fig. shows, addition of any of the mint odorants to the HPC composition results in a substantially and sufficiently flexible film, while addition of lemon oil does not sufficiently lower the elastic modulus of the film. Thus, where a mint odorant is used, no additional plasticizer is required in the odorant containing layer.

Example XX

Delivery of Peppermint over Extended Times

In this example, the capacity for delivering a breath-freshening substance into an aqueous medium was compared in devices according to the invention and in a "breath mint" that is commercially marketed under the name "Certs®". A flavor containing film was constructed, generally as described in Example XVII. Portions of the film 1/2 inch in diameter and 25 mils thick, each containing 8.6 mg menthol were immersed in distilled water, and breath mint tablets each containing 4.3 mg menthol were immersed in distilled water in separate flasks, and the flasks were continuously shaken. Samples were withdrawn from the flasks after elapsed

times of 15 min., 30 min., 45 min., 60 min., and 120 min., and the quantity of menthol was analyzed by gas chromatography.

The results are shown in Fig. 17. On average, the breath freshening device of the invention had by the first (fifteen minute) sample interval released about 0.7 mg menthol, and thereafter the device delivered menthol at a continuous steady rate throughout the sampling period; at the two hour sampling interval, approximately 2.0 mg of the original 8.6 mg of menthol had been released from the device, and rate of delivery was continuing at slightly less than 0.25 mg per hour. By contrast, each breath mint had on average by the first sampling interval released nearly half its total quantity of menthol, and had nearly exhausted their delivery capacity at the second (thirty minute) sampling interval.

In a person's mouth, the saliva is swallowed more or less continuously, and once a conventional breath mint has been completely dissolved, the breath freshening effect wanes quickly as the residual odorant is flushed away. As the example shows, the invention can provide for a sustained and steady supply of the breath freshening odorant to the saliva flow, resulting in an extended breath freshening effect.

Example XXI

Evaluation of Breath-Freshening Effect

In this example, the breath freshening effectiveness of devices according to the invention, constructed generally as described in Example XVII above, were informally evaluated by volunteers. The volunteers reported that the device was convenient to use, was non-obtrusive, did not materially interfere with speech, and left a pleasant taste and odor in the mouth.

Other Embodiments

Other embodiments are within the following claims.

For example, the water-soluble pressure-sensitive adhesives according to the invention can be used to affix transdermal devices to human skin.

Because the materials in the adhesive are GRAS certified, they can result in an adhesive product having very low skin irritation and reaction.

The water-soluble pressure-sensitive adhesives of the invention can act as a reservoir for diffusional delivery of a substance into the mucosa-lined body cavity (such as the oral cavity or gastrointestinal tract, or the vaginal cavity), or for delivery of a substance transmucosally through the area of adhesive contact. Preferably for such applications, the adhesive is provided in film form, and is loaded with a suitable quantity of the substance to be delivered. For use in transmucosal delivery, one surface of the adhesive film makes adhesive contact with the mucosal surface; preferably the other surface of the adhesive film is covered with a substance-occlusive backing layer made of a material that is poorly soluble in water or in the fluid secretions of the body cavity in which the film is used. Examples of substance-occlusive poorly soluble materials that are safe for oral use include poly(dimethyl siloxane), poly(tetrafluoro ethylene), cellulose acetate, and copolymers of neutral methacrylic acid esters with one or both of methacrylic acid and diethylaminoethyl methacrylate.

In a dental prosthesis adhesive film application, for example, the adhesive can be loaded with a flavoring or a mouth deodorant to act as a breath freshener, or with an antibacterial. Suitable flavorings, mouth deodorants, and antibacterials are known in the oral hygiene art. As the adhesive slowly dissolves, the agent is gradually released into the oral cavity.

Or, in a dental prosthesis adhesive film application, the adhesive can be loaded with a substance to be delivered transmucosally; in this configuration, the dental prosthesis works as an occlusive backing.

The water-soluble pressure-sensitive adhesives of the invention can be employed as an adhesive layer in a laminated device for diffusional delivery of an agent within a mucosa-lined body cavity. Such laminated devices can take any of a variety of forms, and may have just one layer in addition to

the adhesive (such as the substance-occlusive poorly soluble layer described above, for example), or many additional layers.

Water-soluble pressure-sensitive adhesive films according to the invention can be made by other processes than described above. Where a press is used to form the film, for example, different temperatures may be used, according to the particular polymer composition.

Alternatively, the molten polymer may be extruded through a slit die to form a film of the desired thickness; or it can be extruded or cast as a single film between release surfaces. In the latter case, the product can be cut to a shape appropriate to the particular application, and the release liners can be peeled away just prior to use.

Other embodiments are within the following claims, and variations on the embodiments shown by way of example above have been made and can be altered as may be desired. For example, with reference to Examples 1 and 2, aspartame can be left out and a flavor imparting a different taste or odor can be added instead. Also, the loading of actives dyclonine HCl, menthol, and cineole can be controlled by either varying the concentration or changing the thickness of the disc. Other active substances useful for relief of sore throat pain or cough can be delivered according to the invention.

Claims

1. A water-soluble pressure-sensitive adhesive comprising a water-soluble polymer and a water-soluble plasticizer, said polymer having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than
80 °C.

2. The water-soluble pressure sensitive adhesive of claim 1 wherein said polymer has a T(g) or a T(m) greater than about 30 °C.

3. The water-soluble pressure-sensitive adhesive of claim 1, said polymer comprising poly(vinyl pyrrolidone) and said plasticizer comprising glycerol.

4. The water-soluble pressure-sensitive adhesive of claim 3, said polymer further comprising hydroxy propyl cellulose.

5. The water-soluble pressure-sensitive adhesive of claim 3, comprising 95 - 40 weight % poly(vinyl pyrrolidone), 0 - 50 weight % hydroxy propyl cellulose, and 11 - 60 weight % glycerol.

6. The water-soluble pressure-sensitive adhesive of claim 5, said glycerol being present in the range 30 - 50 weight %.

7. The water-soluble pressure-sensitive adhesive of claim 1, in film form.

8. A dental prosthesis adhesive, comprising the water-soluble pressure-sensitive adhesive film of claim 7, shaped to conform to a portion of the mucosal surface-contacting surface of the dental prosthesis.

9. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer; and

a water-soluble polymer layer;

wherein the substance is dissolved or dispersed in either or both of said adhesive or polymer layers.

10. The device of claim 9 wherein delivery of the substance is characterized by a delayed onset.

11. The device of claim 10 wherein the polymer layer is substantially impermeable to the substance and does not contain the substance.

12. The laminated device of claim 11, said polymer layer being insoluble in water that is below 40 °C.

13. The laminated device of claim 12, said polymer layer comprising hydroxypropyl cellulose and sorbitan monostearate.

14. The device of claim 13 wherein the substance is a breath reodorant.

15. The device of claim 9 wherein the adhesive layer comprises and an adhesive selected from the group consisting of a pressure-sensitive adhesive and a moistenable adhesive.

16. The device of claim 15 wherein the adhesive comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

17. The device of claim 9 comprising one or more polymer layers and two or more substances to be delivered.

18. The device of claim 17 wherein the substances are delivered sequentially.

19. A laminated device for the controlled release of a substance within a mucosa-lined body cavity, said device comprising:

a water-soluble adhesive layer;

a first water-soluble polymer layer; and

a second water-soluble polymer layer;

wherein the substance is dissolved or dispersed in any or all of said adhesive or polymer layers.

20. The device of claim 19 wherein the adhesive layer and the second polymer layer contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer, and wherein the device provides for pulsatile delivery of the substance.

21. The device of claim 20 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

22. The device of claim 19 further comprising a third polymer layer wherein the first and the third polymer layers contain the substance and wherein the first polymer layer is disposed between the adhesive layer and the second polymer layer and the second polymer layer is disposed between the first polymer layer and the third polymer layer and wherein the device provides for pulsatile delivery of the substance.

23. The device of claim 22 wherein the pulsatile delivery is characterized by periods of no delivery of the substance.

24. A laminated device for the controlled release of a substance within a mucosa-lined body cavity comprising the substance dissolved or dispersed in a water-soluble pressure-sensitive adhesive layer.

25. The device of claim 24 wherein the water-soluble adhesive layer comprises a pressure-sensitive polymer adhesive having a T(g) or a T(m) greater than about 25 °C and having a hydrophilicity greater than about 25 %, said plasticizer being miscible with said polymer at room temperature and being liquid at room temperature and having a boiling point higher than 80 °C.

26. A laminated composite device for delivering a substance into the oral cavity for relief of sore throat or cough, comprising a water soluble polymer film layer containing the active ingredient, and a water soluble pressure sensitive mucoadhesive layer.

27. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of sore throat pain.

28. The laminated composite of claim 27 wherein the active ingredient is selected from the group consisting of benzocaine, lidocaine and dyclonine.

29. The laminated composite of claim 26 wherein the active ingredient is a medicament for the relief of cough.

30. The laminated composite of claim 29 wherein the active ingredient is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate, menthol.

31. The laminated composite of claim 27 additionally comprising a medicament for the relief of cough.

32. The laminated composite of claim 26 wherein the active-containing water soluble layer comprises a hydrophobic material that will not dissolve in water below 40°C and is hot water dispersible.

33. The laminated composite of claim 32 wherein the active-containingwater soluble layer is selected from the group of materials consisting of monoglycerides, triglycerides, waxes, fatty acids, fatty alcohols and mixtures thereof.

34. The laminated composite of claim 26 wherein the pressure sensitive adhesive is comprised of a water soluble polymer with a glass transition temperature above about 25°C and a hydrophilicity greater than about 25%, and a plasticizer that is liquid at room temperature and has a boiling point higher than about 80°C.

35. The laminated composite of claim 34 wherein the polymer is selected from the group consisting of poly(vinyl pyrrolidone), poly(vinyl alcohol), hydroxy propyl cellulose, poly(ethylene oxide), poly(acrylic acid), polyacrylates, starch and starch derivatives, polysaccharides, sodium carboxymethyl cellulose, xanthan gum, karaya gum, and gelatin or mixtures thereof.

36. The laminated composite of claim 34 wherein the plasticizer is selected from the group consisting of glycerin, sorbitol, glycol, polysorbate 80, triethyl citrate, acetyl triethyl citrate and tributyl citrate.

37. The laminated composite of claim 26 further including a third polymer layer interposed between the adhesive layer and the active-containing layer.

38. A method for administering a substance over an extended time period for relief of sore throat or cough, comprising dissolving or dispersing the substance in a laminated water soluble device having a water soluble pressure sensitive adhesive layer, and affixing the device onto a mucosal surface of the oral cavity.

39. The method of claim 38 wherein the substance is a medicament for the relief of sore throat pain.

40. The method of claim 39 wherein the medicament is selected from the group consisting of benzocaine, lidocaine and dyclonine.

41. The method of claim 38 wherein the substance is a medicament for the relief of cough.

42. The method of claim 41 wherein the medicament is selected from the group consisting of dextromethorphan HBR, noscpine, codeine phosphate.

43. The method of claim 42 additionally comprising a medicament for the relief of cough.

44. A device for emplacement within a mucosa-lined body cavity of a subject, said device including a portion made of a water-soluble pressure sensitive mucoadhesive composition, said water-soluble pressure sensitive adhesive portion having a surface that forms a basal pressure-sensitive adhesive surface of said device.

45. The device of claim 44, being a device for delivery of a substance to the subject.

46. The delivery device of claim 45, said device being constructed to deliver a substance into the body cavity in which the device is emplaced.

47. The delivery device of claim 45, said device being constructed to deliver a substance across a mucosal surface to which the basal pressure-sensitive adhesive surface of the device is affixed.

48. The device of claim 44, being a laminated device structure, wherein the water-soluble pressure sensitive portion comprises a basal layer of the device.

49. A laminated device for administering a mint aroma into the oral cavity over an extended time, said device including a basal layer comprising a water soluble pressure sensitive mucoadhesive polymer composition, and an upper layer comprising a water soluble polymer composition and a mint flavoring.

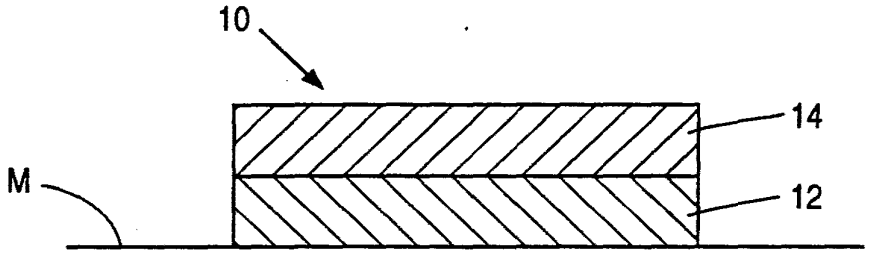

FIG. 1

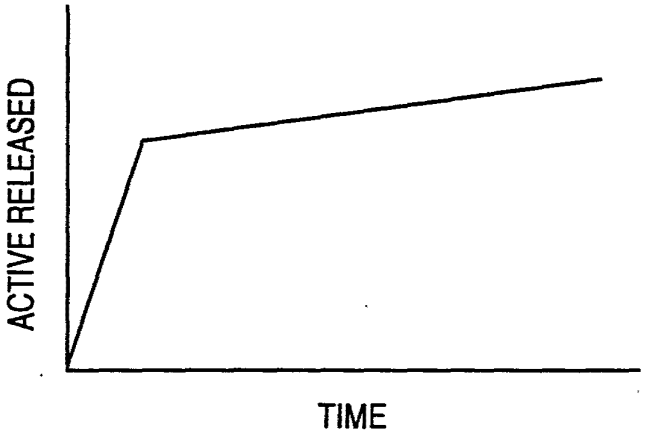

FIG. 5

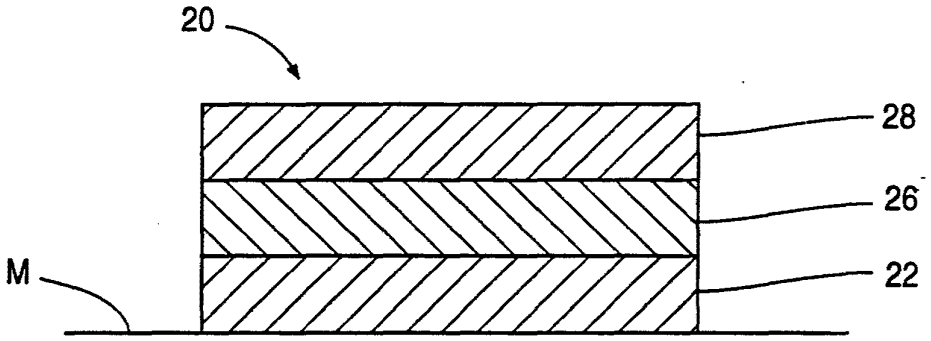

FIG. 2

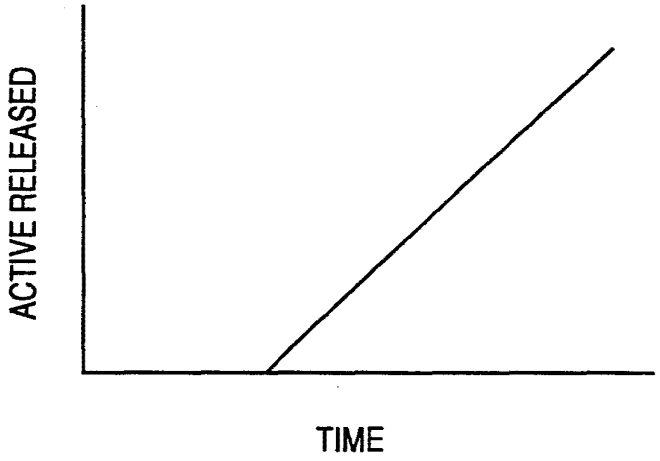

FIG. 6

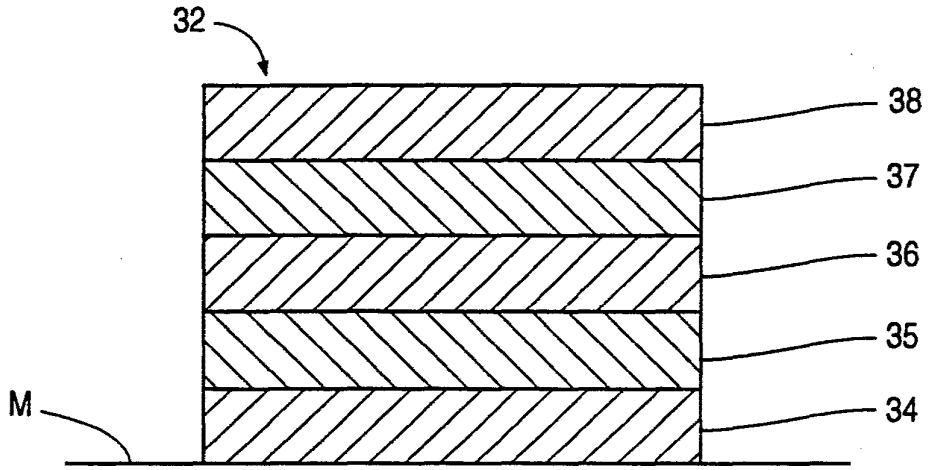

FIG. 3

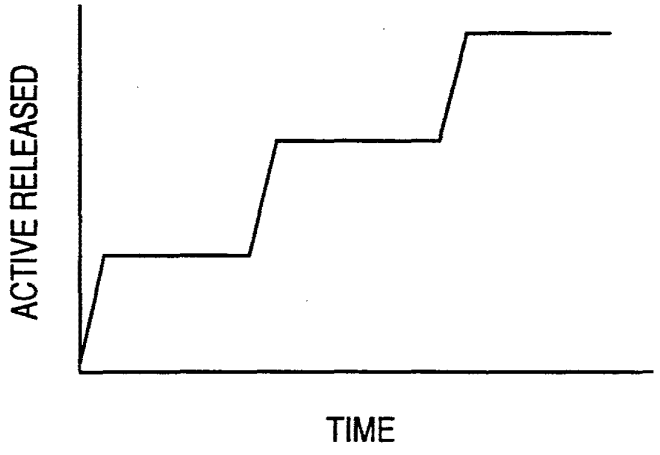

FIG. 7

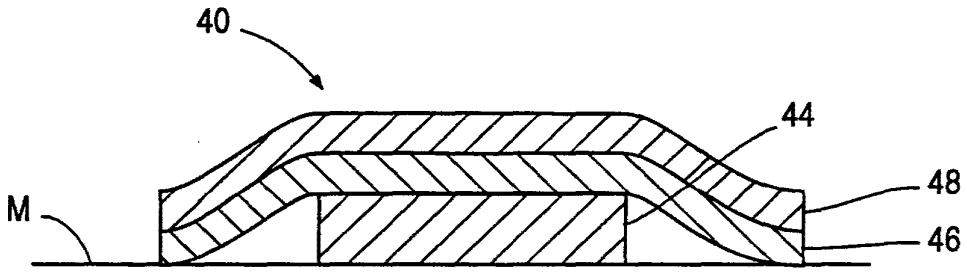

FIG. 4

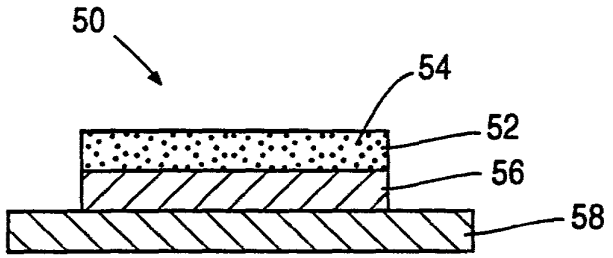

FIG. 8

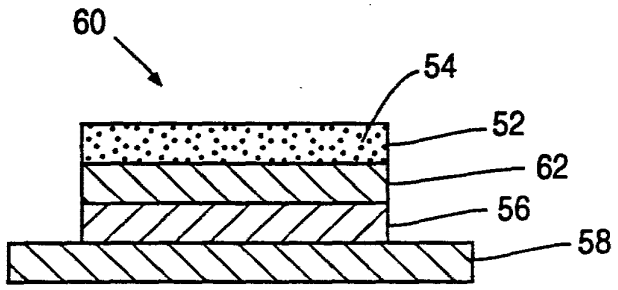

FIG. 9

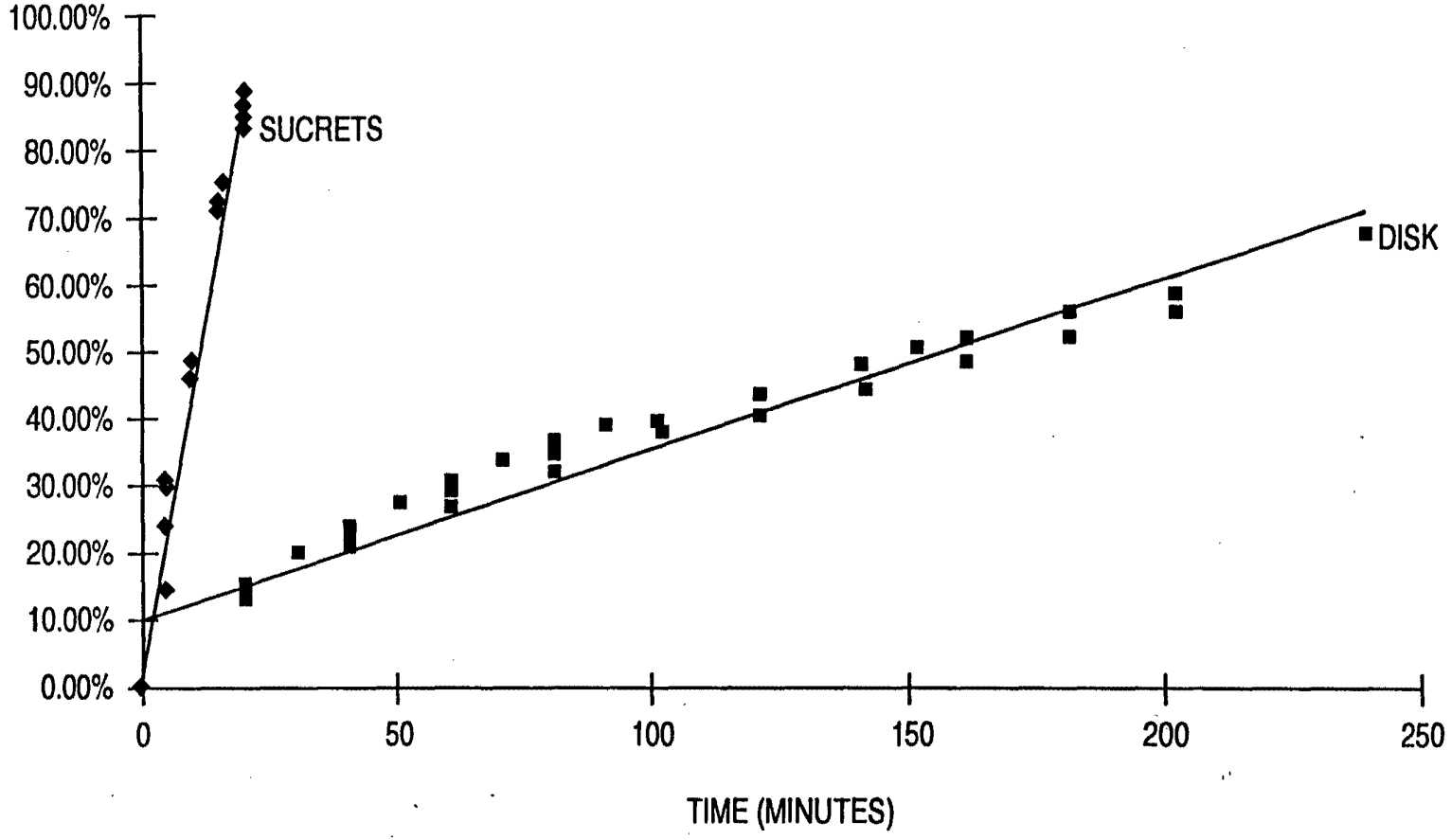

FIG. 10

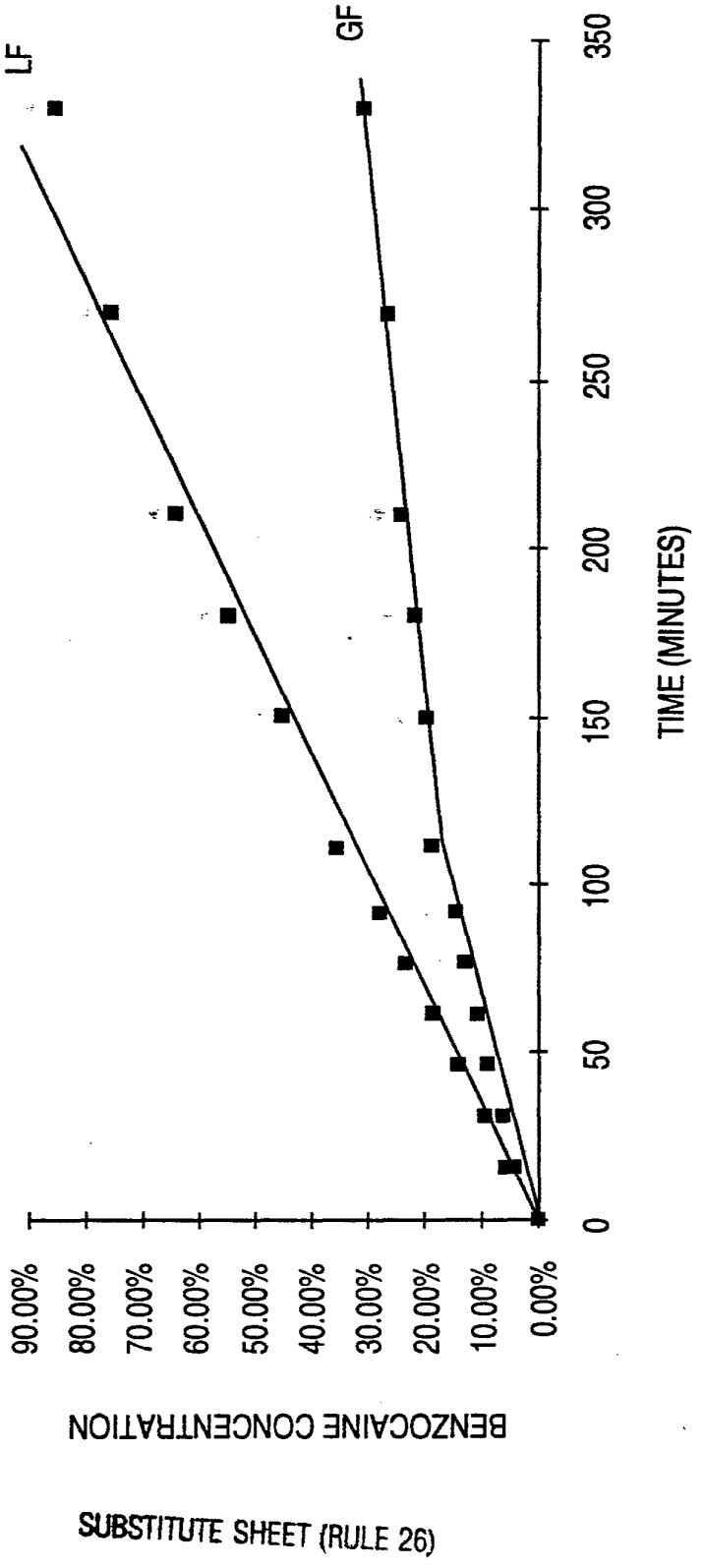

FIG. 11

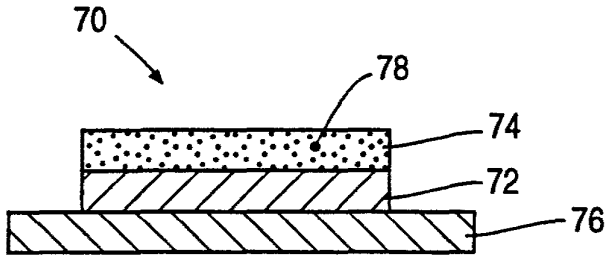

FIG. 12

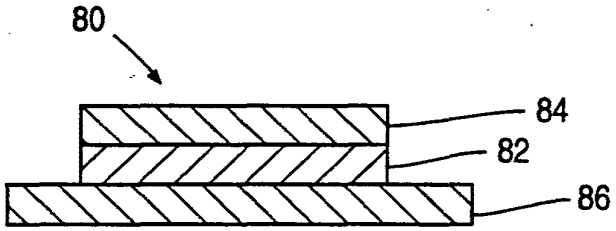

FIG. 13

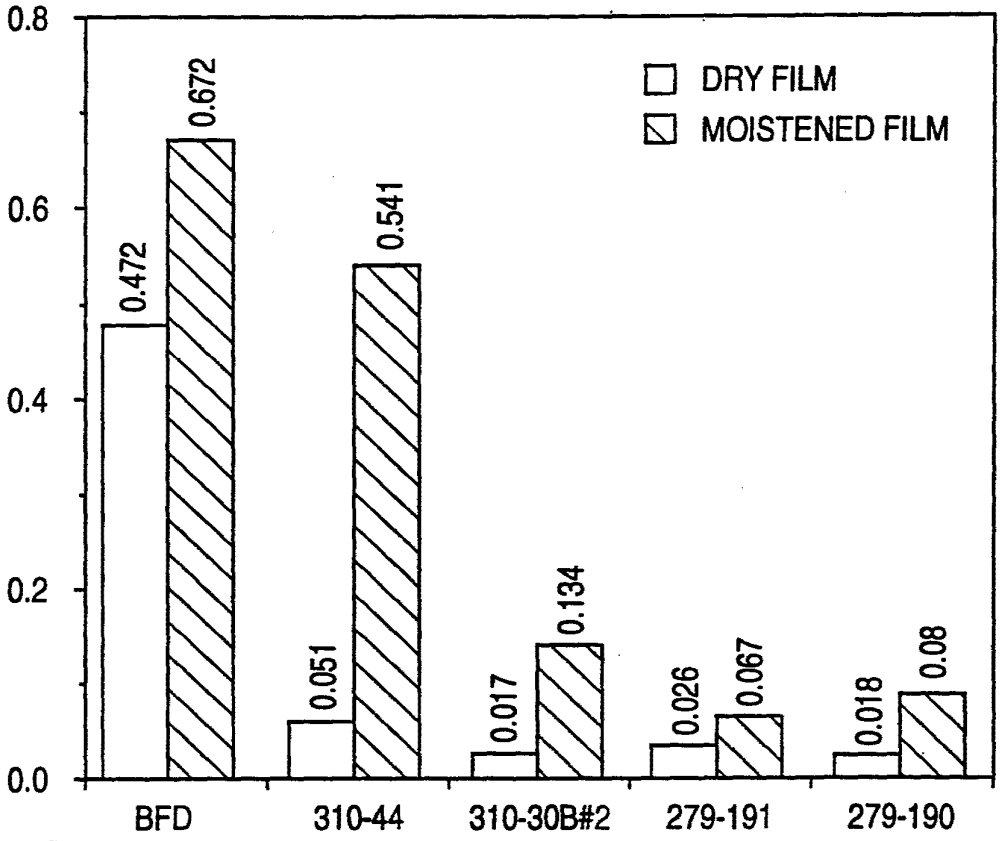

FIG. 14

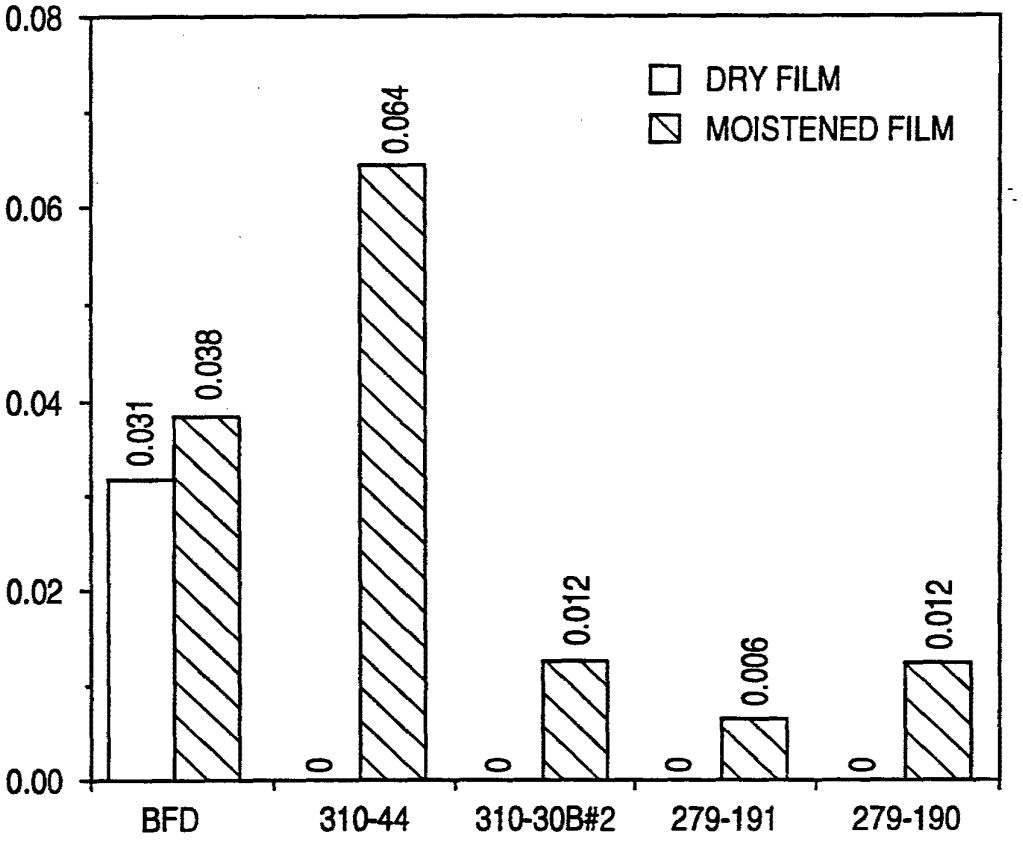

FIG. 15

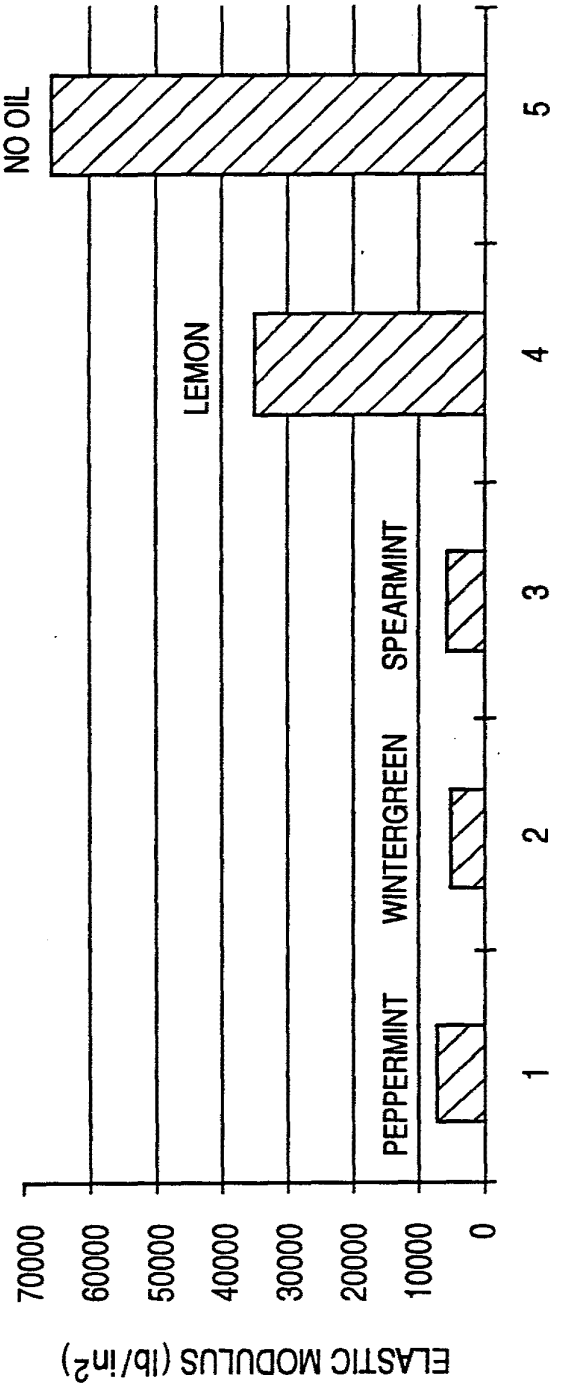

FIG. 16

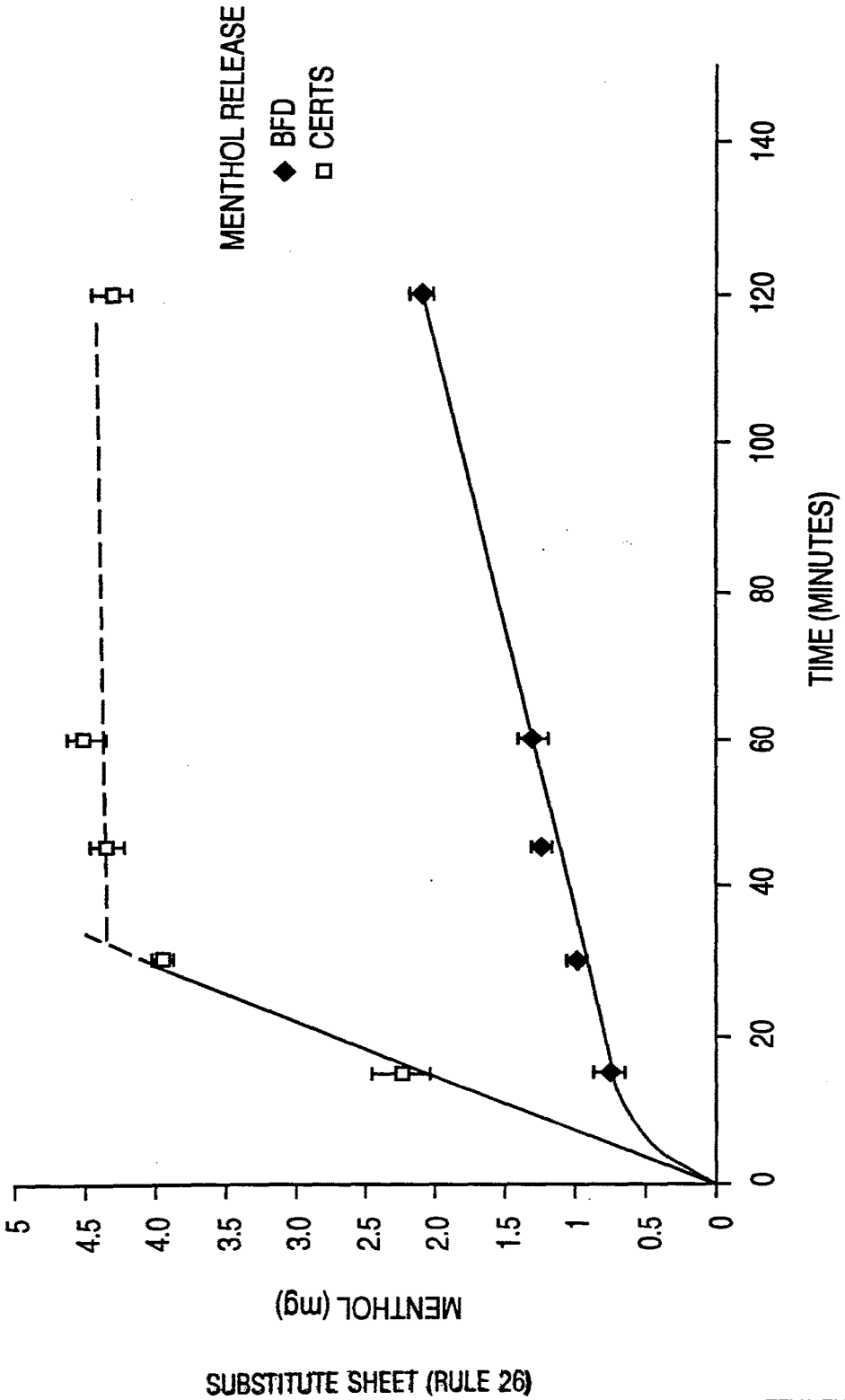

FIG. 17

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

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

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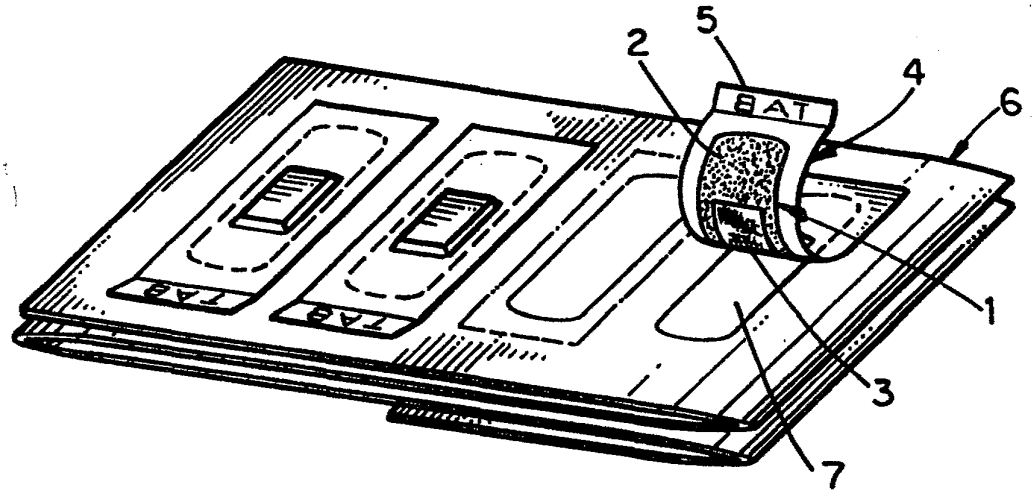

(57) Abstract

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

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PACKAGING AND DISPENSING DEVICE FOR STERILE ARTICLES

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

CLAIMS:

1. An encased adhesive-coated article combination comprising:

a. a support member;

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

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

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

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

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

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

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

a. a support member;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

20. An encased adhesive-coated article combination comprising:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

41. An encased sterile article combination comprising:

a. a support member;

b. a sterile article; and

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

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

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

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

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

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

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

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

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

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

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

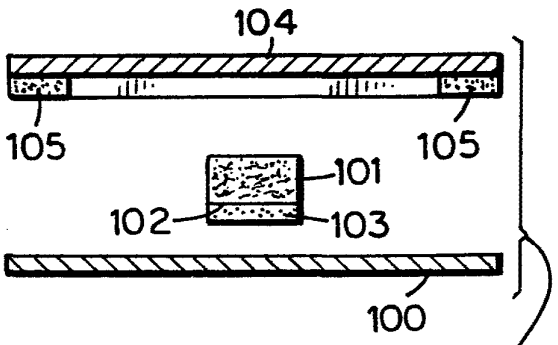


Fig. 1

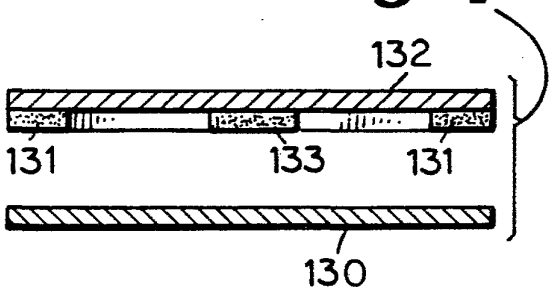


Fig. 4

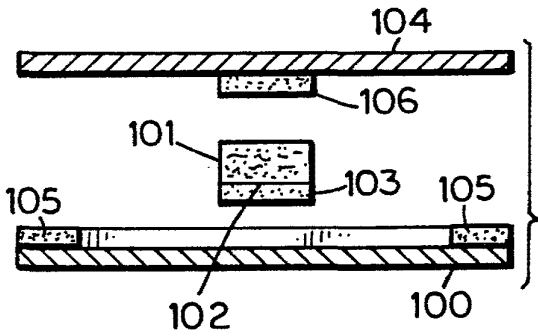


Fig. 2

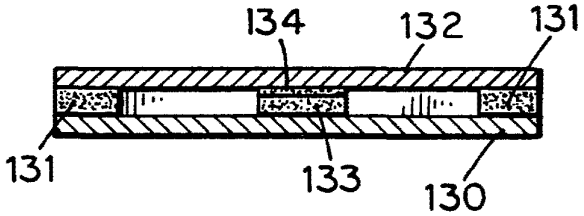


Fig. 5

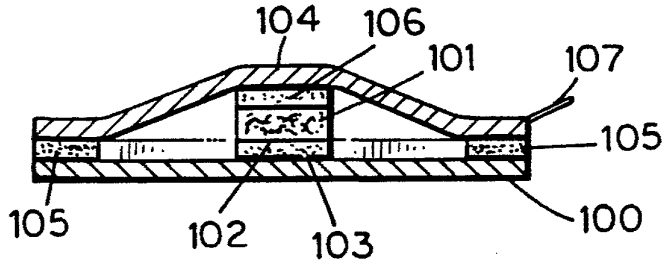


Fig. 3

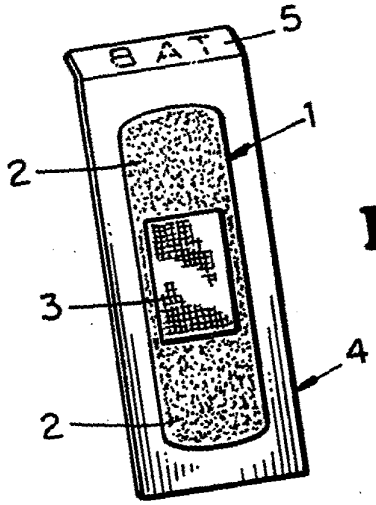


Fig. 6

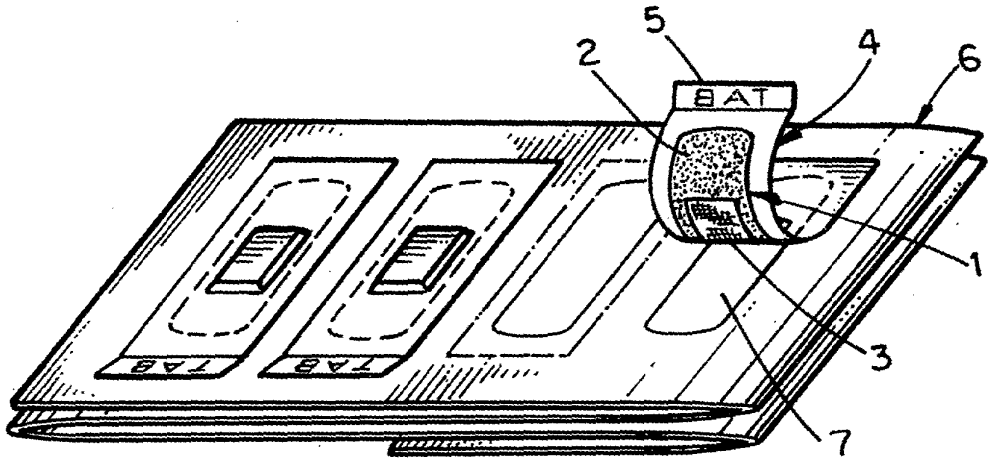


Fig. 7

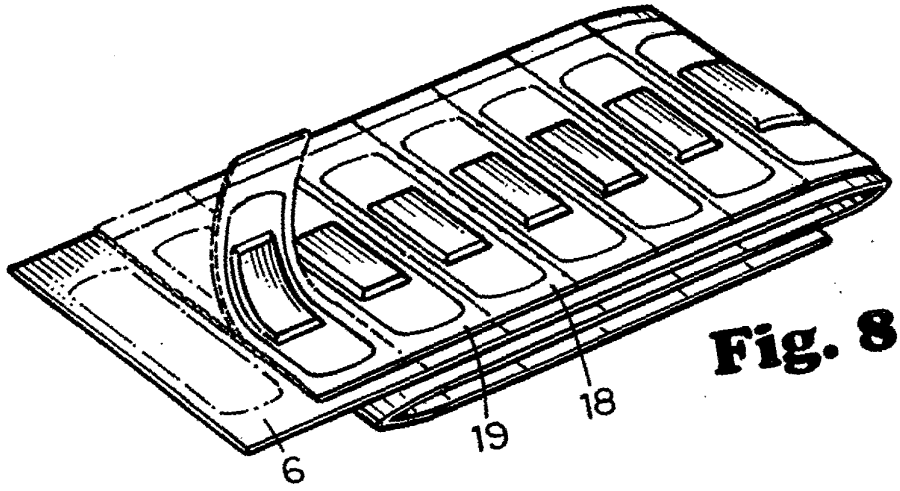


Fig. 8

Fig. 11

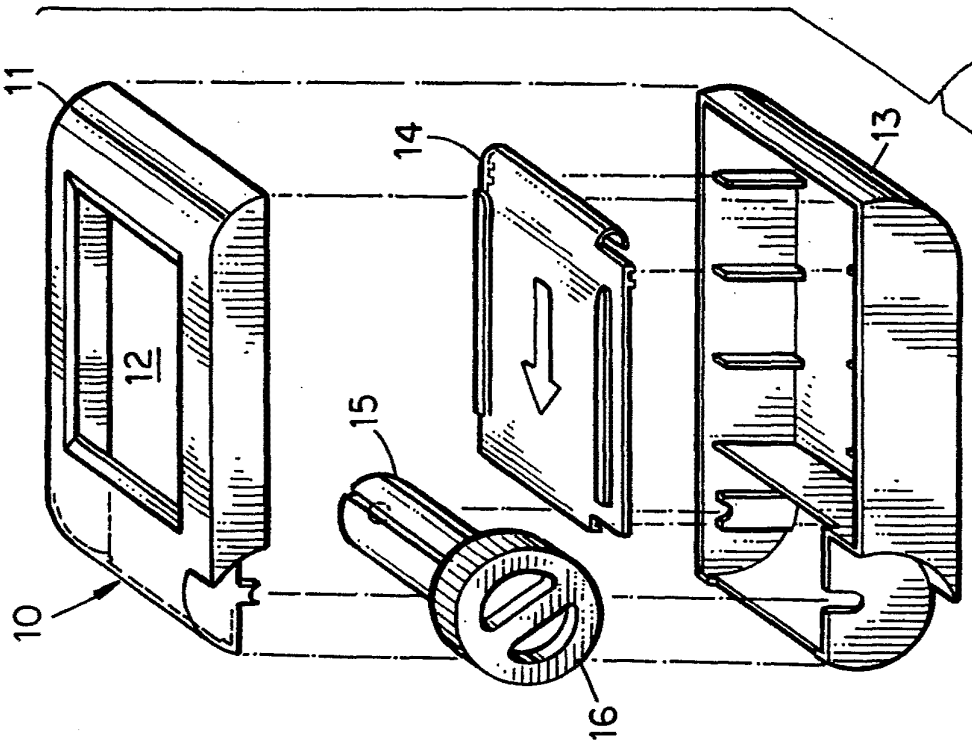


Fig. 9

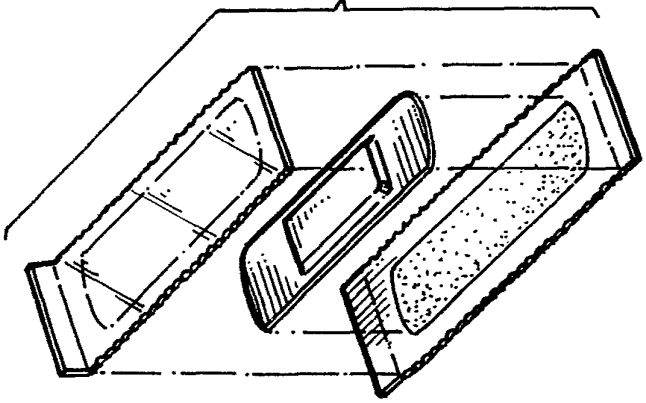
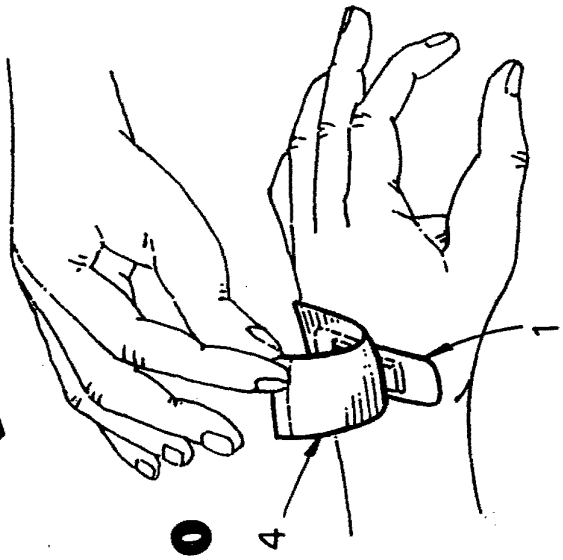


Fig. 10



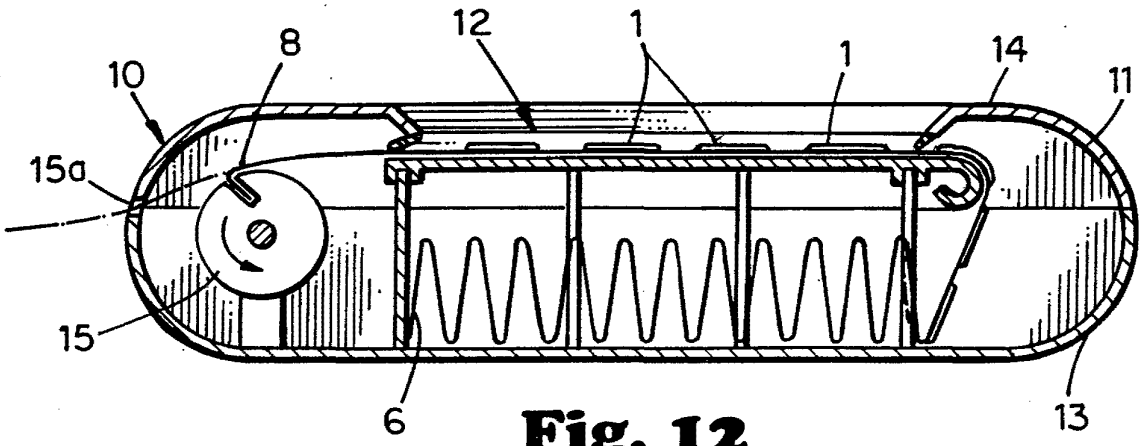


Fig. 12

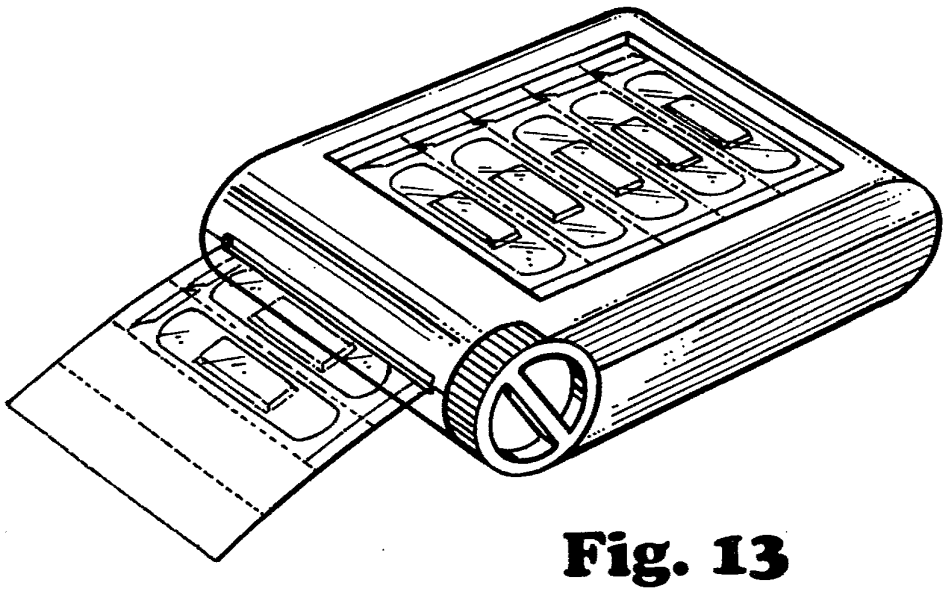


Fig. 13

Fig. 14

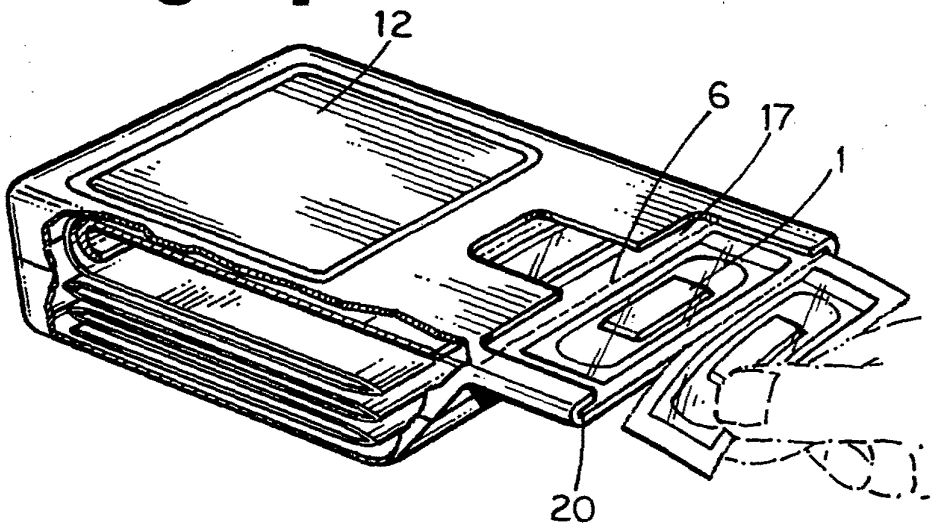


Fig. 15

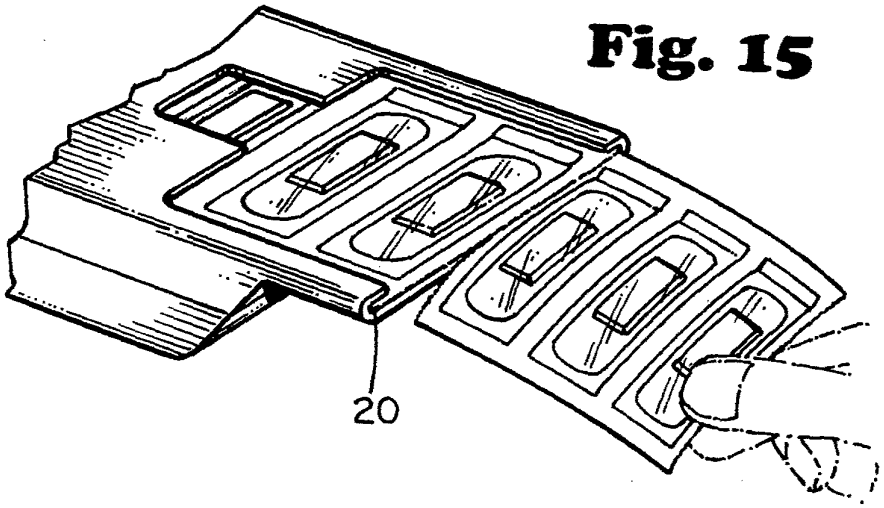
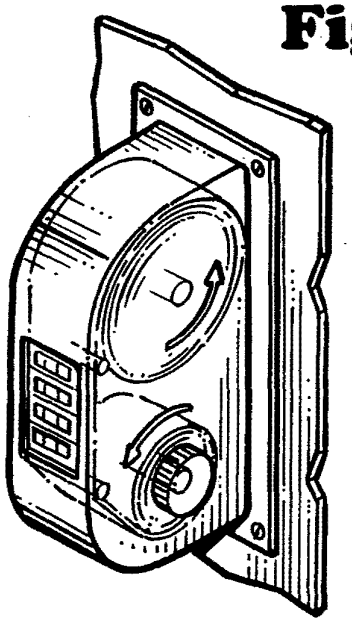


Fig. 16



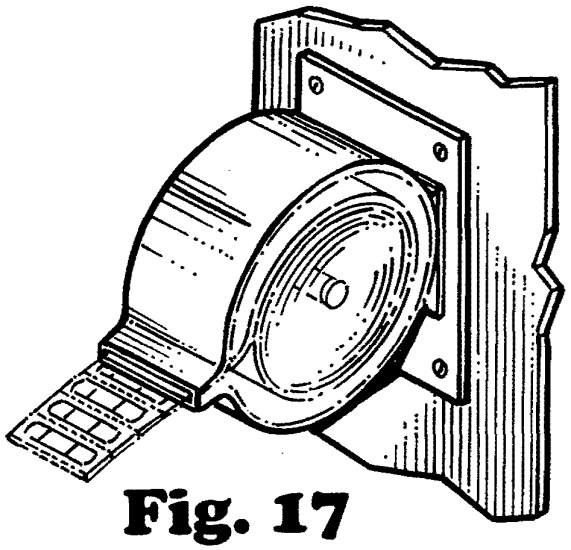


Fig. 17

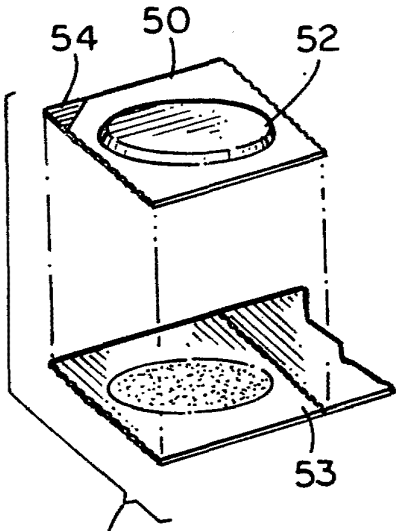


Fig. 18

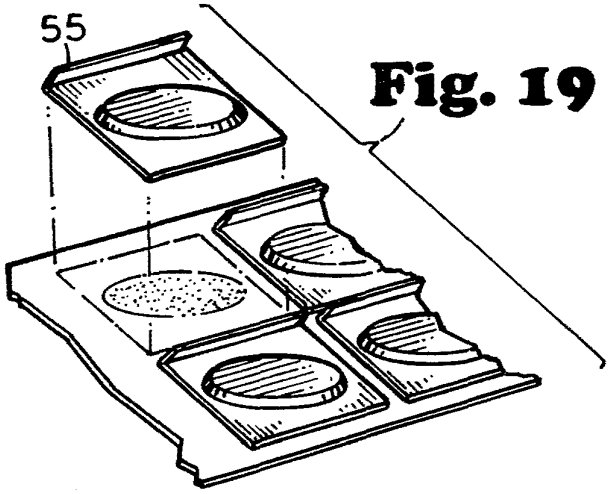


Fig. 19

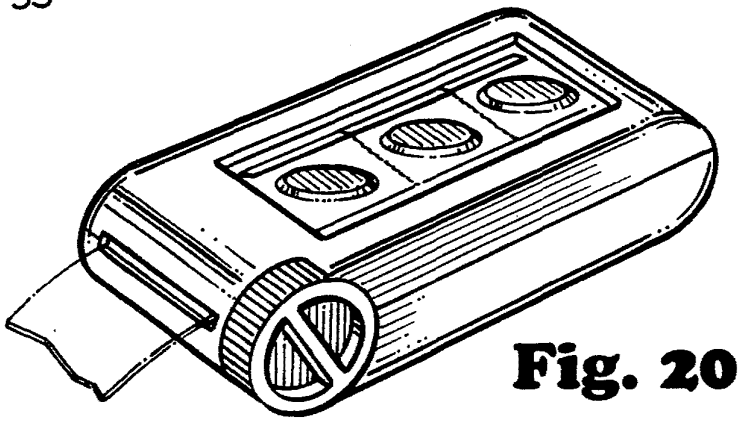
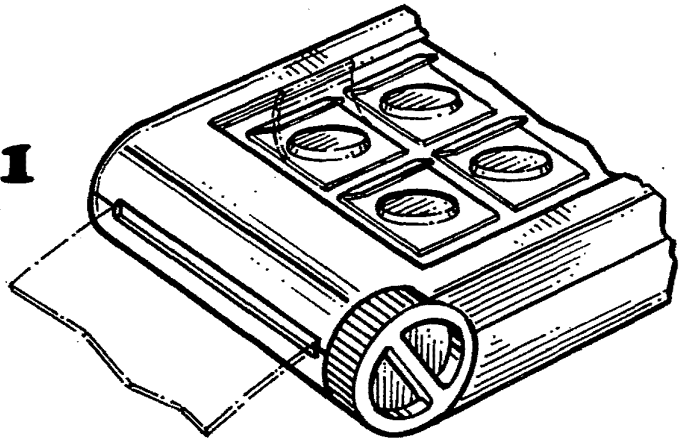


Fig. 20

Fig. 21



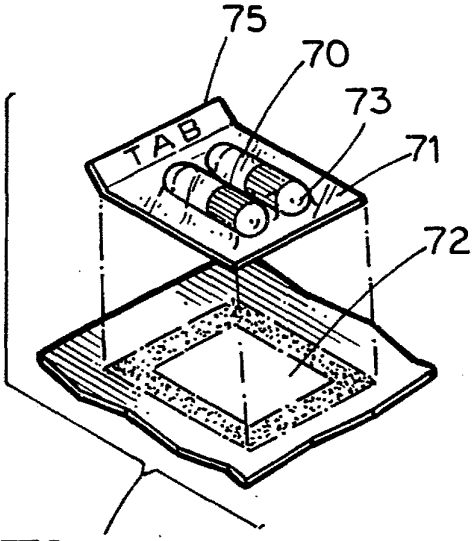


Fig. 22

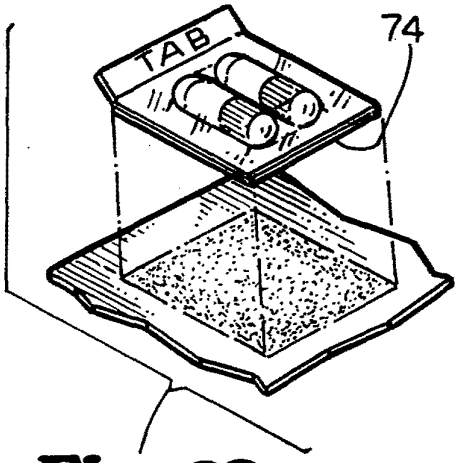


Fig. 23

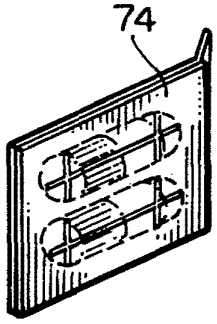


Fig. 24

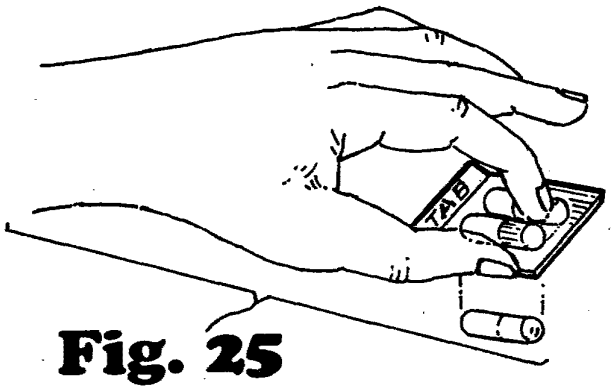


Fig. 25

Fig. 26

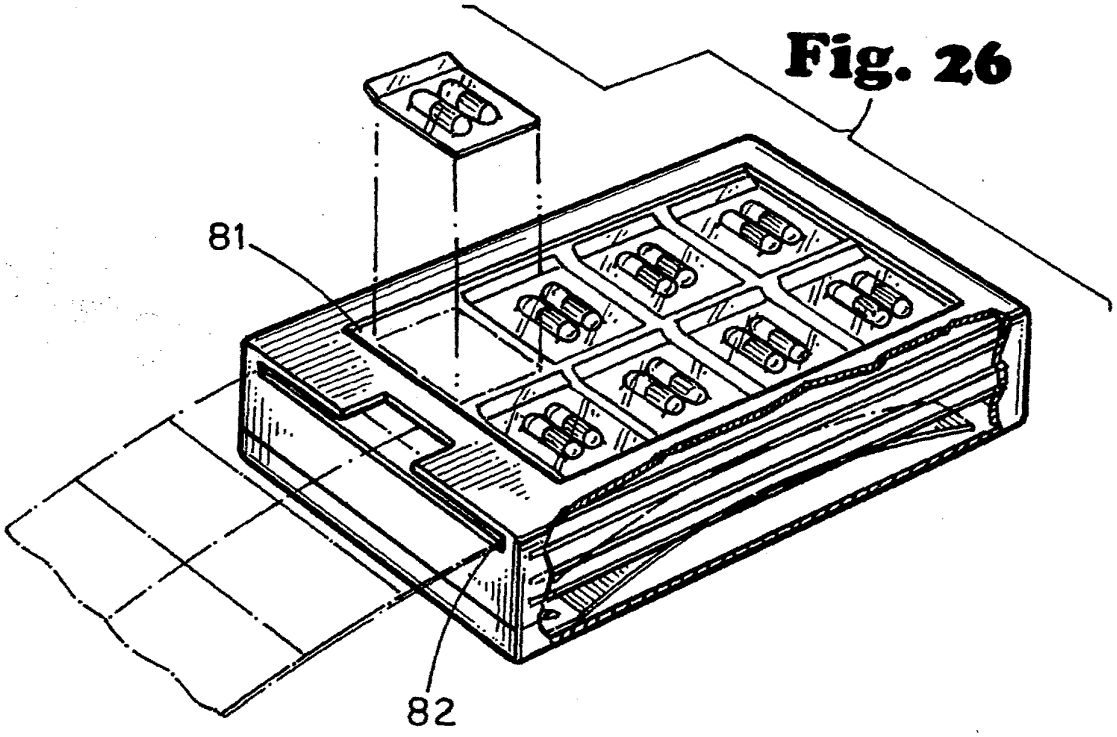
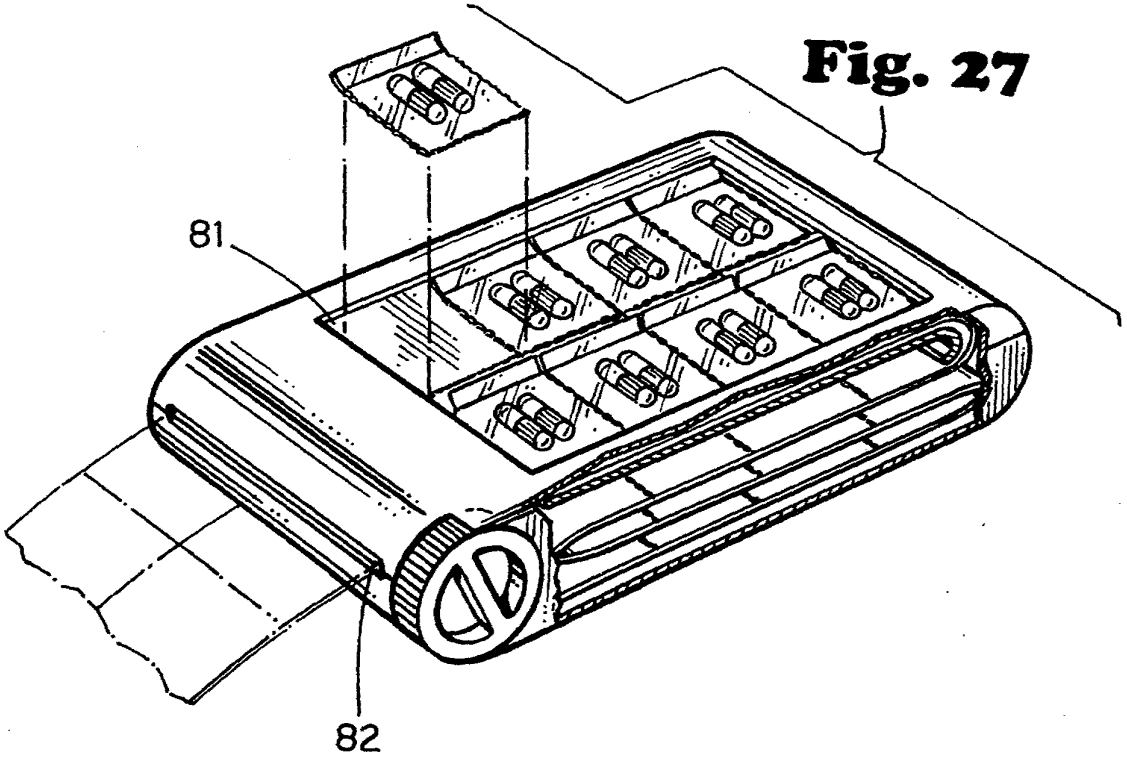


Fig. 27



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OE SUBJECT MATTER

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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

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

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Date of the actual completion of the international search 03 MARCH 1995	Date of mailing of the international search report 22 MAR 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer STEVE MEYERS Telephone No. (703) 308-0771 Stella M. Veney Paralegal Specialist Group 2400

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/14885

A. CLASSIFICATION OF SUBJECT MATTER:
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B65D 1/09; A61B 19/08

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

(72) Inventors: LEUNG, Sau–Hung, Spence; 249 Camden Place, Parsippany, NJ 07054 (US). LEONE, Robert, S.; 6 Byron Lane, Fanwood, NJ 07023 (US). KUMAR, Lori, Dee; 5 Alvamar Court, Skillman, NJ 08558 (US). KULKARNI, Neema; 16 Wilkeshire Boulevard, Randolph, NJ 07869 (US). SORG, Albert, F.; 56 Lime Kiln Road, Columbia, NJ 07832 (US).

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

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(54) Title: FAST DISSOLVING ORALLY CONSUMABLE FILMS

(57) Abstract

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

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FAST DISSOLVING ORALLY CONSUMABLE FILMS

SPECIFICATION

FIELD OF THE INVENTION

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

BACKGROUND OF THE INVENTION

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

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

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

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

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

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

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

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

U.S. Patent No. 5,411,945 to Ozaki et al. (Hayashibara) discloses a pullulan binder and products produced therewith, including edible films (Example B-2). The products can include a variety of ingredients in addition to pullulan, such as other polysaccharides, antibacterial agents, flavor-imparting agents and pharmaceutically active substances (column 4, lines 5-15). None of the essential oils are mentioned as suitable ingredients.

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

U.S. Patent No. 3,784,390 Hijiya et al. discloses pullulan films and their use in

coating and packing materials for foods, pharmaceuticals and other oxygen sensitive materials. All of the examples in this patent teach mixing pullulan in hot water.

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

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

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

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

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

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

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

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

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

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

SUMMARY OF THE INVENTION

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

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

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

combining the film-forming mixture and the aqueous solution to provide a hydrated polymer gel; mixing oils to form an oil mixture; adding the oil mixture to the hydrated polymer gel and mixing to provide a uniform emulsified gel; casting the uniform gel on a substrate; and drying the cast gel to provide a film.

BRIEF DESCRIPTION OF THE DRAWINGS

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

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

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

Description of Oral Care Film Compositions

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

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

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

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

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

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

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

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

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

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

The film-forming agent used in the films according to the present invention can be selected from the group consisting of pullulan, hydroxypropylmethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, xanthan gum, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan,

elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof. A preferred film former is pullulan, in amounts ranging from about 0.01 to about 99 wt %, preferably about 30 to about 80 wt %, more preferably from about 45 to about 70 wt % of the film and even more preferably from about 60 to about 65 wt % of the film.

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

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

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

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

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

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

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

Preferred surfactants include mono and diglycerides of fatty acids and polyoxyethylene sorbitol esters, such as, Atmos 300 and Polysorbate 80. The

surfactant can be added in amounts ranging from about 0.5 to about 15 wt %, preferably about 1 to about 5 wt % of the film. Other suitable surfactants include pluronic acid, sodium lauryl sulfate, and the like.

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

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

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

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

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

A. water-soluble sweetening agents such as monosaccharides, disaccharides and polysaccharides such as xylose, ribose, glucose (dextrose), mannose, galactose, fructose (levulose), sucrose (sugar), maltose, invert sugar (a mixture of

fructose and glucose derived from sucrose), partially hydrolyzed starch, corn syrup solids, dihydrochalcones, monellin, steviosides, and glycyrrhizin;

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

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

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

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

In general, an effective amount of auxiliary sweetener is utilized to provide the level of sweetness desired for a particular composition, and this amount will vary with

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

The flavorings that can be used include those known to the skilled artisan, such as natural and artificial flavors. These flavorings may be chosen from synthetic flavor oils and flavoring aromatics, and/or oils, oleo resins and extracts derived from plants, leaves, flowers, fruits and so forth, and combinations thereof. Representative flavor oils include: spearmint oil, cinnamon oil, peppermint oil, clove oil, bay oil, thyme oil, cedar leaf oil, oil of nutmeg, oil of sage, and oil of bitter almonds. Also useful are artificial, natural or synthetic fruit flavors such as vanilla, chocolate, coffee, cocoa and citrus oil, including lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, strawberry, raspberry, cherry, plum, pineapple, apricot

and so forth. These flavorings can be used individually or in admixture. Commonly used flavors include mints such as peppermint, artificial vanilla, cinnamon derivatives, and various fruit flavors, whether employed individually or in admixture. Flavorings such as aldehydes and esters including cinnamyl acetate, cinnamaldehyde, citral, diethylacetal, dihydrocarvyl acetate, eugenyl formate, p-methylanisole, and so forth may also be used. Generally, any flavoring or food additive, such as those described in Chemicals Used in Food Processing, publication 1274 by the National Academy of Sciences, pages 63-258, may be used. Further examples of aldehyde flavorings include, but are not limited to acetaldehyde (apple); benzaldehyde (cherry, almond); cinnamic aldehyde (cinnamon); citral, i.e., alpha citral (lemon, lime); neral, i.e. beta citral (lemon, lime); decanal (orange, lemon); ethyl vanillin (vanilla, cream); heliotropine, i.e., piperonal (vanilla, cream); vanillin (vanilla, cream); alpha-amyl cinnamaldehyde (spicy fruity flavors); butyraldehyde (butter, cheese); valeraldehyde (butter, cheese); citronellal (modifies, many types); decanal (citrus fruits); aldehyde C-8 (citrus fruits); aldehyde C-9 (citrus fruits); aldehyde C-12 (citrus fruits); 2-ethyl butyraldehyde (berry fruits); hexenal, i.e. trans-2 (berry fruits); tolyl aldehyde (cherry, almond); veratraldehyde (vanilla); 2,6-dimethyl- 5-heptenal, i.e. melonal (melon); 2-6-dimethyloctanal (green fruit); and 2-dodecenal (citrus, mandarin); cherry; grape; mixtures thereof; and the like.

The amount of flavoring employed is normally a matter of preference subject to such factors as flavor type, individual flavor, and strength desired. Thus, the amount

may be varied in order to obtain the result desired in the final product. Such variations are within the capabilities of those skilled in the art without the need for undue experimentation. In general, amounts of about 0.1 to about 30 wt % are useable with amounts of about 2 to about 25 wt % being preferred and amounts from about 8 to about 10 wt % are more preferred.

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

Antimicrobial Efficacy of Oral Care Films

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

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

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

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

The extended antimicrobial activity is shown in the following experiments.

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

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

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

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

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

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

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

Experimental Procedures

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

In vivo Germ Kill Assay

1. Materials

Test tubes containing 10 ml of sterile 0.01% peptone

Sterile Swabs

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

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

Glutathione[c] (Sigma G4251) 1.2 grams

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

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

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

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

2. Procedure

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

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

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

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

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

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

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

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

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

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

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

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

Table A. Exponential Volume Constants for Segment Pairs

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

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

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

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

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

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

Methods For Preparing Essential Oil Containing Films

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

In certain methods for preparing films according to the invention, the film-forming ingredients are mixed and hydrated with water separately from the water-soluble ingredients, which are mixed in aqueous solution separately from the organic

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

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

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

The aqueous phase can include ingredients such as coloring agent(s), copper gluconate and sweetener. The water is preferably deionized and the amount of water

used is about 5 to about 80 wt % of the final gel mixture.

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

In a preferred method of producing essential oil containing films according to the invention, it is possible to hydrate the film-forming ingredients and combine all of the ingredients without heating. The preferred method of producing films comprises dissolving the water-soluble ingredients in water to form an aqueous mixture; mixing the film-forming ingredients in powder form to form a powder mixture; adding the powder mixture to the aqueous mixture to form a hydrated polymer gel; stirring the hydrated polymer at room temperature for about 30 minutes to about 48 hours; mixing the cooling agent, thymol and menthol in the flavor oil to form an oil mixture; adding methyl salicylate; eucalyptol and surfactants to the oil mixture; adding the oil mixture to the hydrated polymer gel and mixing until uniform; deaerating the film until air bubbles are removed, casting the uniform mixture on a suitable substrate; and drying the cast mixture to form a film.

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

two steps minimizes the amount of flavor lost.

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

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

Description of Film Compositions That Deliver Pharmaceutical Agents

A second embodiment of the invention is a fast dissolving film that includes at least one physiologically acceptable, pharmaceutically active agent. The expression "physiologically acceptable" as used herein is intended to encompass compounds, which upon administration to a patient, are adequately tolerated without causing undue negative side effects. The expression encompasses edible compounds.

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

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

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

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

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

E. anti-histamines, such as brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenylpyraline hydrochloride, azatadine meleate, diphenhydramine citrate, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine

hydrochloride, acrivastine, loratadine, brompheniramine, dexbrompheniramine, and the like,

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

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

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

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

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

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

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

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

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

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

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

The amount of medicament that can be used in the rapidly dissolving films, according to the present invention, is dependent upon the dose needed to provide an effective amount of the medicament. Examples of doses for specific medicaments that can be delivered per one strip of rapidly dissolving oral film are reviewed in Table 1.

TABLE 1

MEDICAMENT	DOSE
Chlorpheniramine Maleate	4 mg.
Brompheniramine Maleate	4 mg.
Dexchlorpheniramine	2 mg.
Dexbrompheniramine	2 mg.
Triprolidine Hydrochloride	2.5 mg.
Acrivastine	8 mg.
Azatadine Maleate	1 mg.
Loratidine	10 mg.
Phenylephrine Hydrochloride	10 mg.
Dextromethorphan Hydrochloride	10-20 mg.
Ketoprofen	12.5 mg.
Sumatriptan Succinate	35 - 70 mg.
Zolmitriptan	2.5 mg.
Loperamide	2 mg.
Famotidine	10 mg.
Nicotine	2 mg.
Diphenhydramine Hydrochloride	25 mg.
Pseudoephedrine Hydrochloride	30 mg.

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

The films that deliver a pharmaceutical agent can also include a triglyceride. Examples of triglycerides include vegetable oils such as corn oil, sunflower oil, peanut oil, olive oil, canola oil, soybean oil and mixtures thereof. A preferred triglyceride is olive oil. The triglyceride is added to the film in amounts from about 0.1 wt % to about 12 wt %, preferably in a range from about 0.5 wt % to about 9 wt %, of the film.

The films that contain pharmaceutical agents also can include a preservative. The preservative is added in amounts from about 0.001 wt % to about 5 wt %, preferably from about 0.01 wt % to about 1 wt % of the film. Preferred preservatives include sodium benzoate and potassium sorbate.

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

The pharmaceutical agent containing films can also include propylene glycol.

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

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

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

Examples

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

Preparation Method I

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

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

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

dissolved in purified water to form preparation B.

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

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

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

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

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

Preparation Method II

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

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

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

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

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

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

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

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

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

I. dry the cast mixture to form a film.

Example 1

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

Examples 2-4

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

Examples 5-6

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

long time frame.

Examples 7-9

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

Examples 10-15

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

Example 16

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

Example 17

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

Example 18

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

Example 19

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

Example 20

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

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

Table 2

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

Table 2 cont.

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

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

TABLE 3

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

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

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

Table 4

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

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

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

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

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

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

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

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

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

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

hydrobromide.

Processes For Making Pharmecutical Containing Films

Example 22A was made using the following procedure.

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

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

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

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

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

CLAIMS

WHAT IS CLAIMED IS:

1. A consumable film adapted to adhere to and dissolve in a mouth of a consumer, wherein said film comprises at least one water soluble polymer and an antimicrobial effective amount of at least one essential oil selected from the group consisting of thymol, methyl salicylate, eucalyptol and menthol.

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

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

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

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

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

7. The consumable film according to claim 1, wherein said water soluble polymer is selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid,

methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

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

9. The consumable film of claim 8, comprising:

about 40 to about 80 wt % pullulan;

about 0.01 to about 4 wt % thymol;

about 0.01 to about 4 wt % methyl salicylate;

about 0.01 to about 4 wt % eucalyptol; and

about 0.01 to about 15 wt % menthol.

10. The consumable film according to claim 7, further comprising:

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

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

about 0.1 to about 8 wt % of water;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

mixing oils to form an oil mixture;

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

casting the uniform gel on a substrate; and

drying the cast gel to provide said film.

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

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

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

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

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

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

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

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

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

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

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

29. The method according to claim 18, wherein the water soluble film former is selected from the group consisting of pullulan, hydroxyproplymethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium alginate, polyethylene glycol, tragacanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl polymer, amylose, high amylose starch, hydroxypropylated high amylose starch, dextrin, pectin, chitin, chitosan, levan, elsinan, collagen, gelatin, zein, gluten, soy protein isolate, whey protein isolate, casein and mixtures thereof.

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

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

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

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

33. The consumable film according to claim 32, wherein the antimicrobial agent is selected from the group consisting of triclosan, cetyl pyridium chloride, domiphen bromide, quaternary ammonium salts, zinc compounds, sanguinarine, fluorides, alexidine, octonidine, EDTA and mixtures thereof.

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

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

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

37. The consumable film according to claim 32, wherein the anti-histamine is selected from the group consisting of brompheniramine maleate, chlorpheniramine maleate, carbinoxamine maleate, clemastine fumarate, dexchlorpheniramine maleate, diphenhydramine hydrochloride, diphenhydramine citrate, diphenylpyraline hydrochloride, doxylamine succinate, promethazine hydrochloride, pyrilamine maleate, tripelennamine citrate, triprolidine hydrochloride and mixtures thereof.

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

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

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

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

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

cavity.

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

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

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

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

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

FIG-1

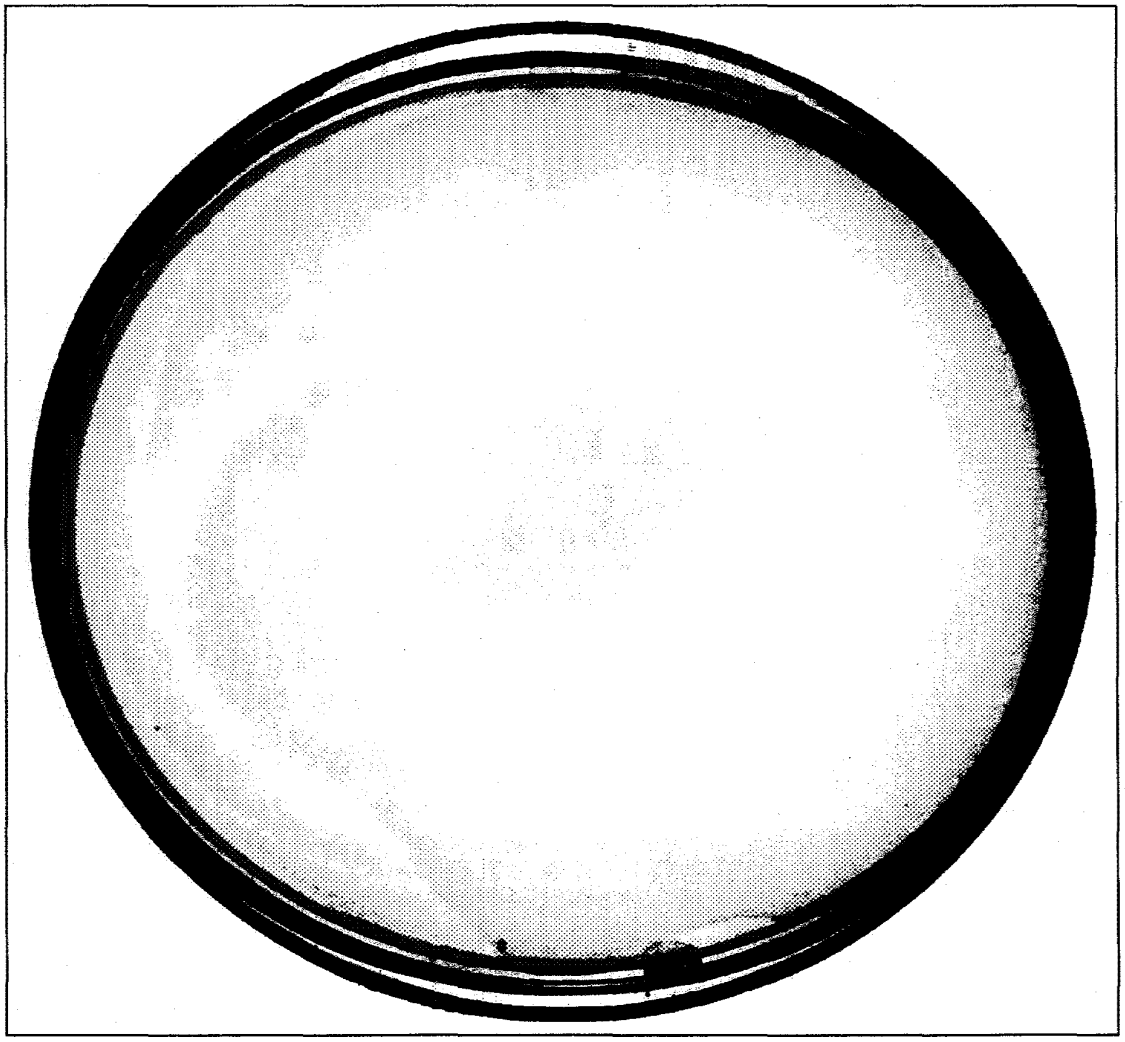
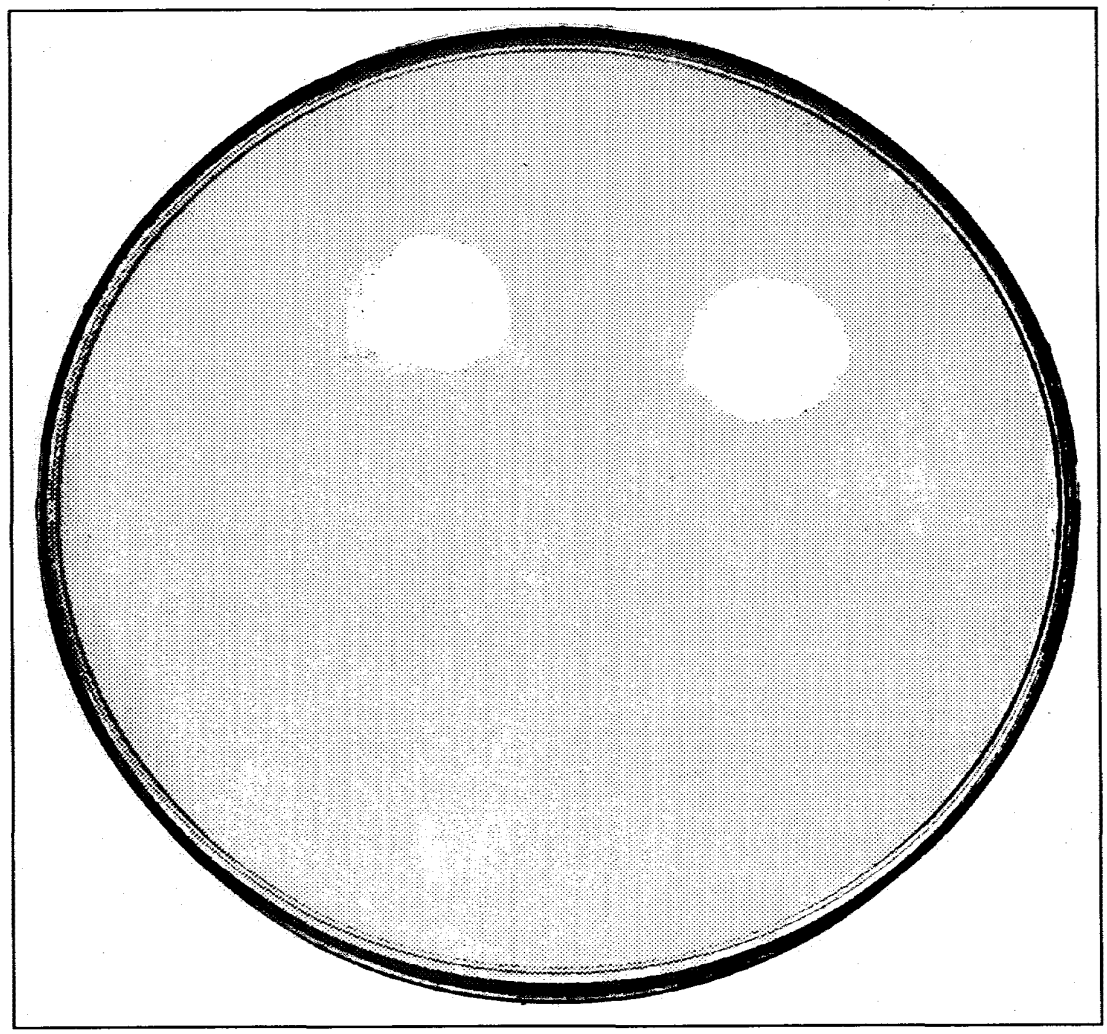


FIG-2



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(71) Applicant: LAVIPHARM LABORATORIES, INC. [US/US]; Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).

(72) Inventors: CHEN, Li–Lan, H.; 3906 Victory Court, Edison, NJ 08817 (US). PFISTER, William, R.; 16 Saxony Lane, Robbinsville, NJ 08691 (US). RENN, Donald, W.; 4 Brewster Point, Glen Cove, ME 04846–0088 (US). BURANA-CHOKPAISAN, Thitiwan; 4 Stout Court, Lawrenceville, NJ 08648 (US). OSBORNE, James; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US). TAN, Hock, Seng; 25 Jaime Court, Old Bridge, NJ 08857 (US). TAO, Li; Lavipharm Laboratories, Inc., Suite 6, 131 Ethel Road West, Piscataway, NJ 08854 (US).

(74) Agent: STRIMPEL, Harriet, M.; Bromberg & Sunstein LLP, 125 Summer Street, Boston, MA 02110–1618 (US).

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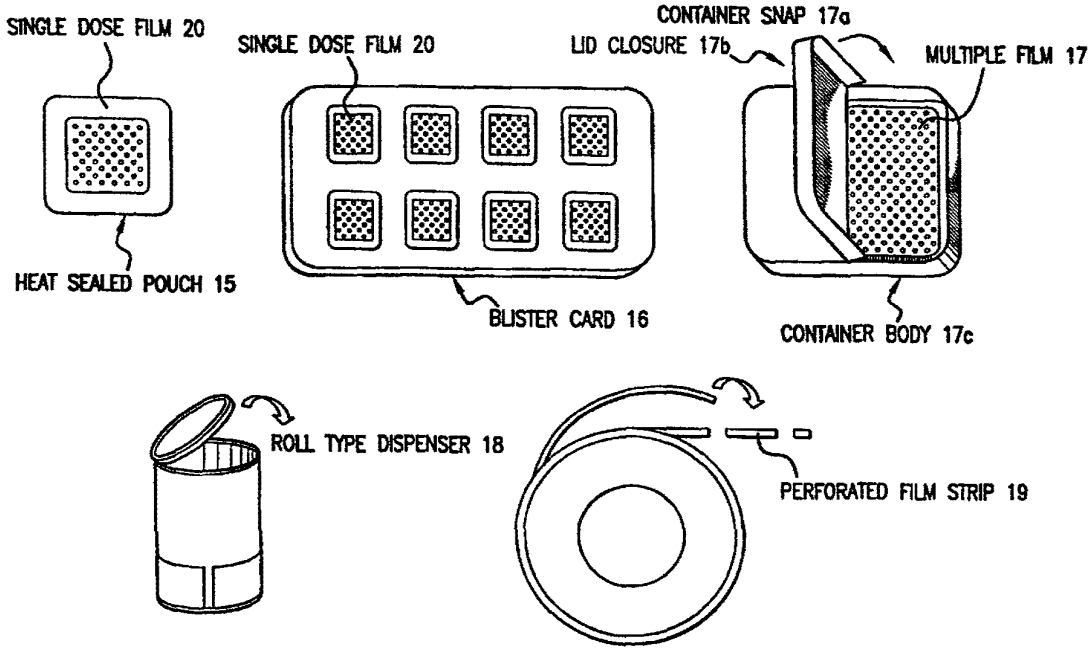

(57) Abstract

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

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CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
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COMPOSITIONS AND METHODS FOR MUCOSAL DELIVERY

Technical Description

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

Background to the Invention

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

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

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

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

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

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

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

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

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

Summary of the Invention

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

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

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

In embodiments of the invention, methods are provided for making a dosage unit, that include in one embodiment, dissolving a hydrocolloid in a solvent so as to form a substantially homogeneous preparation; adding to the hydrocolloid preparation, an active agent and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer and a buffering agent to form a coatable mixture; and forming a mucosal surface-coat forming film from the mixture for packaging as a dosage unit. The method may further include the step of coating the mixture onto a backing film. In a further embodiment, the reagents including: a hydrocolloid, an active agent,

and at least one reagent selected from the group consisting of an emulsifier, a plasticizer, a taste modifier, a water soluble inert filler, a coloring agent, a preservative, a permeation enhancer, a stabilizer, and a buffering agent, may be combined in any order in a vessel having a heating source and a mechanical mixing device, the combined ingredients being mixed during and after the addition of the ingredients to the vessel, an effective amount of heat being applied for melting a substantial portion of the mixture. The mixture may then be formed into a film in a dry extrusion process.

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

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

Brief Description of the Figures

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

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

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

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

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

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

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

Detailed Description of Invention

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

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

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

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

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

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

tissue surface.

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

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

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

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

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

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

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

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

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

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

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

the dry weight of the film.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Examples

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 5:

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

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

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

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

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

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

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

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

hydroxypropylmethylcellulose polymers

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

Table 9a: Properties of selected commercial hydroxypropylmethylcellulose polymers.

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

* Each value is the mean S±D, n=6

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

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

Example 10: Enhancement of mucoadhesion

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

Table 10

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

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

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

Example 11: Preparation of film using dry extrusion techniques

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

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

Example 12: Human clinical acute irritation study

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

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

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

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

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

dosage unit are described in Table 8.

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

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

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

* Area under the curve

What is claimed:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

time in a range from 10-600 seconds.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

(c) forming the mixture into a film.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

58. A method of treating erectile dysfunction; comprising:

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

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

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

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

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

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

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

(c) forming the mixture into a film.

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

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

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

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

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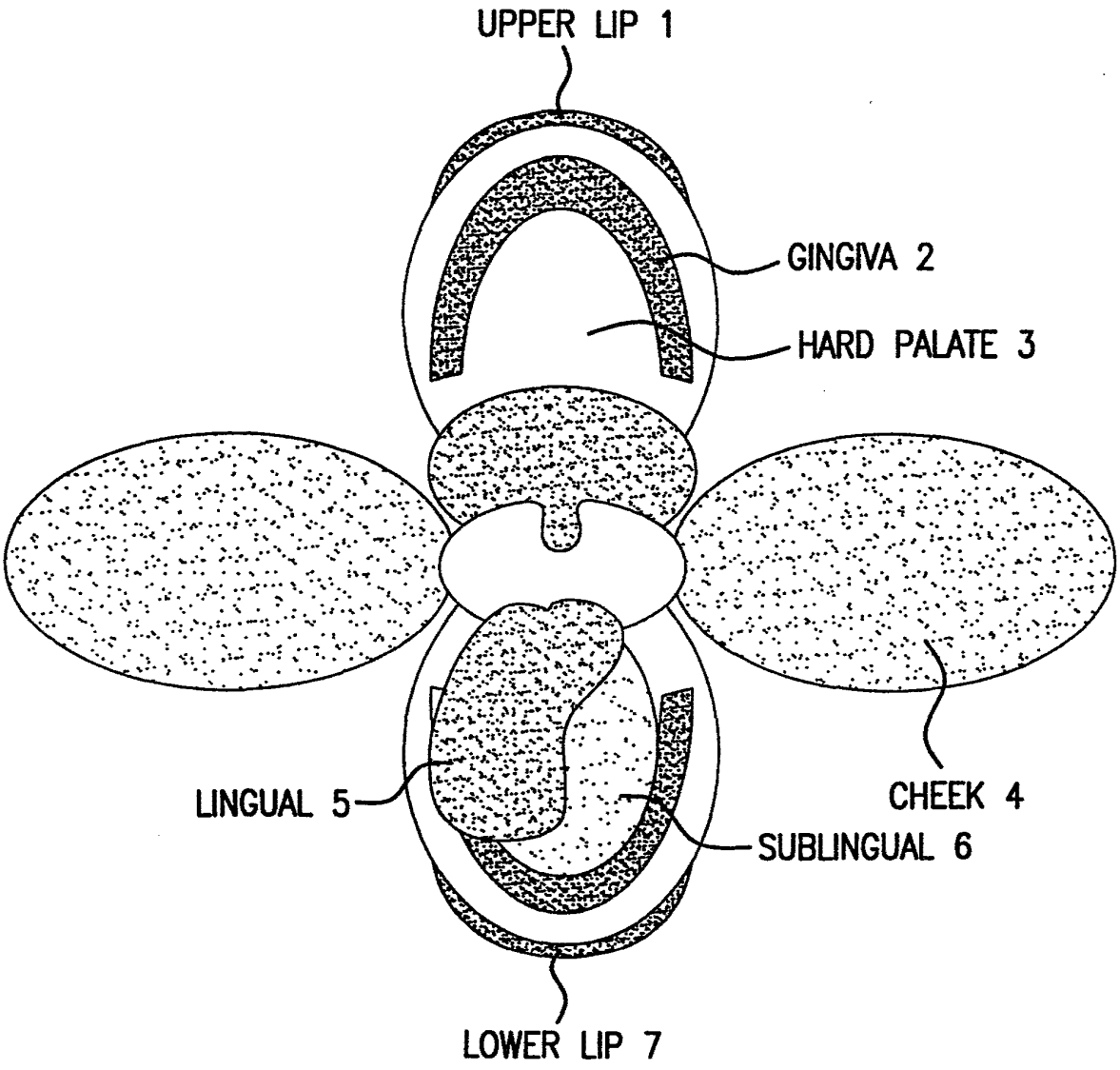

FIG.1

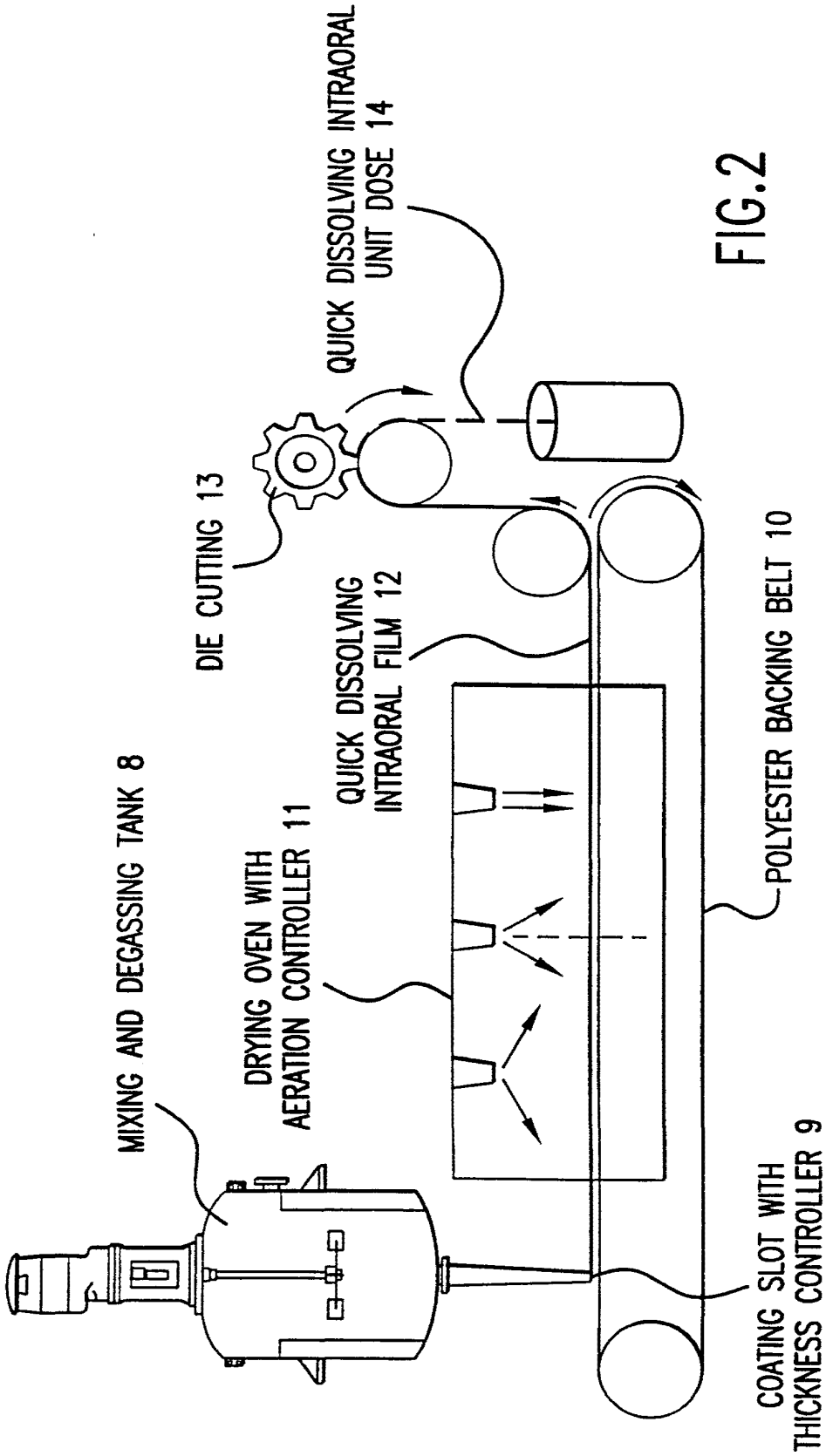

FIG.2

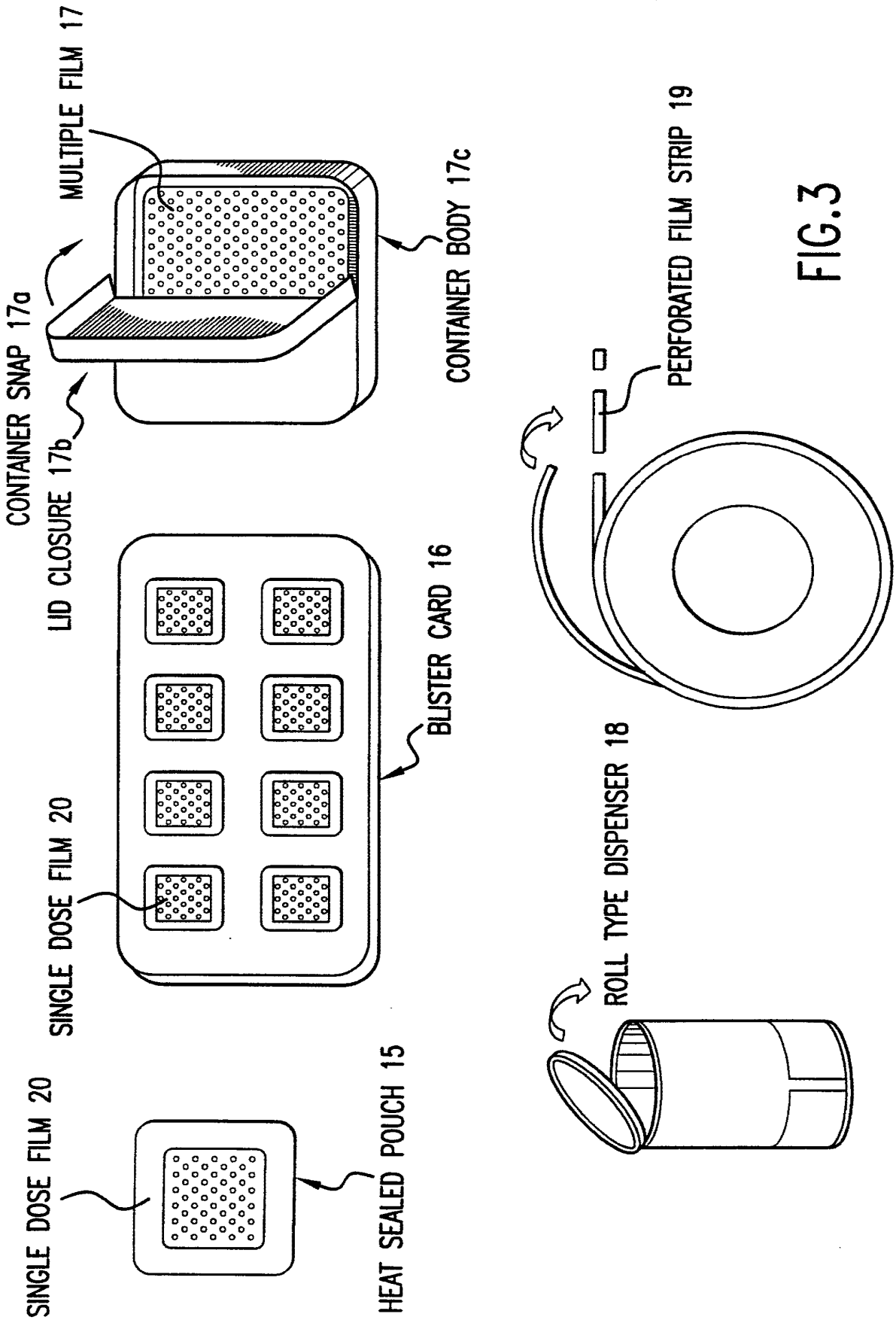

FIG.3

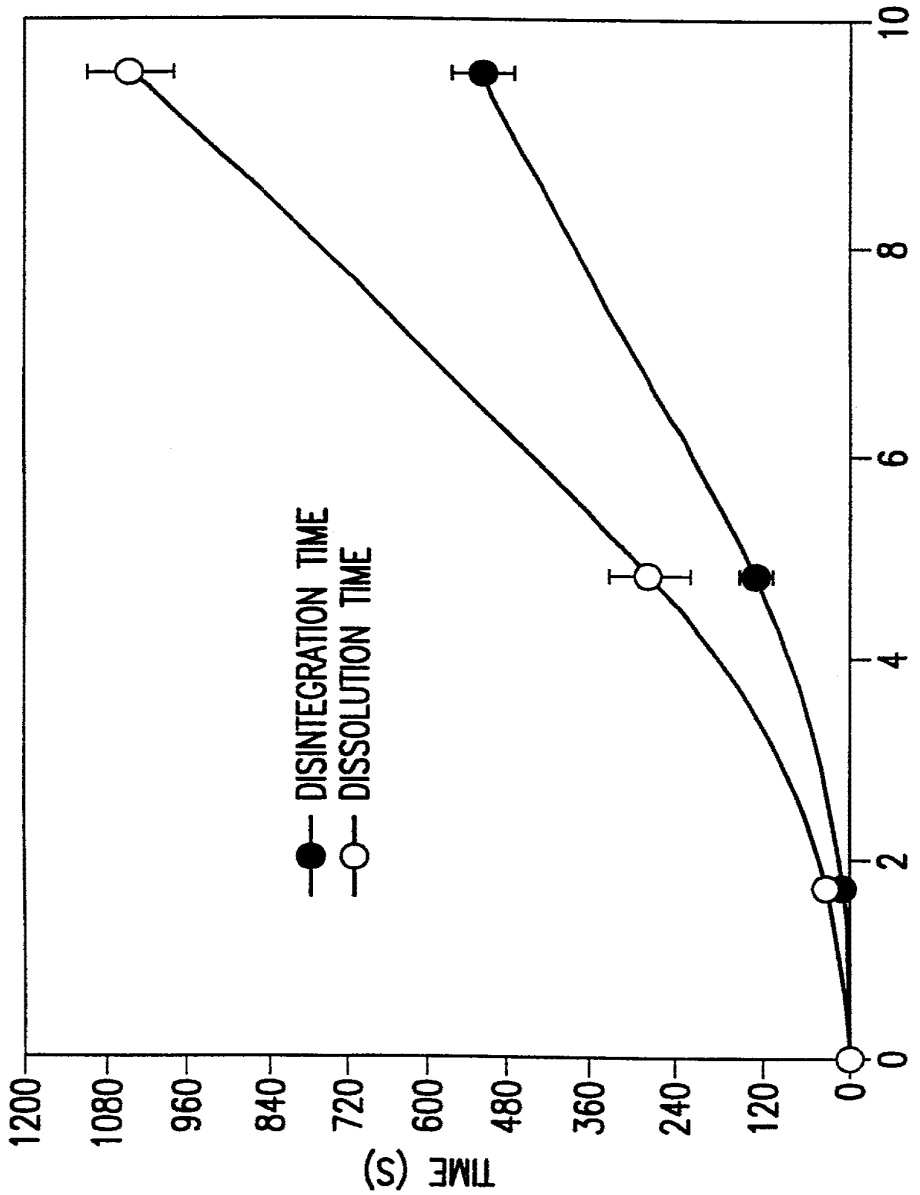

FIG.4

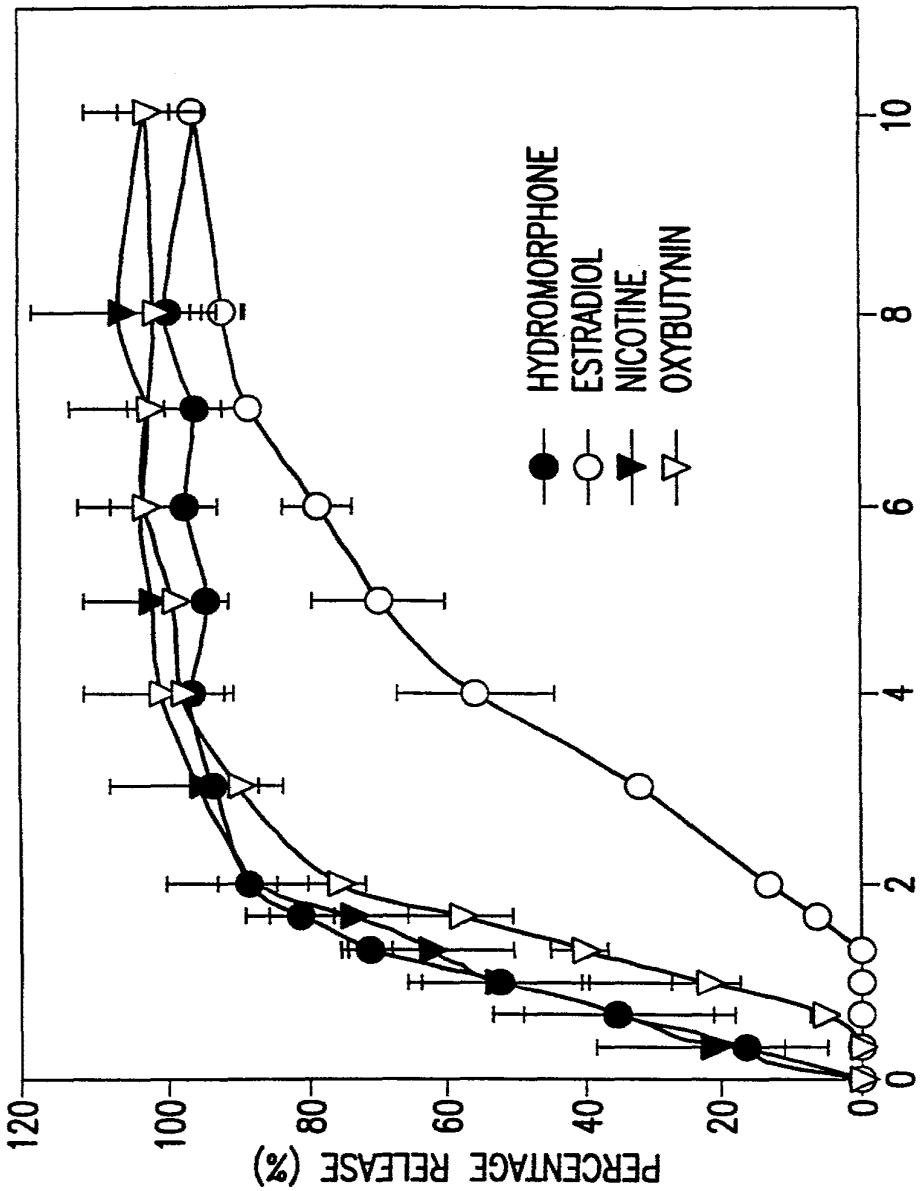

FIG.5

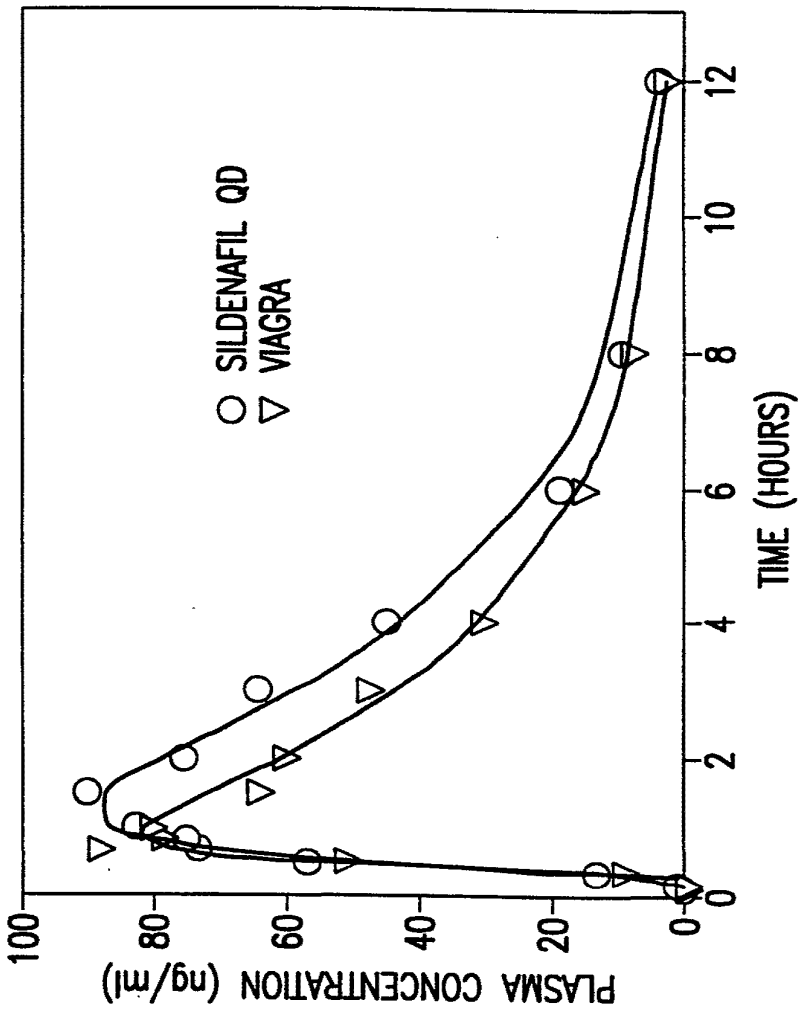

FIG.6

Electronic Acknowledgement Receipt

EFS ID:	3718341
Application Number:	12107389
International Application Number:	
Confirmation Number:	9641
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jon Anthony Chiodo/Barbara Thomas
Filer Authorized By:	Jon Anthony Chiodo
Attorney Docket Number:	1199-26 DIV
Receipt Date:	01-AUG-2008
Filing Date:	22-APR-2008
Time Stamp:	16:23:30
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Information Disclosure Statement (IDS) Filed	1199-26_DIV_IDS_Part_3.pdf	13202001 ac803a80c7b447be7f2161212749da7ad5ffe256	no	8

Warnings:	
Information:	

2	Foreign Reference	DE2432925A1.pdf	799270 9dc715572e4fa76e845f32e64d9f5281f67a7e59	no	24
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14	Foreign Reference	EP01110546A1.pdf	258701 89be4f073ba87b8a60de50db9104a365 e798d797	no	15
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Warnings:	
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Total Files Size (in bytes):	34031461

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

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

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

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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
12/107,389	04/22/2008	1794	435	1199-26 DIV	18	2

CONFIRMATION NO. 9641

UPDATED FILING RECEIPT

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

OC000000030914339

Date Mailed: 07/14/2008

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**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Gary L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOL RX, 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 DIV of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003
and is a CIP of PCT/US2002/032575 10/11/2002
and is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and said 10/856,176 05/28/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002

Foreign Applications

If Required, Foreign Filing License Granted: 05/06/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/107,389**

Projected Publication Date: 10/23/2008

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Preliminary Class

428

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.

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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 (1-866-999-4158).

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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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Electronic Acknowledgement Receipt

EFS ID:	3573623
Application Number:	12107389
International Application Number:	
Confirmation Number:	9641
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jamie Mercer Larmann/Barbara Thomas
Filer Authorized By:	Jamie Mercer Larmann
Attorney Docket Number:	1199-26 DIV
Receipt Date:	07-JUL-2008
Filing Date:	22-APR-2008
Time Stamp:	15:34:12
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		1199-26_DIV_Response-Correct_Papers_7-7-08.pdf	868757 2239157 5f6647e5338564deef71b33b08ce67ca6	yes	25

	Multipart Description/PDF files in .zip description		
	Document Description	**Start**	**End**
	Applicant Response to Pre-Exam Formalities Notice	1	2
	Drawings-only black and white line drawings	3	25
Warnings:			
Information:			
	Total Files Size (in bytes):	868757	

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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

Applicant:	Yang, et al.	Examiner:	Unassigned
Serial No.:	12/107,389	Group Art Unit:	1794
Confirmation No.:	9641	Docket:	1199-26 DIV
Filed:	April 22, 2008	Dated:	July 7, 2008

For: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 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: July 7, 2008

Signature: Barbara Thomas/

RESPONSE TO NOTICE TO FILE CORRECTED APPLICATION PAPERS - FILING DATE GRANTED

Sir:

This submission is in response to the Notice to File Corrected Application Papers - Filing Date Granted mailed on May 9, 2008. This response is timely filed on July 7, 2008. Enclosed herewith are the following:

Replacement Drawings for pages 5-27 representing Figs. 9-31.

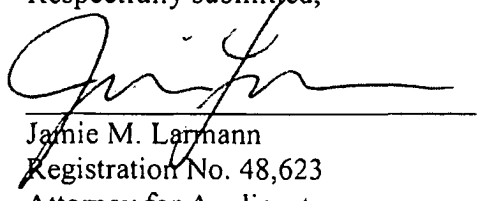
It is respectfully submitted that the drawings submitted herewith overcome the objections raised in the Notice to File Corrected Application Papers. In particular, the drawings submitted herewith include illustrations of the photographs originally submitted for Figs. 9-17 and clearer

reproductions of the photographs originally submitted for Figs. 18-31. Entry of the drawings is respectfully requested.

If any additional fees are due, the Commissioner is hereby authorized to charge payment of such fees to Deposit Account No. 08-2461. Such authorization includes authorization to charge fees for extensions of time, if any, under 37 C.F.R §1.17 and also should be treated as a constructive petition for an extension of time in this reply or any future reply pursuant to 37 C.F.R. §1.136.

In view of the documents submitted herewith, Applicants respectfully submit that the application is in condition for examination. Please direct any questions regarding this submission to the undersigned.

Respectfully submitted,



Jamie M. Larmann
Registration No. 48,623
Attorney for Applicants

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

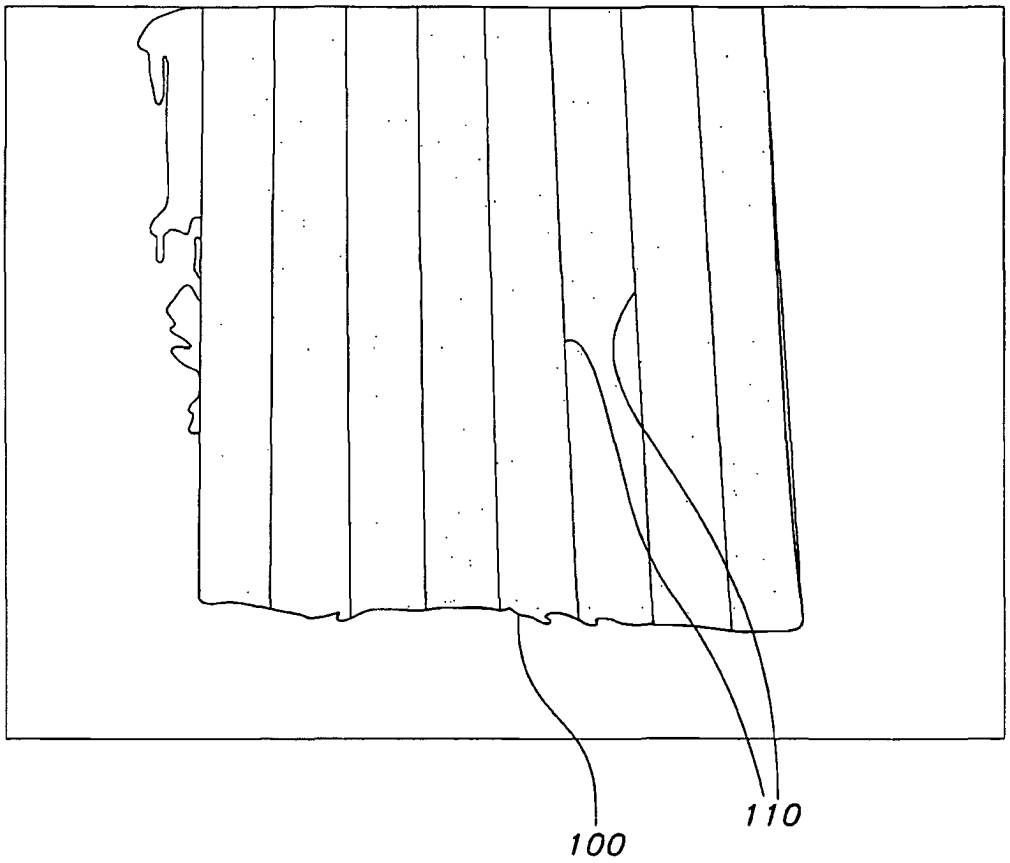


FIG. 9

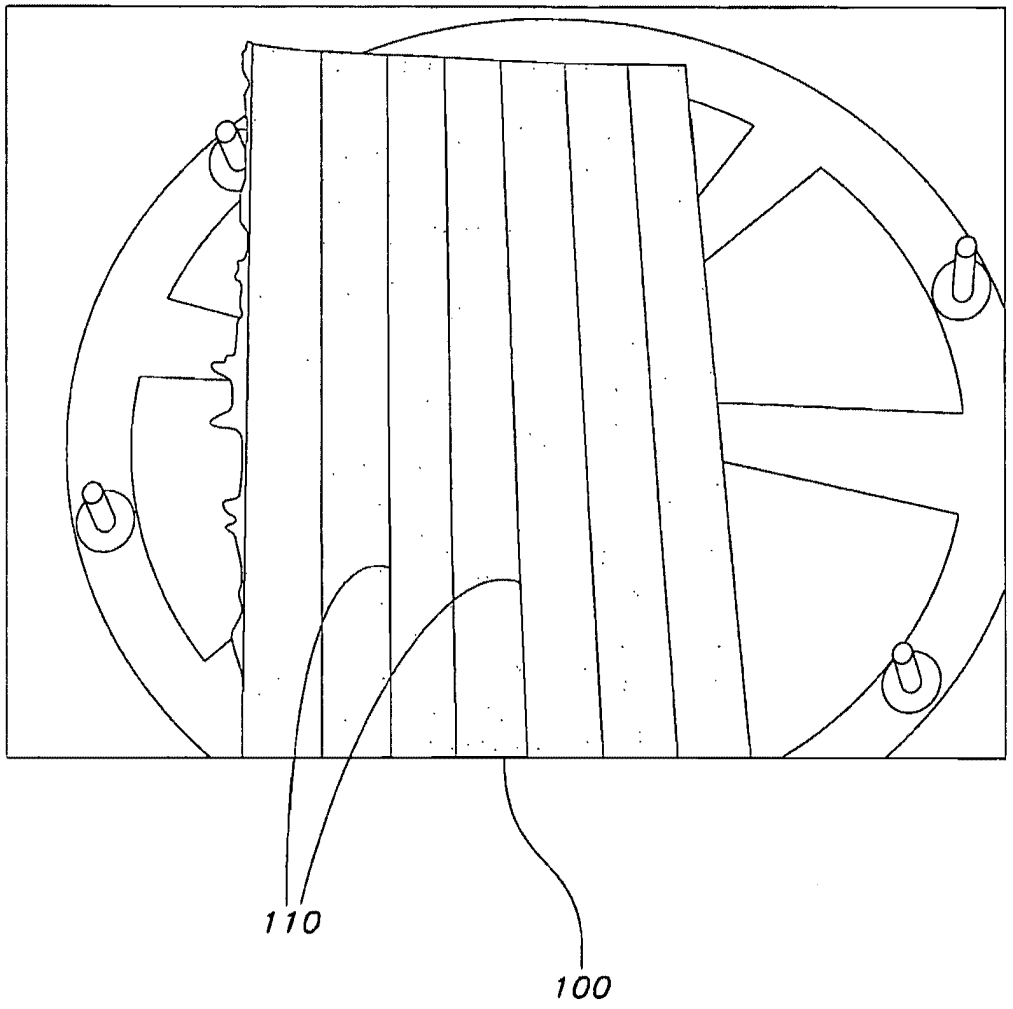


FIG. 10

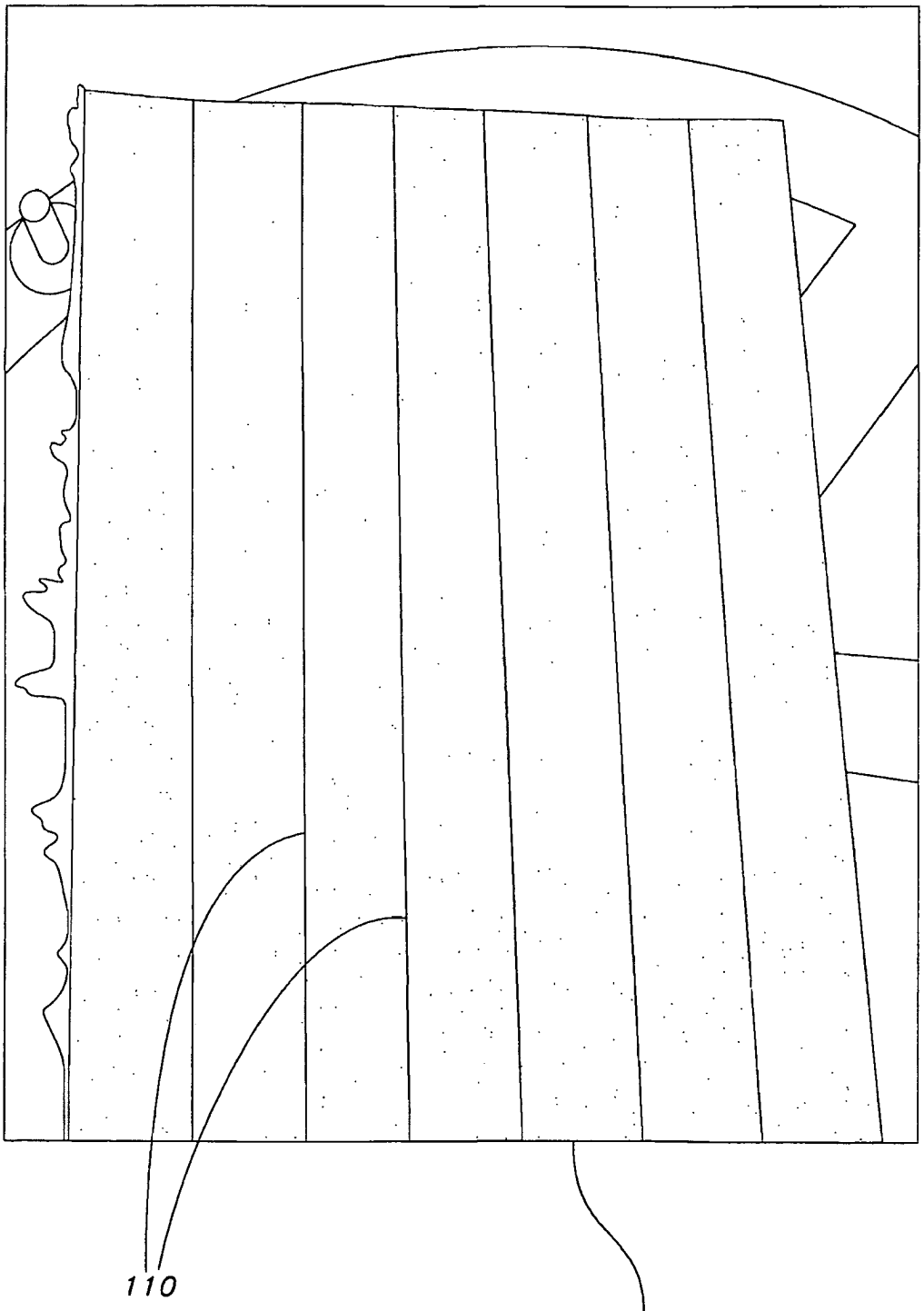


FIG. 11

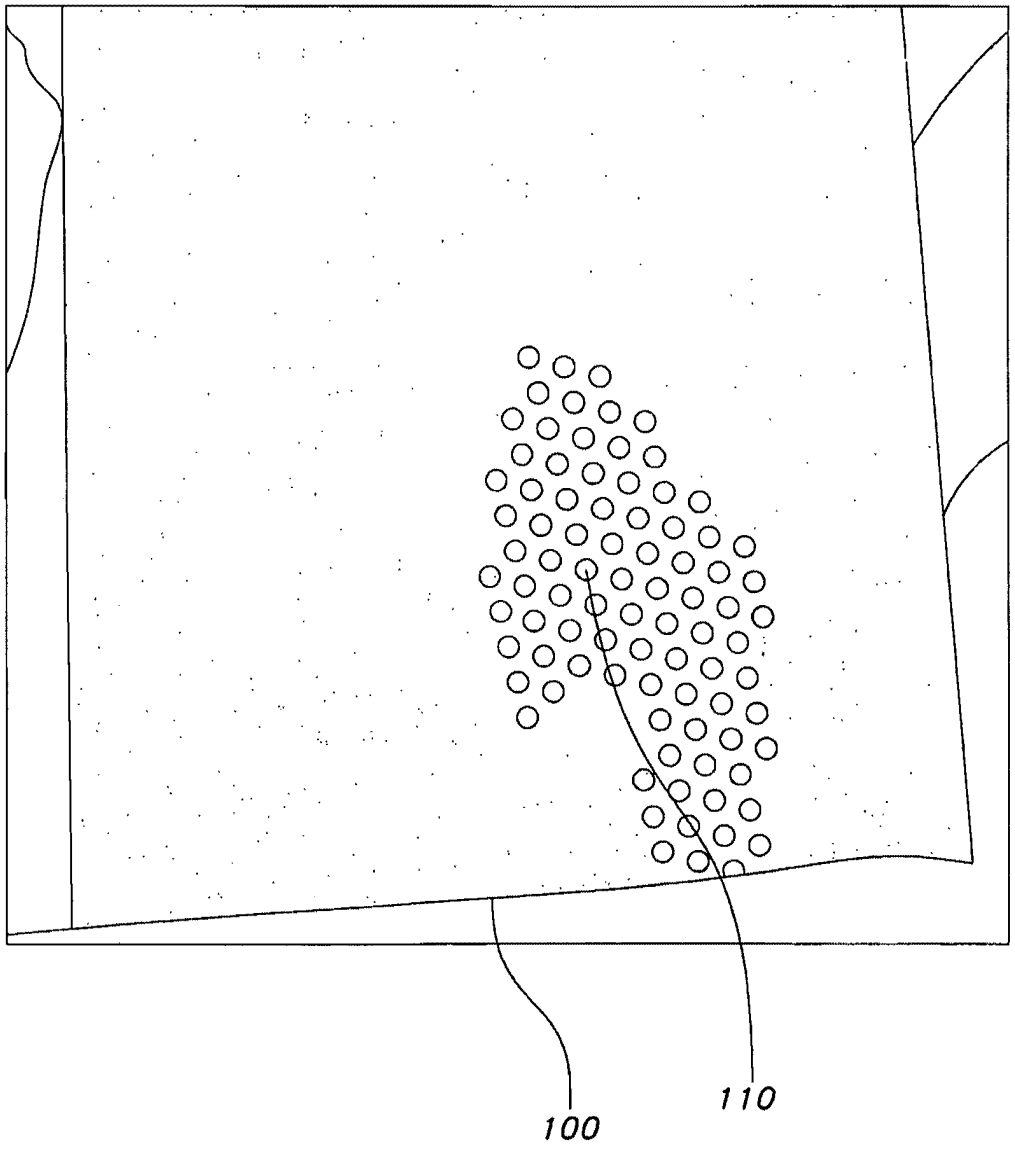


FIG. 12

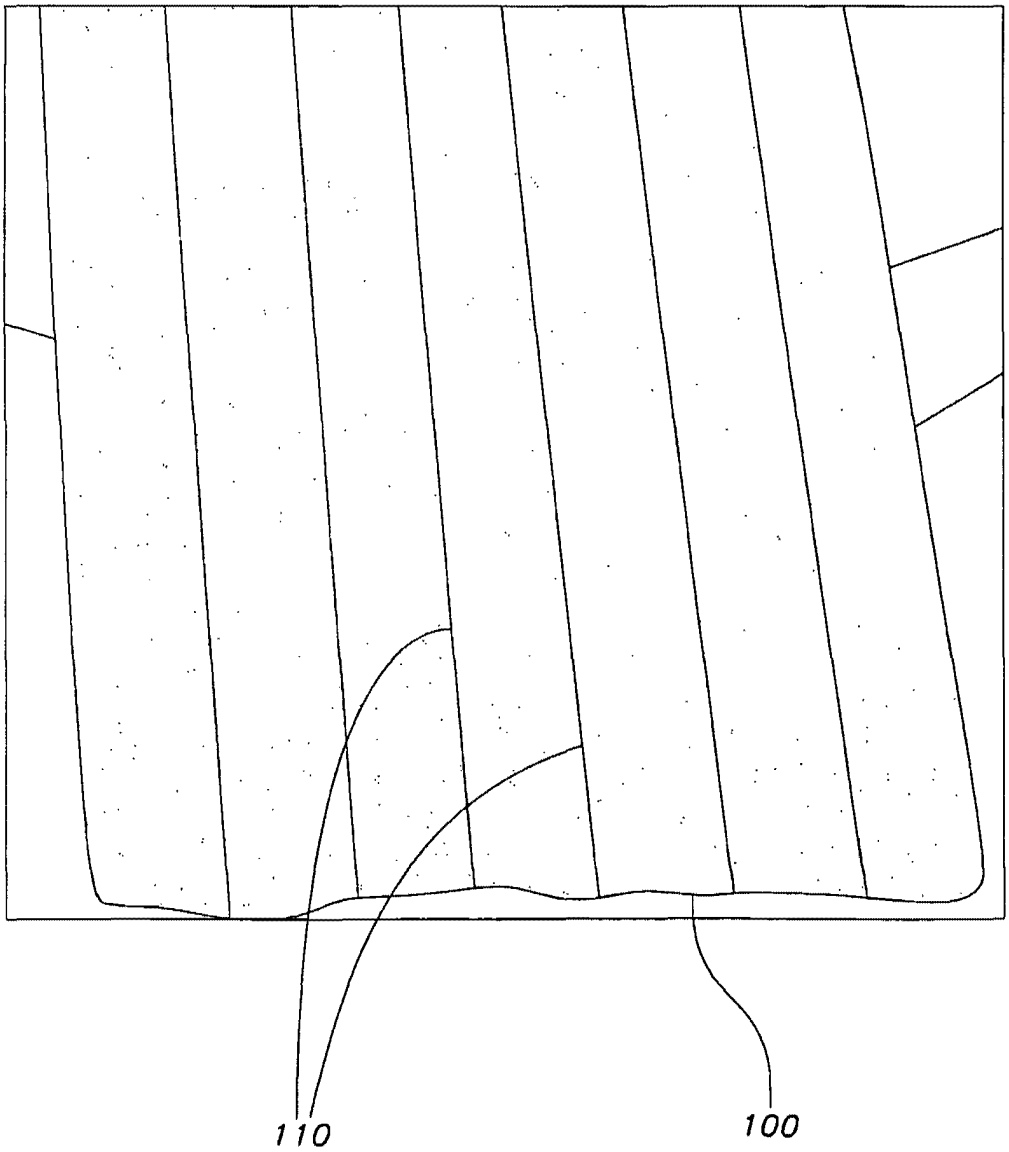


FIG. 13

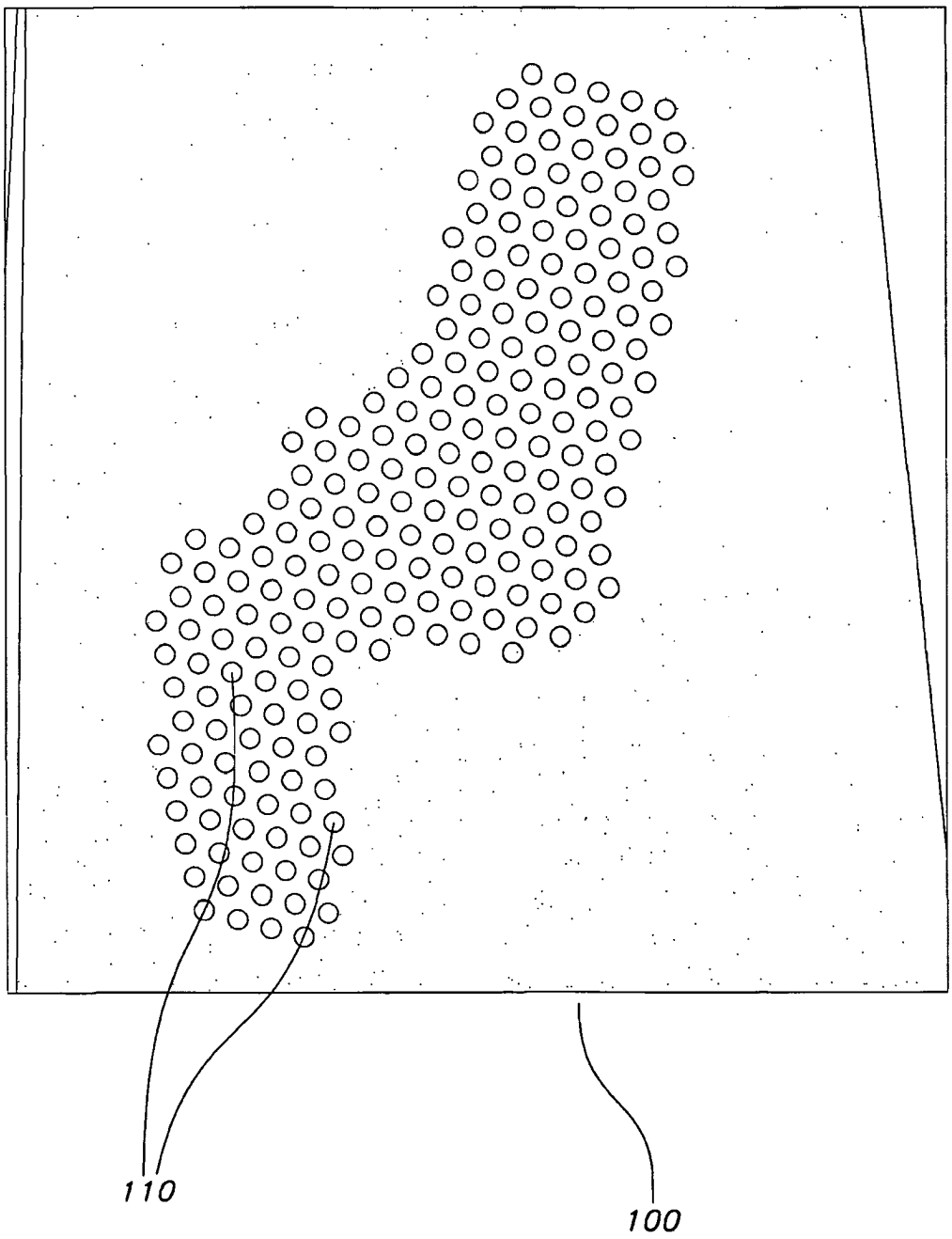


FIG. 14

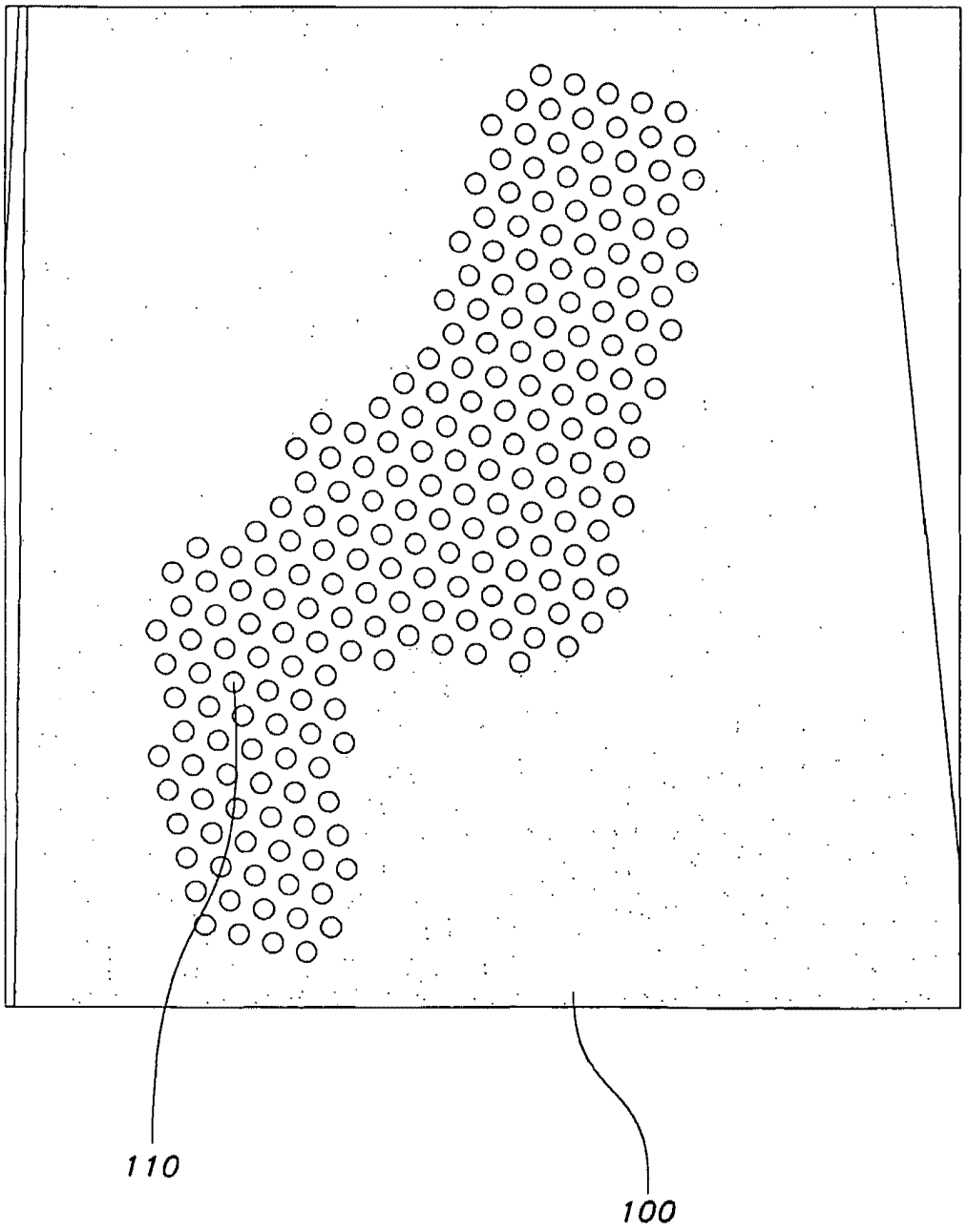


FIG. 15

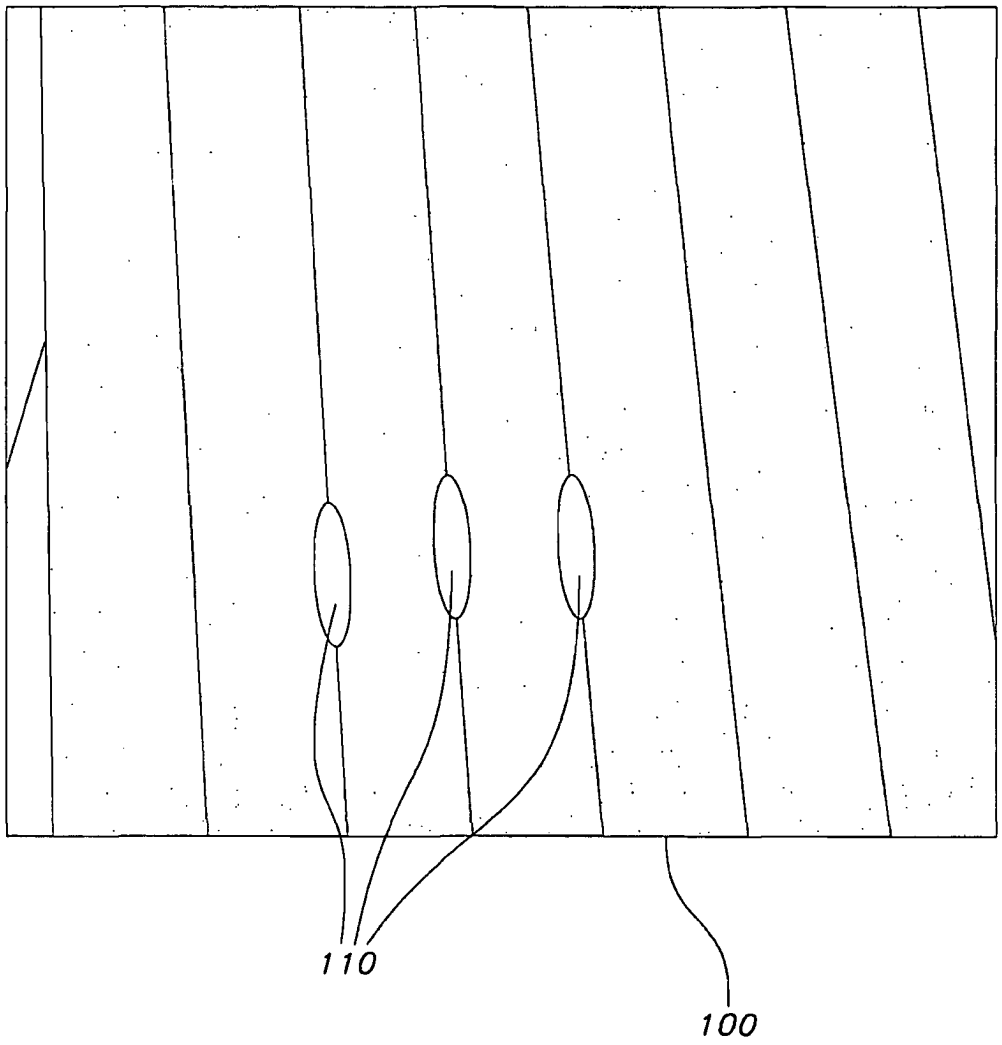


FIG. 16

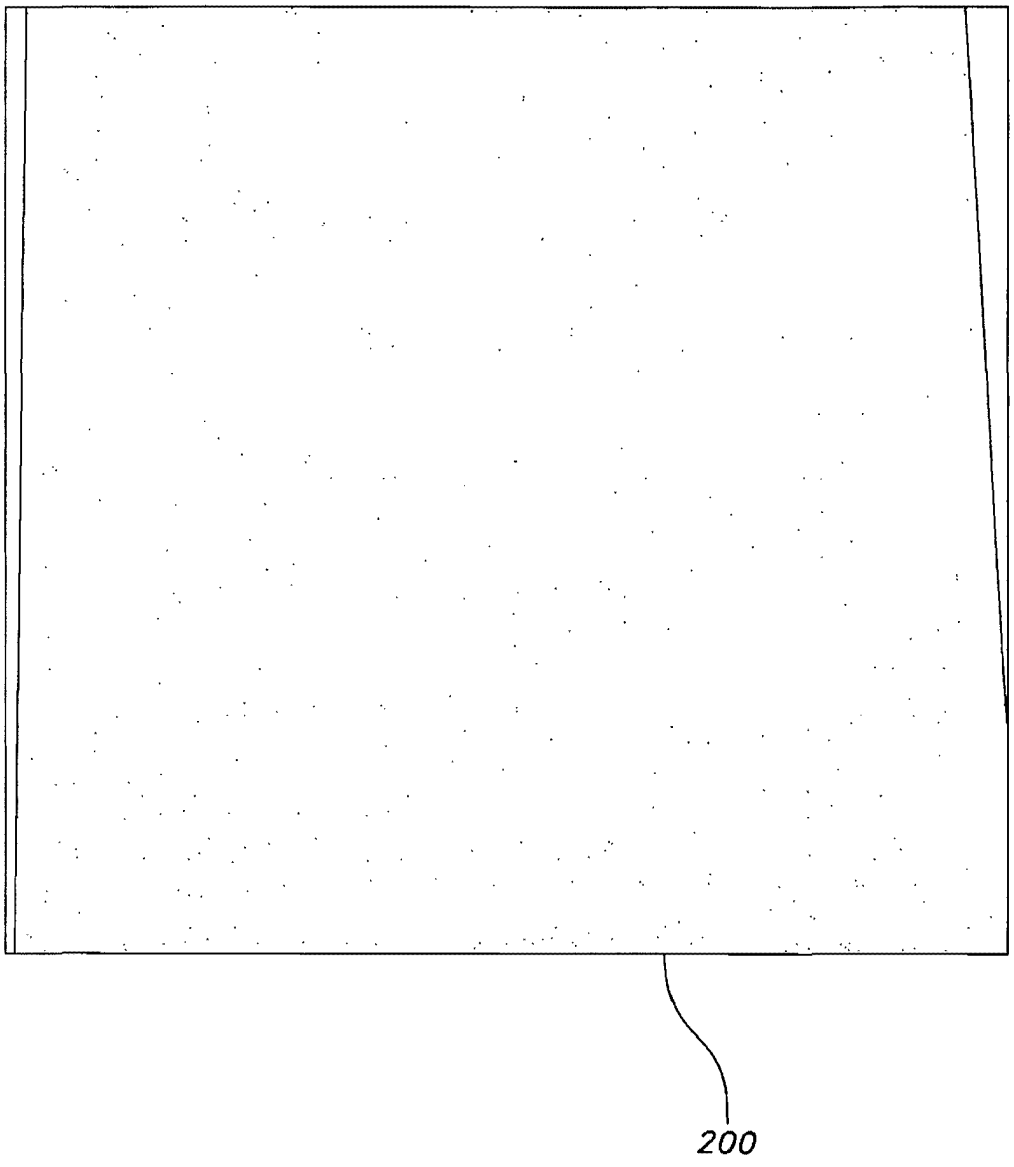


FIG. 17

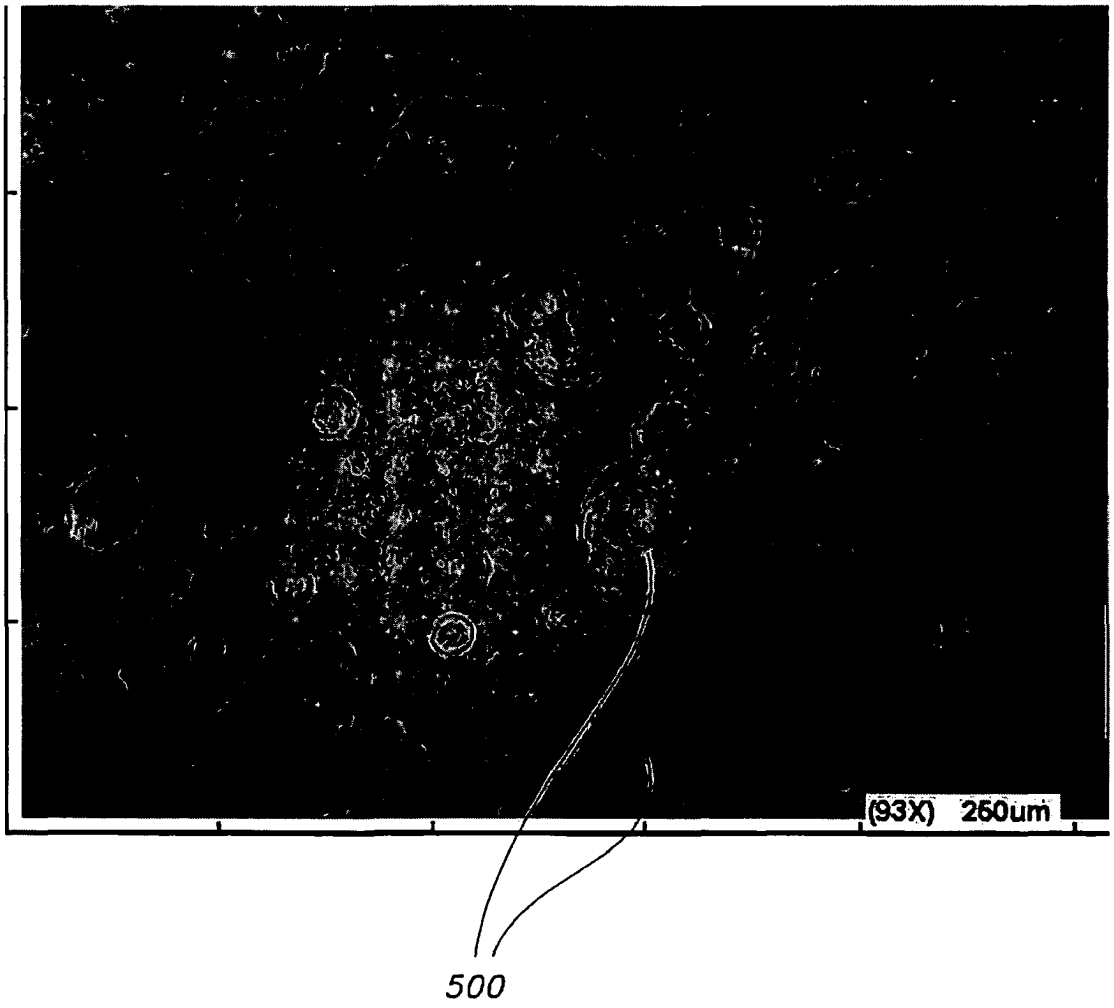


FIG. 18

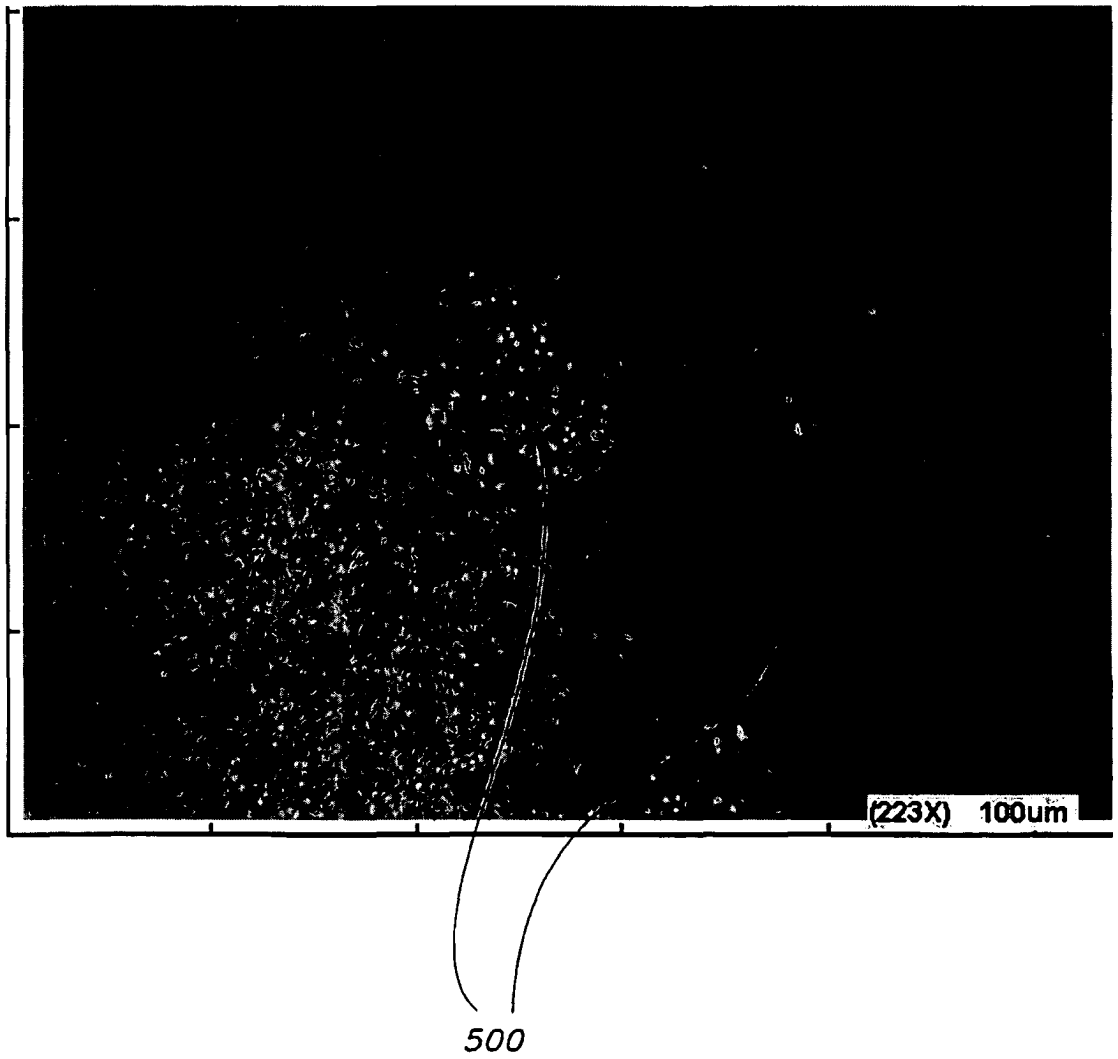


FIG. 19

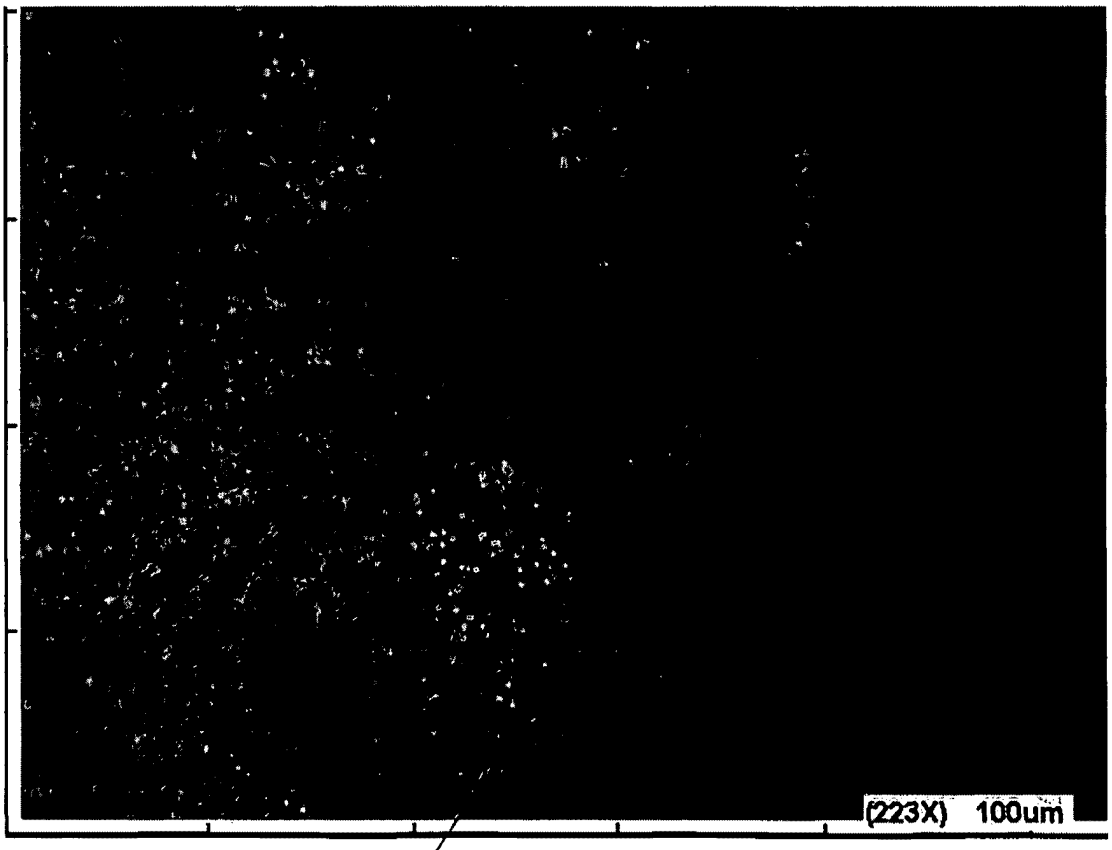


FIG. 20

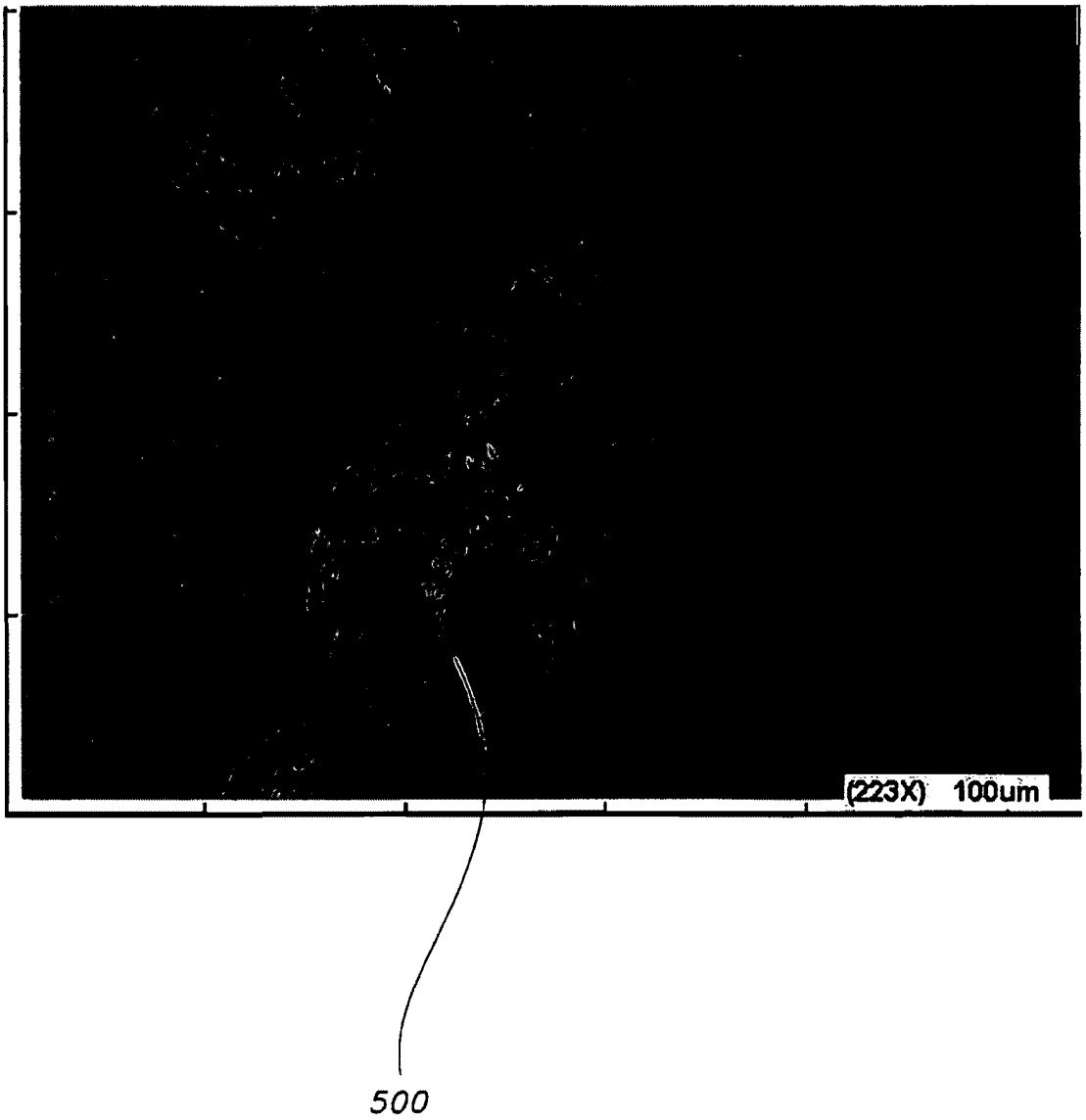


FIG. 21

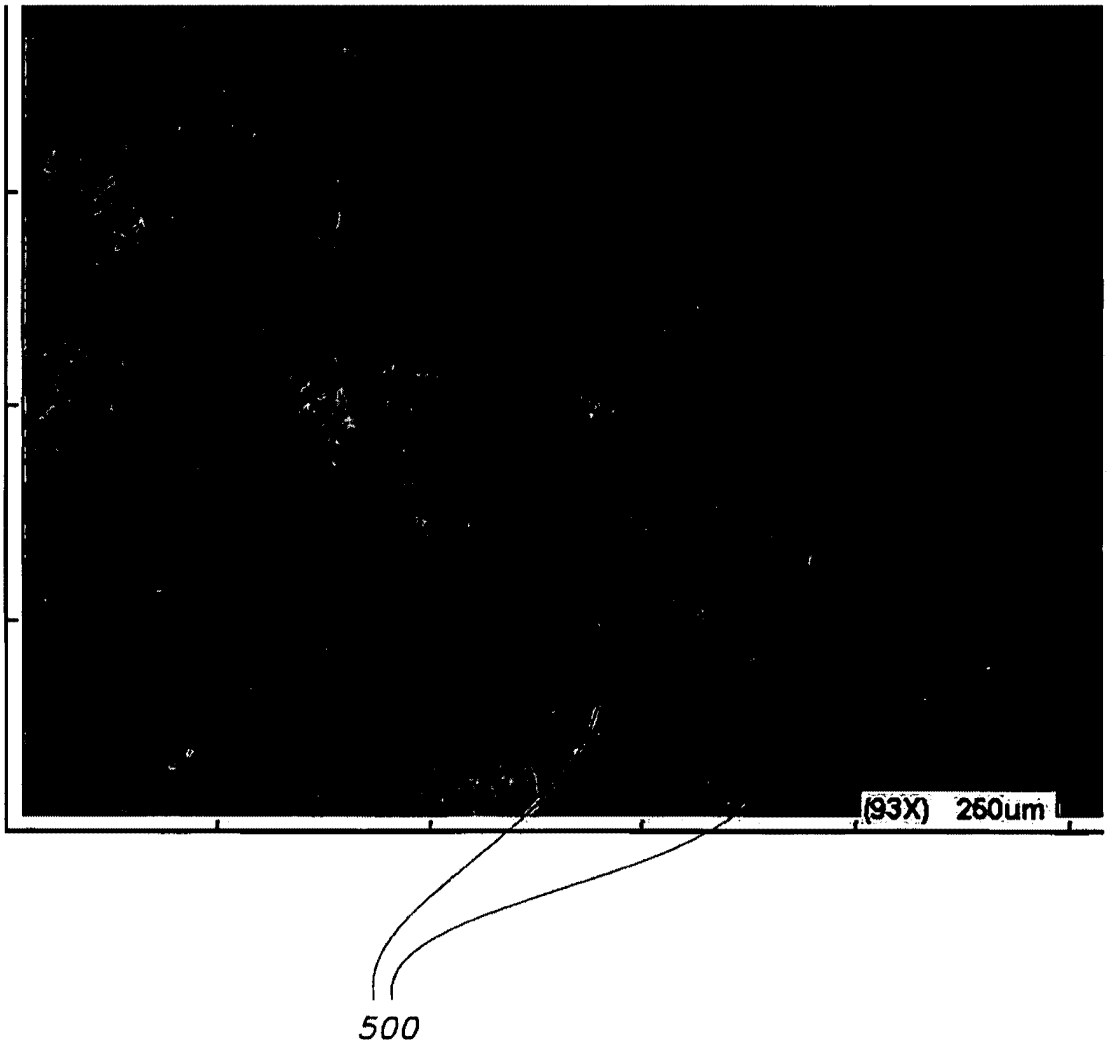


FIG. 22

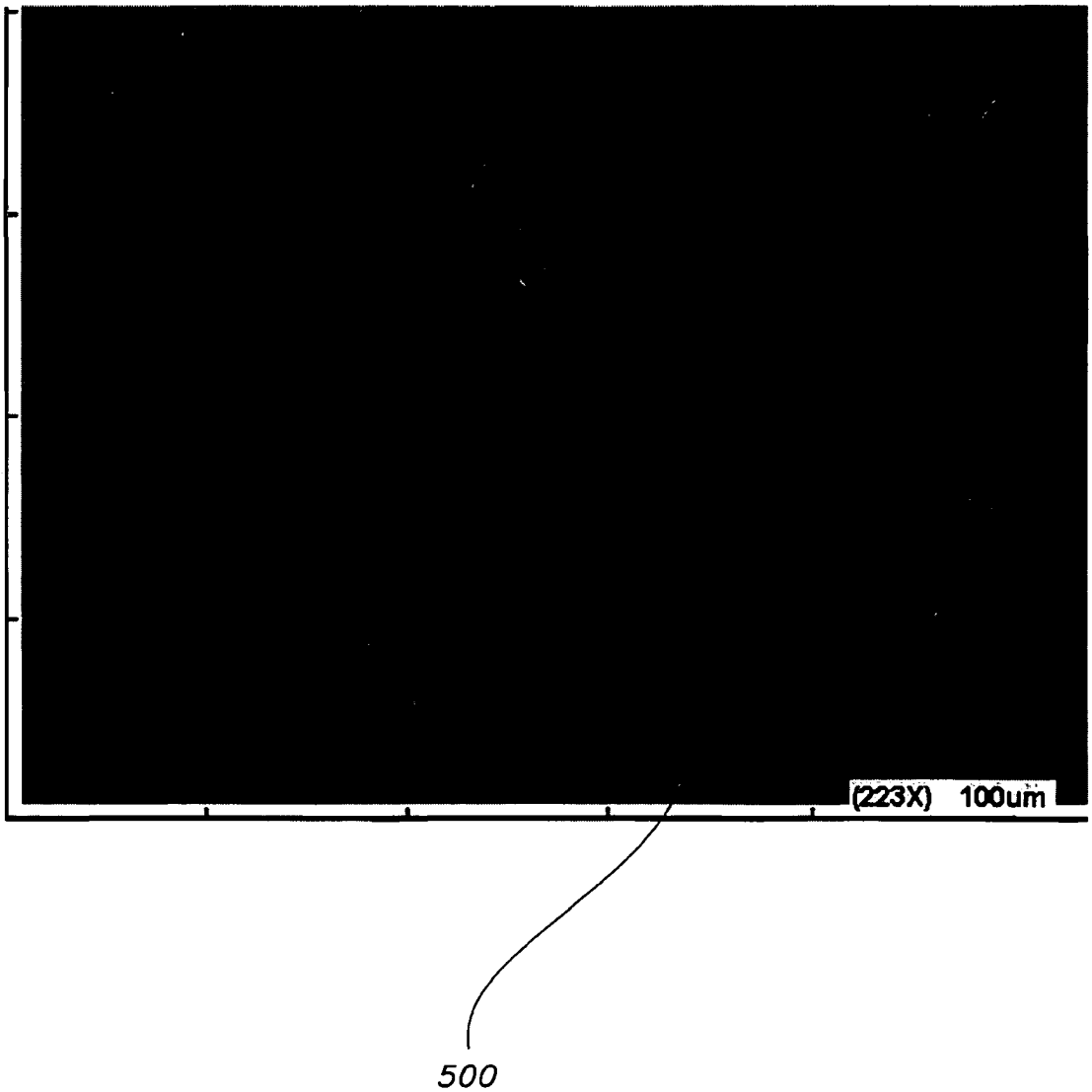


FIG. 23

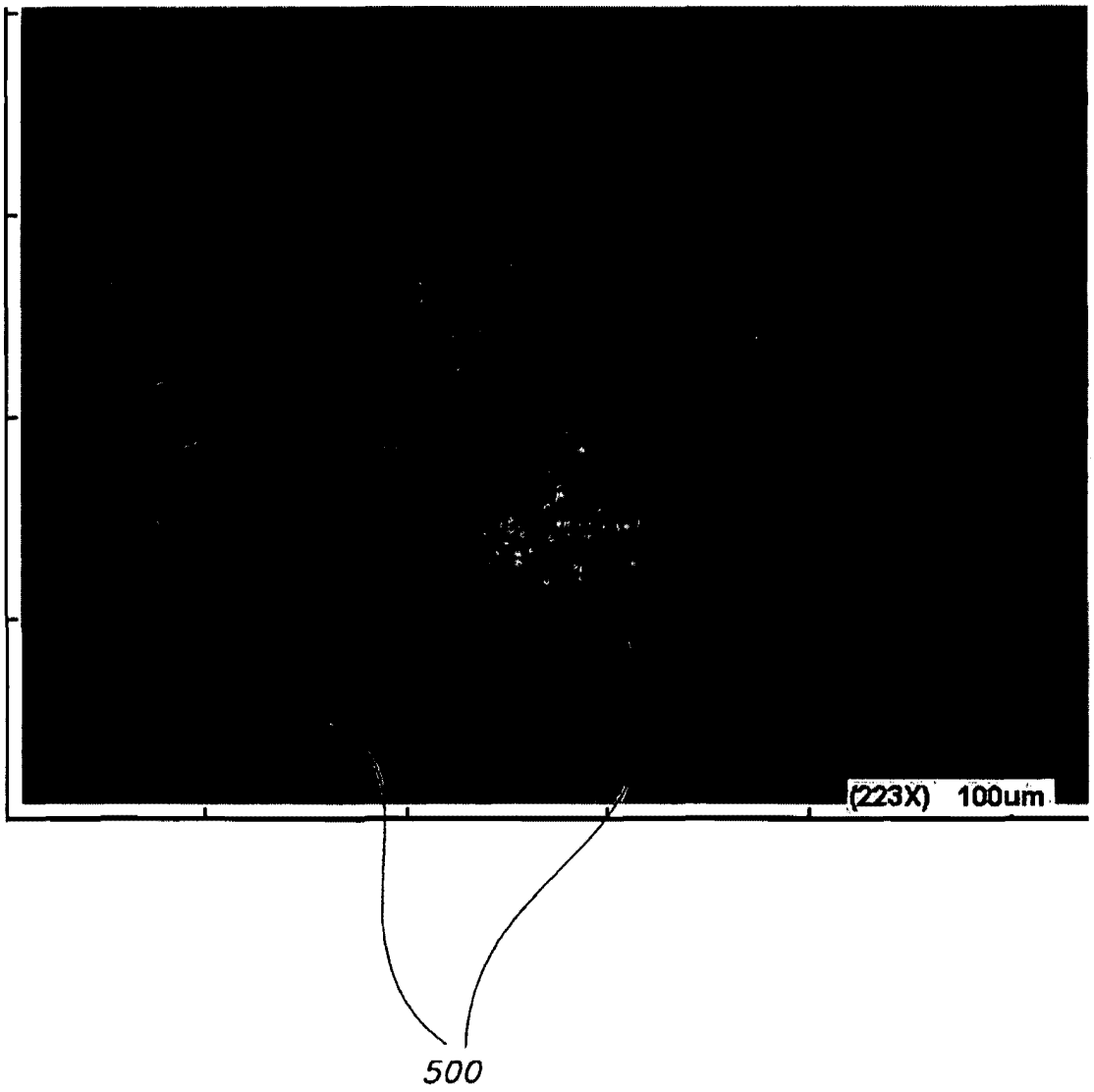


FIG. 24

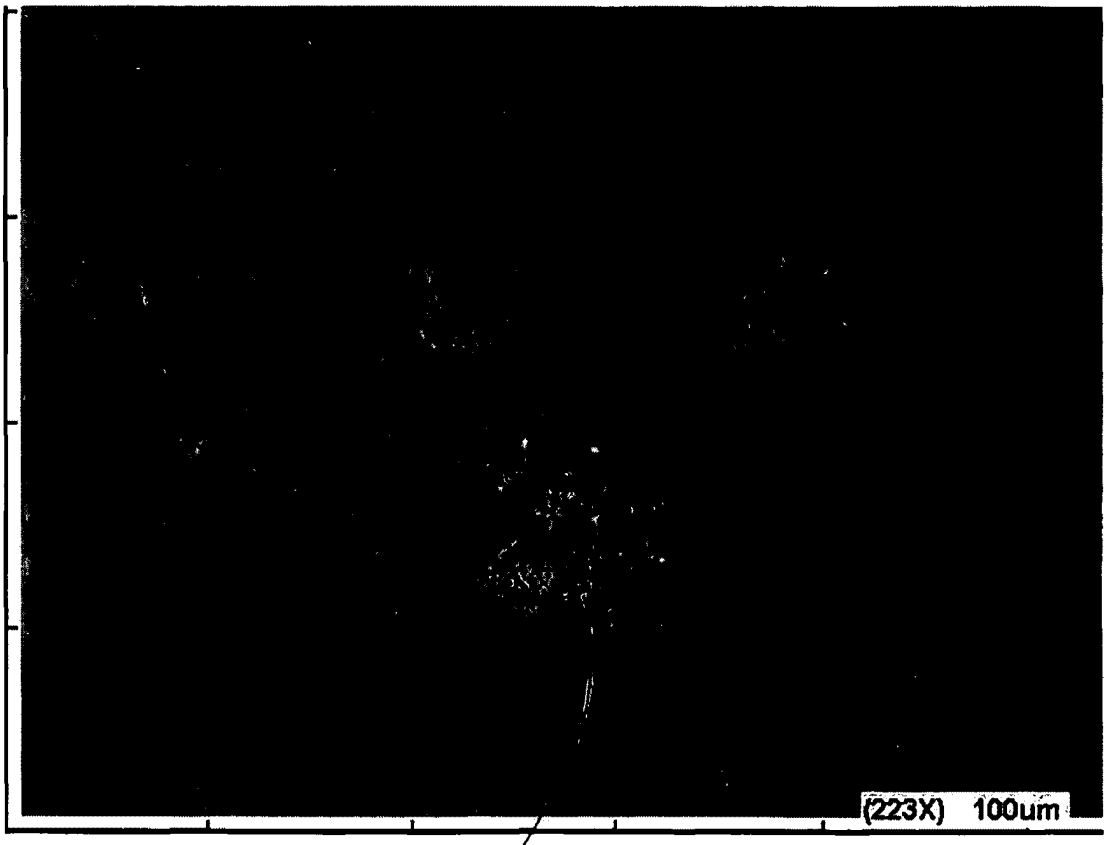


FIG. 25

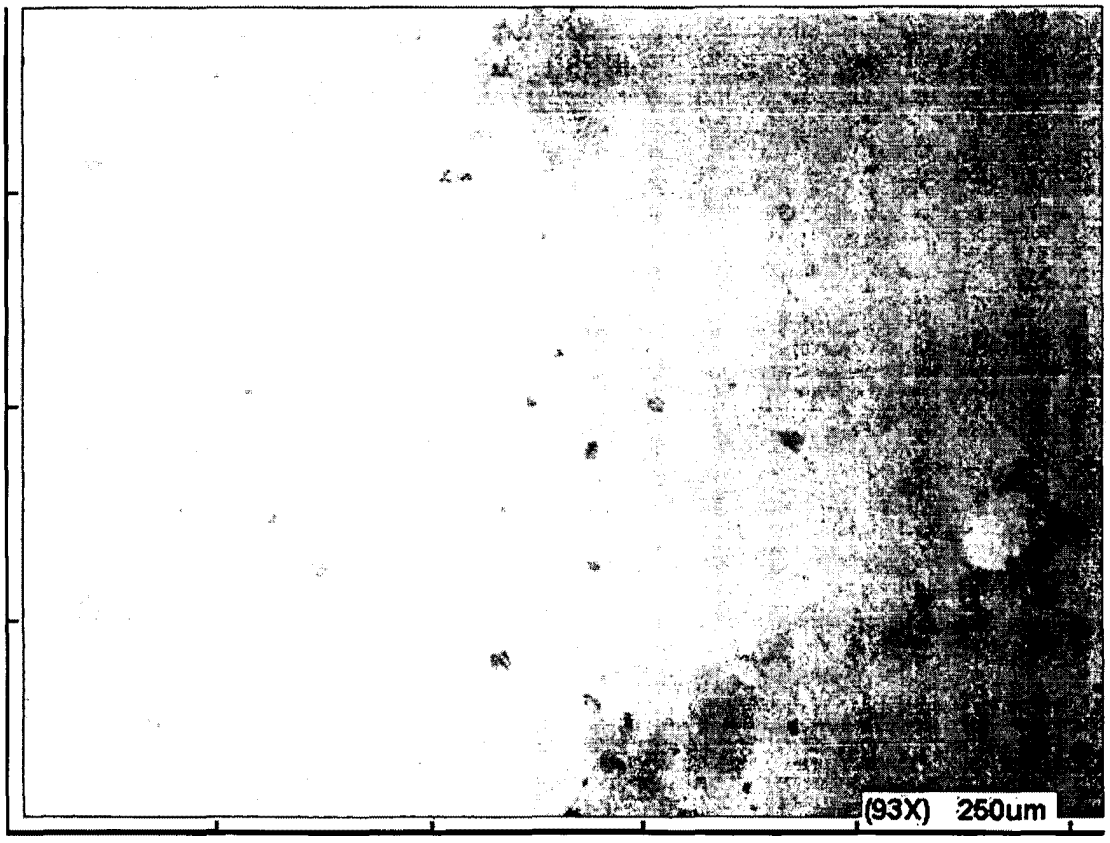


FIG. 26

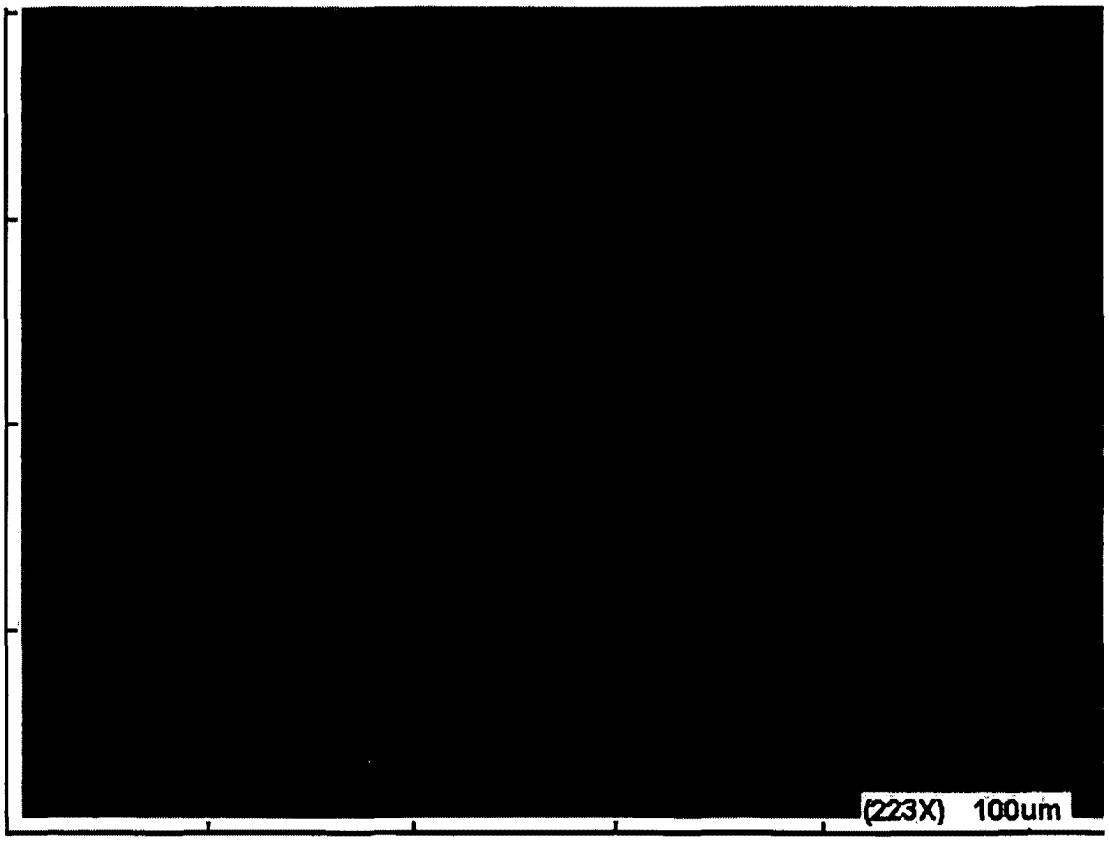


FIG. 27

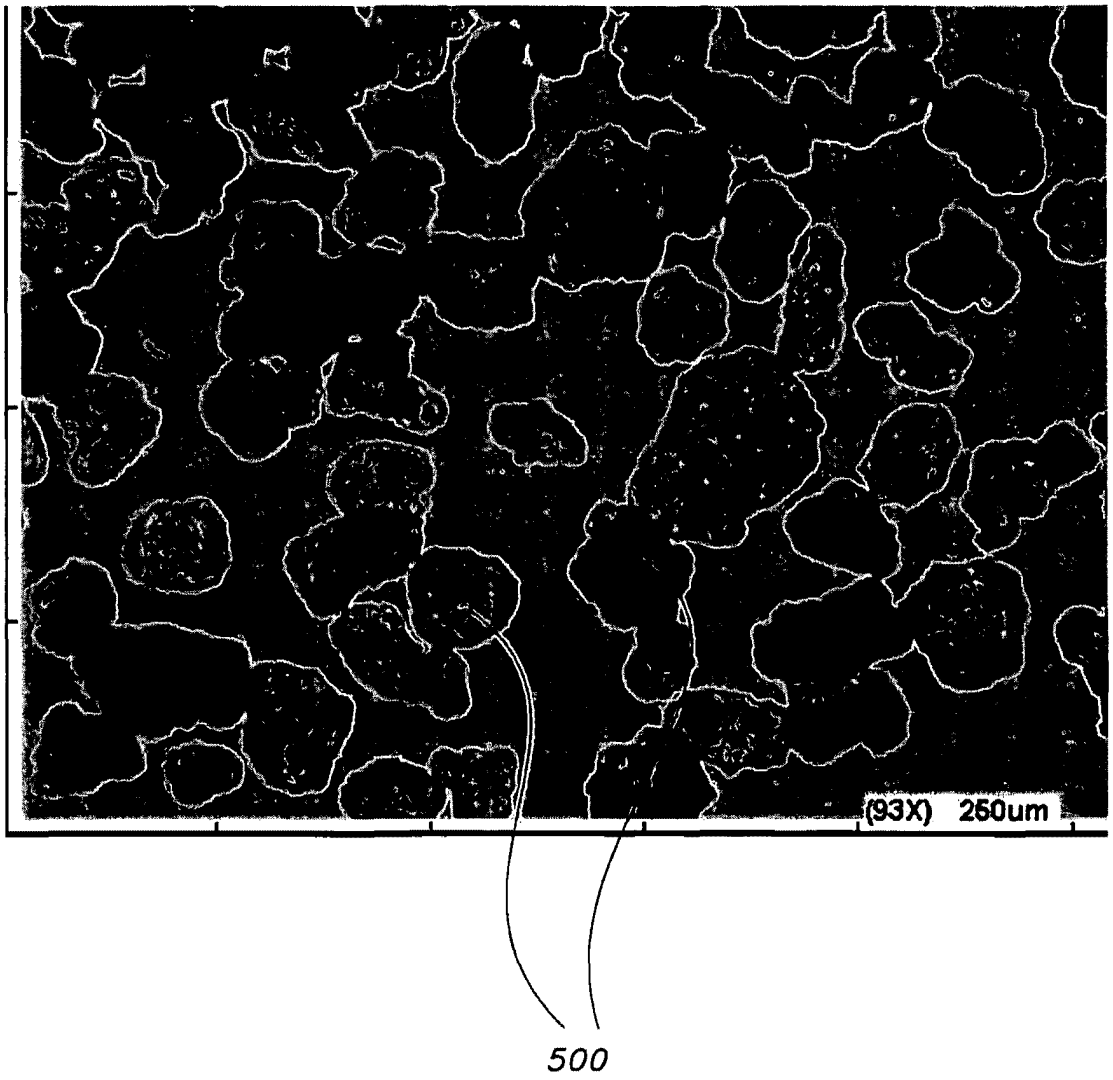


FIG. 28

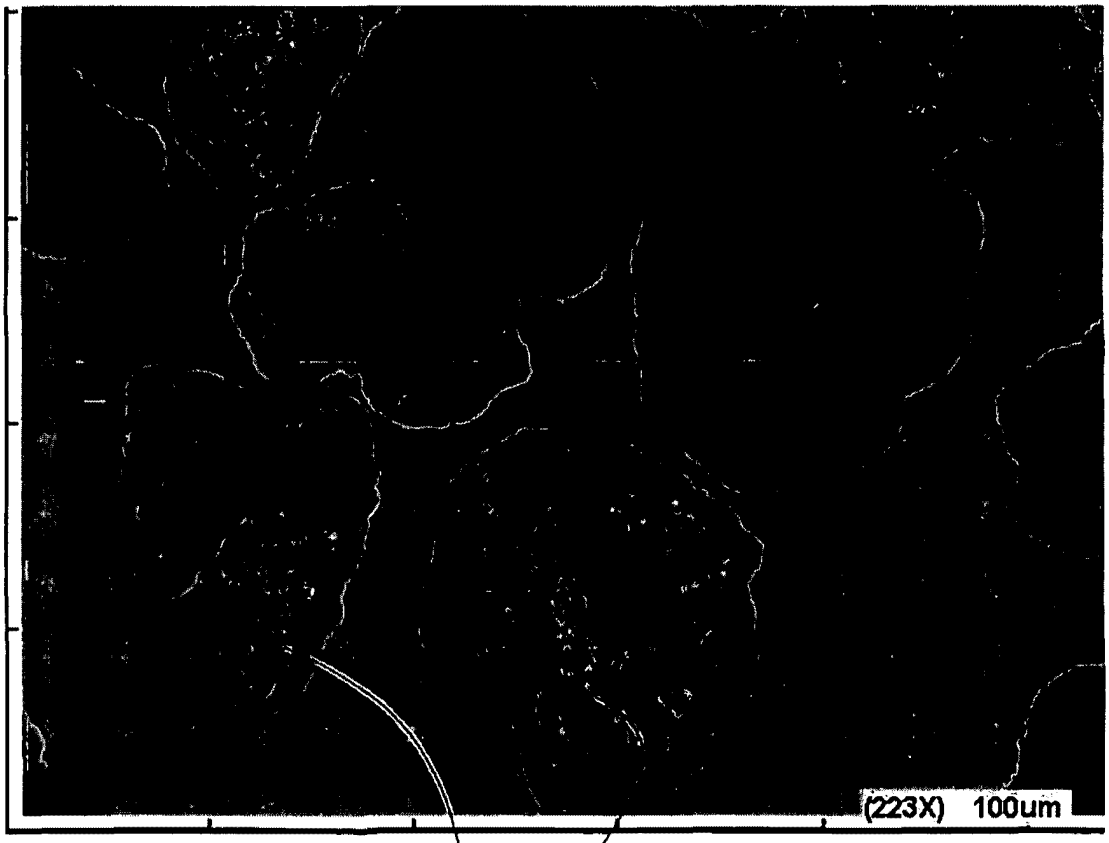


FIG. 29

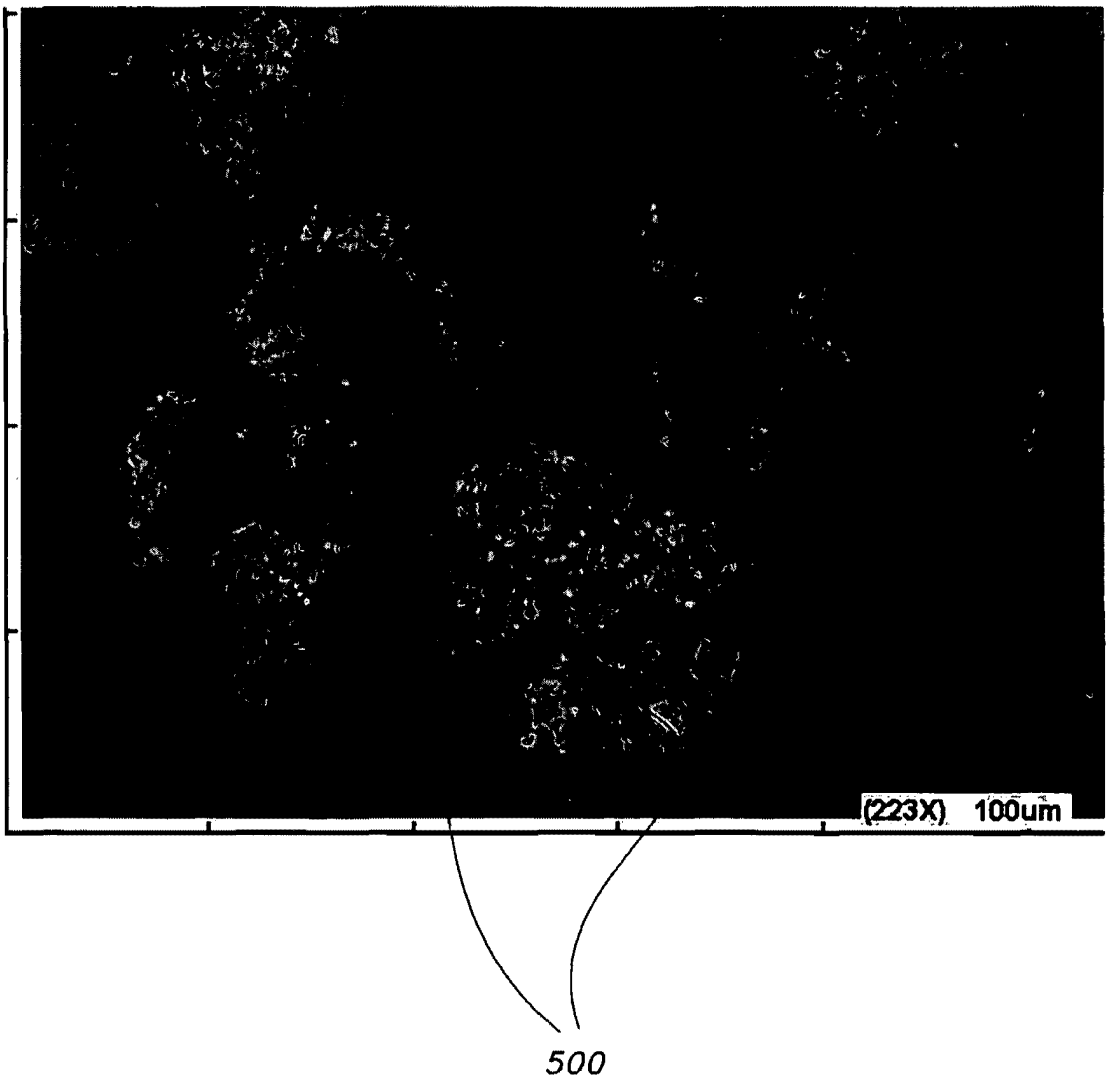


FIG. 30

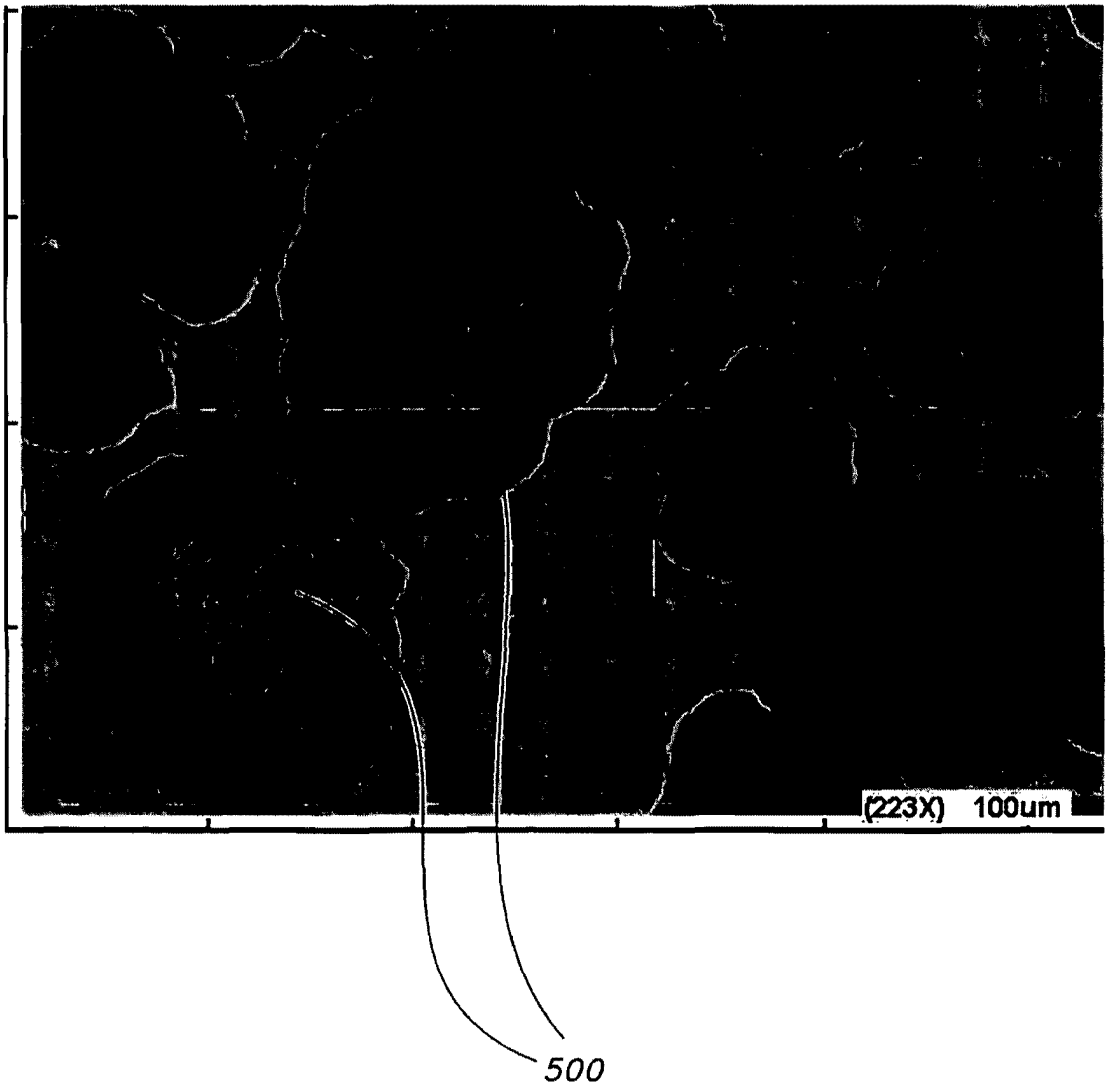


FIG. 31

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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/107,389	04/22/2008	1794	435	1199-26 DIV	18	2

CONFIRMATION NO. 9641

CORRECTED FILING RECEIPT

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

OC000000030734953

Date Mailed: 07/01/2008

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**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Gary L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOL RX, 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 DIV of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003
and is a CIP of PCT/US2002/032575 10/11/2002
and is a CIP of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and said 10/856,176 05/28/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002

Foreign Applications

If Required, Foreign Filing License Granted: 05/06/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/107,389**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Preliminary Class

428

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.

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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 (1-866-999-4158).

LICENSE FOR FOREIGN FILING UNDER

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

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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Yang, et al.	Examiner:	Unassigned
Serial No.:	12/107,389	Group Art Unit:	1794
Confirmation No.:	9641	Docket:	1199-26 DIV
Filed:	April 22, 2008	Dated:	June 26, 2008

For: POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 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 26, 2008

Signature: K.J. Goodhand/

REQUEST FOR CORRECTED FILING RECEIPT

Sir:

Applicant has reviewed the Filing Receipt in the above-identified application and has noted an error contained therein.

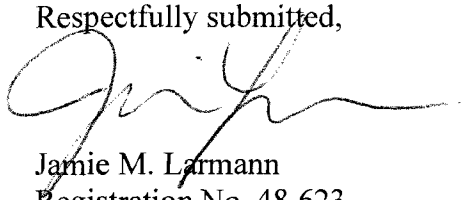
The domestic priority data for one of the applications is incorrect. In particular, U.S. Application No. 10/856,176 is a continuation-in-part (CIP) of International Application No. PCT/US02/32594, filed on 10/11/2002. This data is incorrectly listed as a "CON" on the Filing Receipt.

In view of the above, correction of the Filing Receipt is respectfully requested. Applicant submits that no fees are required to make these corrections. However, if any fees are required, please charge the same to Deposit Account No. 08-2461.

A copy of the Filing Receipt with the requested change indicated thereon is enclosed. Also enclosed is a copy of the application data sheet with the correct domestic priority data shown thereon.

If there are any comments or questions with respect to this matter, please contact the undersigned.

Respectfully submitted,



Jamie M. Larmann
Registration No. 48,623
Attorney for Applicants

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

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12/107,389	04/22/2008	1794	435	1199-26 DIV	18	2

CONFIRMATION NO. 9641

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

MAY 12 2008

FILING RECEIPT

OC000000029801735

Date Mailed: 05/09/2008

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**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
~~Gary~~ L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

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MAY 14 2008
HOFFMANN & BARON, NJ

Assignment For Published Patent Application

MONOSOL RX, 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 DIV of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003
and is a CIP of PCT/US2002/032575 10/11/2002
CIP and is a ~~CON~~ of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and said 10/856,176 05/28/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002

Foreign Applications

If Required, Foreign Filing License Granted: 05/06/2008

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Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
** **SMALL ENTITY** **
Title

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Preliminary Class

428

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NOT GRANTED

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PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Robert	K.	Yang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Flushing	State/Province	NY	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	138-10 Franklin Avenue, Apt. 2C		
Address 2			
City	Flushing	State/Province	NY
Postal Code	11355	Country i	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Richard	C.	Fuisz	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	McLean	State/Province	VA	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	1127 Langley Lane		
Address 2			
City	McLean	State/Province	VA
Postal Code	22101	Country i	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	L.	Myers	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Kingsport	State/Province	TN	Country of Residence i	US

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	908 Colfax Avenue				
Address 2					
City	Kingsport	**State/Province**	TN		
Postal Code	37660	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Joseph	M.	Fuisz	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Washington	**State/Province**	DC	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	1200 23rd Street, Apt. 905				
Address 2					
City	Washington	**State/Province**	DC		
Postal Code	20037	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23869		
Email Address	jlarmann@hoffmannbaron.com	Add Email	Remove Email

Application Information:

Title of the Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		
Attorney Docket Number	1199-26 DIV	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	34	**Suggested Figure for Publication (if any)**	1

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23869		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	10856176	2004-05-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	non provisional of	60473902	2003-05-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32575	2002-10-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32575	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32594	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	60414276	2002-09-27
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32542	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	60371940	2002-04-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. [X]

Organization Name	MonoSol Rx, LLC		
Mailing Address Information:			
Address 1	6560 Melton Road		
Address 2			
City	Portage	**State/Province**	IN
Country [i]	US	Postal Code	46368
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Jamie M. Larmann, Reg. No. 48,623/			Date (YYYY-MM-DD)	2008-04-22
First Name	Jamie M.	Last Name	Larmann	Registration Number	48623

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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

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.

Electronic Acknowledgement Receipt

EFS ID:	3523685
Application Number:	12107389
International Application Number:	
Confirmation Number:	9641
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jamie Mercer Larmann/Kathleen Goodhand
Filer Authorized By:	Jamie Mercer Larmann
Attorney Docket Number:	1199-26 DIV
Receipt Date:	26-JUN-2008
Filing Date:	22-APR-2008
Time Stamp:	14:30:22
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	1199-26_DIV_-_Request_For_Corrected_Filing_Receipt.pdf	22909 a328a5b24db050140da297d327e7113d65fb5b4f	no	2

Warnings:	
Information:	

2	Request for Corrected Filing Receipt	1199-26_DIV_-_Filing_Receipt.pdf	158800 695033440d832ea8685af35969b62f01d5680885	no	3
Warnings:					
Information:					
3	Request for Corrected Filing Receipt	1199-26_DIV_ADS.pdf	14980469 2de90c00a9e251f0dd7cc398bf715b7a734455b1	no	6
Warnings:					
Information:					
			Total Files Size (in bytes):	15162178	

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 NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
12/107,389	04/22/2008	Robert K. Yang	1199-26 DIV

CONFIRMATION NO. 9641

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

FORMALITIES LETTER

OC000000029801736

Date Mailed: 05/09/2008

NOTICE TO FILE CORRECTED APPLICATION PAPERS

Filing Date Granted

An application number and filing date have been accorded to this application. The application is informal since it does not comply with the regulations for the reason(s) indicated below. Applicant is given TWO MONTHS from the date of this Notice within which to correct the informalities indicated below. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

The required item(s) identified below must be timely submitted to avoid abandonment:

- Replacement drawings in compliance with 37 CFR 1.84 and 37 CFR 1.121(d) are required. The drawings submitted are not acceptable because:
  - The drawings submitted to the Office are not electronically reproducible because portions of figures 9 - 31 are missing and/or blurry.

Applicant is cautioned that correction of the above items may cause the specification and drawings page count to exceed 100 pages. If the specification and drawings exceed 100 pages, applicant will need to submit the required application size fee.

Replies should be mailed to:

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Commissioner for Patents
P.O. Box 1450
Alexandria VA 22313-1450

Registered users of EFS-Web may alternatively submit their reply to this notice via EFS-Web.
https://sportal.uspto.gov/authenticate/AuthenticateUserLocalEPF.html

For more information about EFS-Web please call the USPTO Electronic Business Center at **1-866-217-9197** or visit our website at http://www.uspto.gov/ebc.

If you are not using EFS-Web to submit your reply, you must include a copy of this notice.

/hnguyen/

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

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 NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	TOT CLAIMS	IND CLAIMS
12/107,389	04/22/2008	1794	435	1199-26 DIV	18	2

CONFIRMATION NO. 9641

23869
HOFFMANN & BARON, LLP
6900 JERICHO TURNPIKE
SYOSSET, NY 11791

FILING RECEIPT

OC00000029801735

Date Mailed: 05/09/2008

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**

Applicant(s)

Robert K. Yang, Flushing, NY;
Richard C. Fuisz, McLean, VA;
Gary L. Myers, Kingsport, TN;
Joseph M. Fuisz, Washington, DC;

Assignment For Published Patent Application

MONOSOL RX, 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 DIV of 10/856,176 05/28/2004
which claims benefit of 60/473,902 05/28/2003
and is a CIP of PCT/US2002/032575 10/11/2002
and is a CON of PCT/US02/32594 10/11/2002
which claims benefit of 60/414,276 09/27/2002
and said 10/856,176 05/28/2004
is a CIP of PCT/US02/32542 10/11/2002
which claims benefit of 60/371,940 04/11/2002

Foreign Applications

If Required, Foreign Filing License Granted: 05/06/2008

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 12/107,389**

Projected Publication Date: To Be Determined - pending completion of Corrected Papers

Non-Publication Request: No

Early Publication Request: No
**** SMALL ENTITY ****
Title

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

Preliminary Class

428

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 (1-866-999-4158).

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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).

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76.
This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.

Secrecy Order 37 CFR 5.2

☐ Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)

Applicant Information:

Applicant 1 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Robert	K.	Yang	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Flushing	State/Province	NY	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	138-10 Franklin Avenue, Apt. 2C		
Address 2			
City	Flushing	State/Province	NY
Postal Code	11355	Country i	US

Applicant 2 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Richard	C.	Fuisz	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	McLean	State/Province	VA	Country of Residence i	US

Citizenship under 37 CFR 1.41(b) i: US

Mailing Address of Applicant:

Address 1	1127 Langley Lane		
Address 2			
City	McLean	State/Province	VA
Postal Code	22101	Country i	US

Applicant 3 Remove

Applicant Authority ◉ Inventor ○ Legal Representative under 35 U.S.C. 117 ○ Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Garry	L.	Myers	

Residence Information (Select One) ◉ US Residency ○ Non US Residency ○ Active US Military Service

City	Kingsport	State/Province	TN	Country of Residence i	US

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	908 Colfax Avenue				
Address 2					
City	Kingsport	**State/Province**	TN		
Postal Code	37660	**Country**i	US		

Applicant 4 Remove

Applicant Authority (•) Inventor ( ) Legal Representative under 35 U.S.C. 117 ( ) Party of Interest under 35 U.S.C. 118

Prefix	Given Name	Middle Name	Family Name	Suffix
	Joseph	M.	Fuisz	

Residence Information (Select One) (•) US Residency ( ) Non US Residency ( ) Active US Military Service

City	Washington	**State/Province**	DC	**Country of Residence** i	US
Citizenship under 37 CFR 1.41(b) i	US				
Mailing Address of Applicant:					
Address 1	1200 23rd Street, Apt. 905				
Address 2					
City	Washington	**State/Province**	DC		
Postal Code	20037	**Country**i	US		

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button. Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.
For further information see 37 CFR 1.33(a).

☐ **An Address is being provided for the correspondence Information of this application.**

Customer Number	23869		
Email Address	jlarmann@hoffmannbaron.com	Add Email	Remove Email

Application Information:

Title of the Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM		
Attorney Docket Number	1199-26 DIV	**Small Entity Status Claimed**	☒
Application Type	Nonprovisional		
Subject Matter	Utility		
Suggested Class (if any)		**Sub Class (if any)**	
Suggested Technology Center (if any)			
Total Number of Drawing Sheets (if any)	34	**Suggested Figure for Publication (if any)**	1

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S. C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32).
Enter either Customer Number or complete the Representative Name section below. If both sections are completed the Customer Number will be used for the Representative Information during processing.

Please Select One:	◉ Customer Number	○ US Patent Practitioner	○ Limited Recognition (37 CFR 11.9)
Customer Number	23869		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, or 365(c) or indicate National Stage entry from a PCT application. Providing this information in the application data sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78(a)(2) or CFR 1.78(a)(4), and need not otherwise be made part of the specification.

Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
	Division of	10856176	2004-05-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	non provisional of	60473902	2003-05-28
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32575	2002-10-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32575	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32594	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	60414276	2002-09-27
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32594	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-21
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10856176	Continuation in part of	PCT/US02/32542	2002-10-11
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	60371940	2002-04-11
Prior Application Status	Pending		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
PCT/US02/32542	non provisional of	10074272	2002-02-14
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60328868	2001-10-12
Prior Application Status	Expired		Remove
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)
10074272	non provisional of	60386937	2002-06-07
Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.			Add

Foreign Priority Information:

PTO/SB/14 (07-07)
Approved for use through 06/30/2010. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	1199-26 DIV
	Application Number	
Title of Invention	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM	

This section allows for the applicant to claim benefit of foreign priority and to identify any prior foreign application for which priority is not claimed. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55(a).

Remove

Application Number	Country [i]	Parent Filing Date (YYYY-MM-DD)	Priority Claimed
			(•) Yes ( ) No

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button. Add

Assignee Information:

Providing this information in the application data sheet does not substitute for compliance with any requirement of part 3 of Title 37 of the CFR to have an assignment recorded in the Office.

Assignee 1 Remove

If the Assignee is an Organization check here. [X]

Organization Name	MonoSol Rx, LLC		
Mailing Address Information:			
Address 1	6560 Melton Road		
Address 2			
City	Portage	**State/Province**	IN
Country [i]	US	Postal Code	46368
Phone Number		Fax Number	
Email Address			

Additional Assignee Data may be generated within this form by selecting the **Add** button. Add

Signature:

A signature of the applicant or representative is required in accordance with 37 CFR 1.33 and 10.18. Please see 37 CFR 1.4(d) for the form of the signature.

Signature	/Jamie M. Larmann, Reg. No. 48,623/			Date (YYYY-MM-DD)	2008-04-22
First Name	Jamie M.	Last Name	Larmann	Registration Number	48623

This collection of information is required by 37 CFR 1.76. 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 23 minutes to complete, including gathering, preparing, and submitting the completed application data sheet 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.**

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Electronic Patent Application Fee Transmittal

Application Number:	
Filing Date:	
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Filer:	Jamie Mercer Larmann/Barbara Thomas
Attorney Docket Number:	1199-26 DIV

Filed as Small Entity

Utility Filing Fees

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Basic Filing:				
Utility filing Fee (Electronic filing)	4011	1	75	75
Utility Search Fee	2111	1	255	255
Utility Examination Fee	2311	1	105	105
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD($)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
		Total in USD ($)		**435**

Electronic Acknowledgement Receipt

EFS ID:	3190525
Application Number:	12107389
International Application Number:	
Confirmation Number:	9641
Title of Invention:	POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM
First Named Inventor/Applicant Name:	Robert K. Yang
Customer Number:	23869
Filer:	Jamie Mercer Larmann/Barbara Thomas
Filer Authorized By:	Jamie Mercer Larmann
Attorney Docket Number:	1199-26 DIV
Receipt Date:	22-APR-2008
Filing Date:	
Time Stamp:	15:37:53
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	Deposit Account
Payment was successfully received in RAM	$435
RAM confirmation Number	895
Deposit Account	082461
Authorized User	

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File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Application Data Sheet	1199-26_DIV_ADS.pdf	14980469 2de90c00a9e251f0dd7cc398bf715b7a734455b1	no	6
Warnings:					
Information:					
2		1199-26_DIV_Application.pdf	3678435 f198d3ea792199735fe5a65fe9b5ddc95c2fcfb2	yes	94

Multipart Description/PDF files in .zip description

Document Description	Start	End
Specification	1	90
Claims	91	93
Abstract	94	94

Warnings:					
Information:					
3	Drawings-only black and white line drawings	1199-26_DIV_Drawings.pdf	2123661 42063a7ecb28d7c416152f05d3da72d6af87cd66	no	34
Warnings:					
Information:					
4	Oath or Declaration filed	1199-26_DIV_Declaration.pdf	198021 4ea8dda3e045079b17ed73c361d5f687bf238048	no	7
Warnings:					
Information:					
5	Fee Worksheet (PTO-06)	fee-info.pdf	8423 ac1815172546bbe7e711ae3c555d0293e5705275	no	2
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National Stage of an International Application under 35 U.S.C. 371

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New International Application Filed with the USPTO as a Receiving Office

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POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a divisional of U.S. Application No. 10/856,176, filed May 28, 2004, which claims the benefit of U.S. Provisional Application No. 60/473,902, filed May 28, 2003 and which is a continuation-in-part of PCT/US02/32575 filed October 11, 2002, which claims priority to 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. Provisional Application No. 60/386,937, filed June 7, 2002; PCT/US02/32594, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/414,276, filed September 27, 2002, 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. Provisional Application No. 60/386,937, filed June 7, 2002; and PCT/US02/32542, filed October 11, 2002, which claims priority to U.S. Provisional Application No. 60/371,940, filed April 11, 2002, 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. Provisional Application No. 60/386,937, filed June 7, 2002.

FIELD OF THE INVENTION

[0002] The invention relates to rapidly dissolving films and methods of their preparation. The films contain a polymer component, which includes polyethylene oxide optionally blended with cellulosic polymers. The films may also contain an active ingredient that is evenly distributed throughout the film. The even or uniform distribution is achieved by controlling one or more parameters, and particularly the elimination of air pockets prior to and during film formation and the use of a drying process that reduces aggregation or conglomeration of the components in the film as it forms into a solid structure.

BACKGROUND OF THE RELATED TECHNOLOGY

[0003] Active ingredients, such as drugs or pharmaceuticals, may be prepared in a tablet form to allow for accurate and consistent dosing. However, this form of preparing and dispensing medications has many disadvantages including that a large proportion of adjuvants that must be added to obtain a size able to be handled, that a larger medication form requires additional storage space, and that dispensing includes counting the tablets which has a tendency for inaccuracy. In addition, many persons, estimated to be as much as 28% of the population, have difficulty swallowing tablets. While tablets may be broken into smaller pieces or even crushed as a means of overcoming swallowing difficulties, this is not a suitable solution for many tablet or pill forms. For example, crushing or destroying the tablet or pill form to facilitate ingestion, alone or in admixture with food, may also destroy the controlled release properties.

[0004] As an alternative to tablets and pills, films may be used to carry active ingredients such as drugs, pharmaceuticals, and the like. However, historically films and the process of making drug delivery systems therefrom have suffered from a number of unfavorable characteristics that have not allowed them to be used in practice.

[0005] Films that incorporate a pharmaceutically active ingredient are disclosed in expired U.S. Patent No. 4,136,145 to Fuchs, et al. ("Fuchs"). These films may be formed into a sheet, dried and then cut into individual doses. The Fuchs disclosure alleges the fabrication of a uniform film, which includes the combination of water-soluble polymers, surfactants, flavors, sweeteners, plasticizers and drugs. These allegedly flexible films are disclosed as being useful for oral, topical or enteral use. Examples of specific uses disclosed by Fuchs include application of the films to mucosal membrane areas of the body, including the mouth, rectal, vaginal, nasal and ear areas.

[0006] Examination of films made in accordance with the process disclosed in Fuchs, however, reveals that such films suffer from the aggregation or conglomeration of particles, i.e., self-aggregation, making them inherently non-uniform. This result can be attributed to Fuchs' process parameters, which although not disclosed likely include the use of relatively long drying

times, thereby facilitating intermolecular attractive forces, convection forces, air flow and the like to form such agglomeration.

[0007] The formation of agglomerates randomly distributes the film components and any active present as well. When large dosages are involved, a small change in the dimensions of the film would lead to a large difference in the amount of active per film. If such films were to include low dosages of active, it is possible that portions of the film may be substantially devoid of any active. Since sheets of film are usually cut into unit doses, certain doses may therefore be devoid of or contain an insufficient amount of active for the recommended treatment. Failure to achieve a high degree of accuracy with respect to the amount of active ingredient in the cut film can be harmful to the patient. For this reason, dosage forms formed by processes such as Fuchs, would not likely meet the stringent standards of governmental or regulatory agencies, such as the U.S. Federal Drug Administration ("FDA"), relating to the variation of active in dosage forms. Currently, as required by various world regulatory authorities, dosage forms may not vary more than 10% in the amount of active present. When applied to dosage units based on films, this virtually mandates that uniformity in the film be present.

[0008] The problems of self-aggregation leading to non-uniformity of a film were addressed in U.S. Patent No. 4,849,246 to Schmidt ("Schmidt"). Schmidt specifically pointed out that the methods disclosed by Fuchs did not provide a uniform film and recognized that that the creation of a non-uniform film necessarily prevents accurate dosing, which as discussed above is especially important in the pharmaceutical area. Schmidt abandoned the idea that a mono-layer film, such as described by Fuchs, may provide an accurate dosage form and instead attempted to solve this problem by forming a multi-layered film. Moreover, his process is a multi-step process that adds expense and complexity and is not practical for commercial use.

[0009] Other U.S. Patents directly addressed the problems of particle self-aggregation and non-uniformity inherent in conventional film forming techniques. In one attempt to overcome non-uniformity, U.S. Patent 5,629,003 to Horstmann et al. and U.S. Patent 5,948,430 to Zerbe et al. incorporated additional ingredients, i.e. gel formers and polyhydric alcohols respectively, to increase the viscosity of the film prior to drying in an effort to reduce

aggregation of the components in the film. These methods have the disadvantage of requiring additional components, which translates to additional cost and manufacturing steps. Furthermore, both methods employ the use the conventional time-consuming drying methods such as a high-temperature air-bath using a drying oven, drying tunnel, vacuum drier, or other such drying equipment. The long length of drying time aids in promoting the aggregation of the active and other adjuvant, notwithstanding the use of viscosity modifiers. Such processes also run the risk of exposing the active, i.e., a drug, or vitamin C, or other components to prolonged exposure to moisture and elevated temperatures, which may render it ineffective or even harmful.

[0010] In addition to the concerns associated with degradation of an active during extended exposure to moisture, the conventional drying methods themselves are unable to provide uniform films. The length of heat exposure during conventional processing, often referred to as the "heat history", and the manner in which such heat is applied, have a direct effect on the formation and morphology of the resultant film product. Uniformity is particularly difficult to achieve via conventional drying methods where a relatively thicker film, which is well-suited for the incorporation of a drug active, is desired. Thicker uniform films are more difficult to achieve because the surfaces of the film and the inner portions of the film do not experience the same external conditions simultaneously during drying. Thus, observation of relatively thick films made from such conventional processing shows a non-uniform structure caused by convection and intermolecular forces and requires greater than 10% moisture to remain flexible. The amount of free moisture can often interfere over time with the drug leading to potency issues and therefore inconsistency in the final product.

[0011] Conventional drying methods generally include the use of forced hot air using a drying oven, drying tunnel, and the like. The difficulty in achieving a uniform film is directly related to the rheological properties and the process of water evaporation in the film-forming composition. When the surface of an aqueous polymer solution is contacted with a high temperature air current, such as a film-forming composition passing through a hot air oven, the surface water is immediately evaporated forming a polymer film or skin on the surface. This seals the remainder of the aqueous film-forming composition beneath the surface, forming a

barrier through which the remaining water must force itself as it is evaporated in order to achieve a dried film. As the temperature outside the film continues to increase, water vapor pressure builds up under the surface of the film, stretching the surface of the film, and ultimately ripping the film surface open allowing the water vapor to escape. As soon as the water vapor has escaped, the polymer film surface reforms, and this process is repeated, until the film is completely dried. The result of the repeated destruction and reformation of the film surface is observed as a "ripple effect" which produces an uneven, and therefore non-uniform film. Frequently, depending on the polymer, a surface will seal so tightly that the remaining water is difficult to remove, leading to very long drying times, higher temperatures, and higher energy costs.

[0012] Other factors, such as mixing techniques, also play a role in the manufacture of a pharmaceutical film suitable for commercialization and regulatory approval. Air can be trapped in the composition during the mixing process or later during the film making process, which can leave voids in the film product as the moisture evaporates during the drying stage. The film frequently collapse around the voids resulting in an uneven film surface and therefore, non-uniformity of the final film product. Uniformity is still affected even if the voids in the film caused by air bubbles do not collapse. This situation also provides a non-uniform film in that the spaces, which are not uniformly distributed, are occupying area that would otherwise be occupied by the film composition. None of the above-mentioned patents either addresses or proposes a solution to the problems caused by air that has been introduced to the film.

[0013] Therefore, there is a need for methods and compositions for film products, which use a minimal number of materials or components, and which provide a substantially non-self-aggregating uniform heterogeneity throughout the area of the films. Desirably, such films are produced through a selection of a polymer or combination of polymers that will provide a desired viscosity, a film-forming process such as reverse roll coating, and a controlled, and desirably rapid, drying process which serves to maintain the uniform distribution of non-self-aggregated components without the necessary addition of gel formers or polyhydric alcohols and the like which appear to be required in the products and for the processes of prior patents, such as the aforementioned Horstmann and Zerbe patents. Desirably, the films will also incorporate

compositions and methods of manufacture that substantially reduce or eliminate air in the film, thereby promoting uniformity in the final film product.

SUMMARY OF THE INVENTION

[0014] Some embodiments of the present invention provide a mucosally-adhesive water-soluble film product, which includes:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component including polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component includes greater than 75% polyethylene oxide and up to 25% hydrophilic cellulosic polymer;

the polyethylene oxide includes one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight is about 60% or more in the polymer component.

[0015] Another embodiment of the present invention provides a mucosally-adhesive water-soluble film product, which includes:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component including polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component includes the hydrophilic cellulosic polymer in a ratio of up to about 4:1 with the polyethylene oxide;

the polyethylene oxide includes one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular

weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight is about 60% or more in the polymer component.

BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 shows a side view of a package containing a unit dosage film of the present invention.

[0017] 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.

[0018] Figure 3 shows a side view of the adjacently coupled packages of Figure 2 arranged in a stacked configuration.

[0019] 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.

[0020] Figure 5 is a schematic view of a roll of coupled unit dose packages of the present invention.

[0021] 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.

[0022] Figure 7 is a schematic view of an apparatus suitable for drying the films of the present invention.

[0023] Figure 8 is a sequential representation of the drying process of the present invention.

[0024] Figure 9 is a photographic representation of a film dried by conventional drying processes.

[0025] Figure 10 is a photographic representation of a film dried by conventional drying processes.

[0026] Figure 11 is a photographic representation of a film dried by conventional drying processes.

[0027] Figure 12 is a photographic representation of a film dried by conventional drying processes.

[0028] Figure 13 is a photographic representation of a film dried by conventional drying processes.

[0029] Figure 14 is a photographic representation of a film dried by conventional drying processes.

[0030] Figure 15 is a photographic representation of a film dried by conventional drying processes.

[0031] Figure 16 is a photographic representation of a film dried by conventional drying processes.

[0032] Figure 17 is a photographic representation of a film dried by the inventive drying process.

[0033] Figure 18 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0034] Figure 19 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0035] Figure 20 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0036] Figure 21 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0037] Figure 22 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0038] Figure 23 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0039] Figure 24 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0040] Figure 25 is a photomicrographic representation of a film containing fat coated particles dried by the inventive drying process.

[0041] Figure 26 is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80°C.

[0042] Figure 27 is a photomicrographic representation of fat coated particles not in film, heated for 9 minutes at 80°C.

[0043] Figure 28 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0044] Figure 29 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0045] Figure 30 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0046] Figure 31 is a photomicrographic representation of fat coated particles at room temperature prior to processing.

[0047] Figure 32 is a graphical representation of a microarray on the blood of a human after ingestion by the human of a film of the present invention containing a bovine derived protein.

[0048] Figure 33 is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

[0049] Figure 34 is a graphical representation of the temperature differential between the inside and outside of a film of the present invention during drying.

[0050] Figure 35 is a schematic representation of a continuously-linked zone drying apparatus in accordance with the present invention.

[0051] Figure 36 is a schematic representation of a separate zone drying apparatus in accordance with the present invention.

[0052] Figure 37 is a schematic representation of a extrusion device for use in producing films of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

[0053] 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.

[0054] 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.

[0055] 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).

[0056] 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.

[0057] 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.

[0058] 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.

[0059] 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.

[0060] 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:

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

[0061] 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.

[0062] 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.

[0063] 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.

[0064] 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.

[0065] 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

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

[0066] For pseudoplastic fluids, the viscosity in this shear stress regime may well be the zero shear rate viscosity at the Newtonian plateau.

[0067] 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.

[0068] 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.

[0069] 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.

[0070] 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.

[0071] 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.

[0072] 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.

[0073] 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.

[0074] 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.

[0075] While the proper viscosity uniformity in mixture and stable suspension of particles, and casting method are important in the initial steps of forming the composition and film to promote uniformity, the method of drying the wet film is also important. Although these parameters and properties assist uniformity initially, a controlled rapid drying process ensures that the uniformity will be maintained until the film is dry.

[0076] 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.

[0077] Moreover, the films of the present invention may contain particles that are sensitive to temperature, such as flavors, which may be volatile, or drugs, proteins, or antigens, 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.

[0078] During film preparation, it may be desirable to dry films at high temperatures. High heat drying produces uniform films, and leads to greater efficiencies in film production. Films containing sensitive active components, however, may face degradation problems at high temperatures. Degradation is the "decomposition of a compound . . . exhibiting well-defined intermediate products." The American Heritage Dictionary of the English Language (4^{th} ed. 2000). Degradation of an active component is typically undesirable as it may cause instability, inactivity, and/or decreased potency of the active component. For instance, if the active component is a drug or bioactive material, this may adversely affect the safety or efficacy of the final pharmaceutical product. Additionally, highly volatile materials will tend to be quickly released from this film upon exposure to conventional drying methods.

[0079] Degradation of an active component may occur through a variety of processes, such as, hydrolysis, oxidation, and light degradation, depending upon the particular active component. Moreover, temperature has a significant effect on the rate of such reactions. The rate of degradation typically doubles for every 10°C increase in temperature. Therefore, it is commonly understood that exposing an active component to high temperatures will initiate and/or accelerate undesirable degradation reactions.

[0080] Proteins are one category of useful active ingredients that will degrade, denature, or otherwise become inactive when they are exposed to high temperatures for extended periods of time. Proteins serve a variety of functions in the body such as enzymes, structural elements, hormones and immunoglobulins. Examples of proteins include enzymes such as pancreatin, trypsin, pancrelipase, chymotrypsin, hyaluronidase, sutilains, streptokinaw, urokinase, altiplase, papain, bromelainsdiastase, structural elements such as collagen and albumin, hormones such as thyroliberin, gonadoliberin, adrenocorticottropin, corticotrophin, cosyntropin, sometrem, somatropion, prolactin, thyrotropin, somatostatin, vasopressin, felypressin, lypressin, insulin,

glucagons, gastrin, pentagastrin, secretin, cholecystokinin-pancreozymin, and immunomodulators which may include polysaccharides in addition to glycoproteins including cytokines which are useful for the inhibition and prevention of malignant cell growth such as tumor growth. A suitable method for the production of some useful glycoproteins is disclosed in U.S. Patent No. 6,281,337 to Cannon-Carlson, et al., which in incorporated herein in its entirety.

[0081] Temperatures that approach 100°C will generally cause degradation of proteins as well as nucleic acids. For example some glycoproteins will degrade if exposed to a temperature of 70°C for thirty minutes. Proteins from bovine extract are also known to degrade at such low temperatures. DNA also begins to denature at this temperature.

[0082] Applicants have discovered, however, that the films of the present invention may be exposed to high temperatures during the drying process without concern for degradation, loss of activity or excessive evaporation due to the inventive process for film preparation and forming. In particular, the films may be exposed to temperatures that would typically lead to degradation, denaturization, or inactivity of the active component, without causing such problems. According to the present invention, the manner of drying may be controlled to prevent deleterious levels of heat from reaching the active component.

[0083] As discussed herein, the flowable mixture is prepared to be uniform in content in accordance with the teachings of the present invention. Uniformity must be maintained as the flowable mass was formed into a film and dried. During the drying process of the present invention, several factors produce uniformity within the film while maintaining the active component at a safe temperature, *i.e.*, below its degradation temperature. First, the films of the present invention have an extremely short heat history, usually only on the order of minutes, so that total temperature exposure is minimized to the extent possible. The films are controllably dried to prevent aggregation and migration of components, as well as preventing heat build up within. Desirably, the films are dried from the bottom. Controlled bottom drying, as described herein, prevents the formation of a polymer film, or skin, on the top surface of the film. As heat is conducted from the film bottom upward, liquid carrier, e.g., water, rises to the film surface. The absence of a surface skin permits rapid evaporation of the liquid carrier as the temperature

increases, and thus, concurrent evaporative cooling of the film. Due to the short heat exposure and evaporative cooling, the film components such as drag or volatile actives remain unaffected by high temperatures. In contrast, skinning on the top surface traps liquid carrier molecules of increased energy within the film, thereby causing the temperature within the film to rise and exposing active components to high, potentially deleterious temperatures.

[0084] Second, thermal mixing occurs within the film due to bottom heating and absence of surface skinning. Thermal mixing occurs via convection currents in the film. As heat is applied to the bottom of the film, the liquid near the bottom increases in temperature, expands, and becomes less dense. As such, this hotter liquid rises and cooler liquid takes its place. While rising, the hotter liquid mixes with the cooler liquid and shares thermal energy with it, *i.e.*, transfers heat. As the cycle repeats, thermal energy is spread throughout the film.

[0085] Robust thermal mixing achieved by the controlled drying process of the present invention produces uniform heat diffusion throughout the film. In the absence of such thermal mixing, "hot spots" may develop. Pockets of heat in the film result in the formation of particle aggregates or danger areas within the film and subsequent non-uniformity. The formation of such aggregates or agglomerations is undesirable because it leads to non-uniform films in which the active may be randomly distributed. Such uneven distribution may lead to large differences in the amount of active per film, which is problematic from a safety and efficacy perspective.

[0086] Furthermore, thermal mixing helps to maintain a lower overall temperature inside the film. Although the film surfaces may be exposed to a temperature above that at which the active component degrades, the film interior may not reach this temperature. Due to this temperature differential, the active does not degrade.

[0087] For instance, the films of the present invention desirably are dried for 10 minutes or less. Drying the films at 80°C for 10 minutes produces a temperature differential of about 5°C. This means that after 10 minutes of drying, the temperature of the inside of the film is 5°C less than the outside exposure temperature. In many cases, however, drying times of less than 10 minutes are sufficient, such as 4 to 6 minutes. Drying for 4 minutes may be accompanied by a

temperature differential of about 30°C, and drying for 6 minutes may be accompanied by a differential of about 25°C. Due to such large temperature differentials, the films may be dried at efficient, high temperatures without causing heat sensitive actives to degrade.

[0088] Fig. 8 is a sequential representation of the drying process of the present invention. After mechanical mixing, the film may be placed on a conveyor for continued thermal mixing during the drying process. At the outset of the drying process, depicted in Section A, the film **1** preferably is heated from the bottom **10** as it is travels via conveyor (not shown). Heat may be supplied to the film by a heating mechanism, such as, but not limited to, the dryer depicted in Fig. 7. As the film is heated, the liquid carrier, or volatile ("V"), begins to evaporate, as shown by upward arrow **50**. Thermal mixing also initiates as hotter liquid, depicted by arrow **30**, rises and cooler liquid, depicted by arrow **40**, takes its place. Because no skin forms on the top surface **20** of the film **1**, as shown in Section B the volatile liquid continues to evaporate **50** and thermal mixing **30/40** continues to distribute thermal energy throughout the film. Once a sufficient amount of the volatile liquid has evaporated, thermal mixing has produced uniform heat diffusion throughout the film **1**. The resulting dried film **1** is a visco-elastic solid, as depicted in Section C. The components desirably are locked into a uniform distribution throughout the film. Although minor amounts of liquid carrier, i.e., water, may remain subsequent to formation of the visco-elastic, the film may be dried further without movement of the particles, if desired.

[0089] 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.

[0090] 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.

[0091] 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.

[0092] 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.

[0093] 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.

[0094] In alternative embodiments, the film products of the present invention may be formed by extrusion rather than casting methods. Extrusion is particularly useful for film compositions containing polyethylene oxide-based polymer components, as discussed below. For instance, a single screw extrusion process may be employed in accordance with the present invention. According to such an extrusion process, pressure builds in the polymer melt so that it may be extruded through a die or injected into a mold.

[0095] As further explanation, a single screw extruder for use in the process of the present invention may include a barrel 300 containing a number of zones 200, as shown in the extruder 100 depicted in Fig. 37. These zones 200 may have varying temperatures and pressures. For instance, it may be desirable for the zones to increase in temperature as the composition proceeds through the barrel 300 to the extrusion die 400. Any number of zones may be included in accordance with the present invention. In addition, the speed of extrusion may be controlled to produce desired film properties. For example, the extrusion composition may be held for an extended time period in the screw mixing chamber. Although this discussion is directed to single

screw extrusion, other forms of extrusion are known to those skilled in the art and are considered well within the scope of the present invention.

[0096] Consideration of the above discussed parameters, such as but not limited to rheology properties, viscosity, mixing method, casting method and drying method, also impact material selection for the different components of the present invention. Furthermore, such consideration with proper material selection provides the compositions of the present invention, including a pharmaceutical and/or cosmetic dosage form or film product having no more than a 10% variance of a pharmaceutical and/or cosmetic active per unit area. In other words, the uniformity of the present invention is determined by the presence of no more than a 10% by weight of pharmaceutical and/or cosmetic variance throughout the matrix. Desirably, the variance is less than 5% by weight, less than 2% by weight, less than 1% by weight, or less than 0.5% by weight.

Film-Forming Polymers

[0097] The polymer may be water soluble, water swellable, water insoluble, or a combination of one or more either water soluble, water swellable or water insoluble polymers. The polymer may include cellulose or a cellulose derivative. Specific examples of useful water soluble polymers include, but are not limited to, polyethylene oxide (PEO), pullulan, hydroxypropylmethyl cellulose (HPMC), hydroxyethyl cellulose (HPC), hydroxypropyl cellulose, polyvinyl pyrrolidone, carboxymethyl cellulose, polyvinyl alcohol, sodium aginate, polyethylene glycol, xanthan gum, tragancanth gum, guar gum, acacia gum, arabic gum, polyacrylic acid, methylmethacrylate copolymer, carboxyvinyl copolymers, starch, gelatin, and combinations thereof. Specific examples of useful water insoluble polymers include, but are not limited to, ethyl cellulose, hydroxypropyl ethyl cellulose, cellulose acetate phthalate, hydroxypropyl methyl cellulose phthalate and combinations thereof.

[0098] As used herein the phrase "water soluble polymer" and variants thereof refer to a polymer that is at least partially soluble in water, and desirably fully or predominantly soluble in water, or absorbs water. Polymers that absorb water are often referred to as being water swellable polymers. The materials useful with the present invention may be water soluble or

water swellable at room temperature and other temperatures, such as temperatures exceeding room temperature. Moreover, the materials may be water soluble or water swellable at pressures less than atmospheric pressure. Desirably, the water soluble polymers are water soluble or water swellable having at least 20 percent by weight water uptake. Water swellable polymers having a 25 or greater percent by weight water uptake are also useful. Films or dosage forms of the present invention formed from such water soluble polymers are desirably sufficiently water soluble to be dissolvable upon contact with bodily fluids.

[0099] Other polymers useful for incorporation into the films of the present invention include biodegradable polymers, copolymers, block polymers and combinations thereof. Among the known useful polymers or polymer classes which meet the above criteria are: poly(glycolic acid) (PGA), poly(lactic acid) (PLA), polydioxanoes, polyoxalates, poly(α-esters), polyanhydrides, polyacetates, polycaprolactones, poly(orthoesters), polyamino acids, polyaminocarbonates, polyurethanes, polycarbonates, polyamides, poly(alkyl cyanoacrylates), and mixtures and copolymers thereof. Additional useful polymers include, stereopolymers of L- and D-lactic acid, copolymers of bis(p-carboxyphenoxy) propane acid and sebacic acid, sebacic acid copolymers, copolymers of caprolactone, poly(lactic acid)/poly(glycolic acid)/polyethyleneglycol copolymers, copolymers of polyurethane and (poly(lactic acid), copolymers of polyurethane and poly(lactic acid), copolymers of α-amino acids, copolymers of α-amino acids and caproic acid, copolymers of α-benzyl glutamate and polyethylene glycol, copolymers of succinate and poly(glycols), polyphosphazene, polyhydroxy-alkanoates and mixtures thereof. Binary and ternary systems are contemplated.

[0100] Other specific polymers useful include those marketed under the Medisorb and Biodel trademarks. The Medisorb materials are marketed by the Dupont Company of Wilmington, Delaware and are generically identified as a "lactide/glycolide co-polymer" containing "propanoic acid, 2-hydroxy-polymer with hydroxy-polymer with hydroxyacetic acid." Four such polymers include lactide/glycolide 100L, believed to be 100% lactide having a melting point within the range of 338°-347°F (170°-175°C); lactide/glycolide 100L, believed to be 100% glycolide having a melting point within the range of 437°-455°F (225°-235°C); lactide/glycolide 85/15, believed to be 85% lactide and 15% glycolide with a melting point within the range of

338°-347°F (170°-175° C); and lactide/glycolide 50/50, believed to be a copolymer of 50% lactide and 50% glycolide with a melting point within the range of 338°-347°F (170°-175°C).

[0101] The Biodel materials represent a family of various polyanhydrides which differ chemically.

[0102] 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.

[0103] The polymer plays an important role in affecting the viscosity of the film. Viscosity is one property of a liquid that controls the stability of the active in an emulsion, a colloid or a suspension. Generally the viscosity of the matrix will vary from about 400 cps to about 100,000 cps, preferably from about 800 cps to about 60,000 cps, and most preferably from about 1,000 cps to about 40,000 cps. Desirably, the viscosity of the film-forming matrix will rapidly increase upon initiation of the drying process.

[0104] 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.

[0105] It has also been observed that certain polymers which when used alone would ordinarily require a plasticizer to achieve a flexible film, can be combined without a plasticizer and yet achieve flexible films. For example, HPMC and HPC when used in combination provide a flexible, strong film with the appropriate plasticity and elasticity for manufacturing and storage. No additional plasticizer or polyalcohol is needed for flexibility.

[0106] Additionally, polyethylene oxide (PEO), when used alone or in combination with a hydrophilic cellulosic polymer, achieves flexible, strong films. Additional plasticizers or polyalcohols are not needed for flexibility. Non-limiting examples of suitable cellulosic polymers for combination with PEO include HPC and HPMC. PEO and HPC have essentially no gelation temperature, while HPMC has a gelation temperature of 58-64°C (Methocel EF available from Dow Chemical Co.). Moreover, these films are sufficiently flexible even when substantially free of organic solvents, which may be removed without compromising film properties. As such, if there is no solvent present, then there is no plasticizer in the films. PEO based films also exhibit good resistance to tearing, little or no curling, and fast dissolution rates when the polymer component contains appropriate levels of PEO.

[0107] To achieve the desired film properties, the level and/or molecular weight of PEO in the polymer component may be varied. Modifying the PEO content affects properties such as tear resistance, dissolution rate, and adhesion tendencies. Thus, one method for controlling film properties is to modify the PEO content. For instance, in some embodiments rapid dissolving films are desirable. By modifying the content of the polymer component, the desired dissolution characteristics can be achieved.

[0108] In accordance with the present invention, PEO desirably ranges from about 20% to 100% by weight in the polymer component. In some embodiments, the amount of PEO desirably ranges from about 1mg to about 200mg. The hydrophilic cellulosic polymer ranges from about 0% to about 80% by weight, or in a ratio of up to about 4:1 with the PEO, and desirably in a ratio of about 1:1.

[0109] In some embodiments, it may be desirable to vary the PEO levels to promote certain film properties. To obtain films with high tear resistance and fast dissolution rates, levels of about 50% or greater of PEO in the polymer component are desirable. To achieve adhesion prevention, i.e., preventing the film from adhering to the roof of the mouth, PEO levels of about 20% to 75% are desirable. In some embodiments, however, adhesion to the roof of the mouth may be desired, such as for administration to animals or children. In such cases, higher levels of PEO may be employed. More specifically, structural integrity and dissolution of the film can be controlled such that the film can adhere to mucosa and be readily removed, or adhere more firmly and be difficult to remove, depending on the intended use.

[0110] The molecular weight of the PEO may also be varied. High molecular weight PEO, such as about 4 million, may be desired to increase mucoadhesivity of the film. More desirably, the molecular weight may range from about 100,000 to 900,000, more desirably from about 100,000 to 600,000, and most desirably from about 100,000 to 300,000. In some embodiments, it may be desirable to combine high molecular weight (600,000 to 900,000) with low molecular weight (100,000 to 300,000) PEOs in the polymer component.

[0111] For instance, certain film properties, such as fast dissolution rates and high tear resistance, may be attained by combining small amounts of high molecular weight PEOs with larger amounts of lower molecular weight PEOs. Desirably, such compositions contain about 60% or greater levels of the lower molecular weight PEO in the PEO-blend polymer component.

[0112] To balance the properties of adhesion prevention, fast dissolution rate, and good tear resistance, desirable film compositions may include about 50% to 75% low molecular weight PEO, optionally combined with a small amount of a higher molecular weight PEO, with the remainder of the polymer component containing a hydrophilic cellulosic polymer (HPC or HPMC).

Controlled Release Films

[0113] The term "controlled release" is intended to mean the release of active at a pre-selected or desired rate. This rate will vary depending upon the application. Desirable rates

include fast or immediate release profiles as well as delayed, sustained or sequential release. Combinations of release patterns, such as initial spiked release followed by lower levels of sustained release of active are contemplated. Pulsed drug releases are also contemplated.

[0114] The polymers that are chosen for the films of the present invention may also be chosen to allow for controlled disintegration of the active. This may be achieved by providing a substantially water insoluble film that incorporates an active that will be released from the film over time. This may be accomplished by incorporating a variety of different soluble or insoluble polymers and may also include biodegradable polymers in combination. Alternatively, coated controlled release active particles may be incorporated into a readily soluble film matrix to achieve the controlled release property of the active inside the digestive system upon consumption.

[0115] Films that provide a controlled release of the active are particularly useful for buccal, gingival, sublingual and vaginal applications. The films of the present invention are particularly useful where mucosal membranes or mucosal fluid is present due to their ability to readily wet and adhere to these areas.

[0116] The convenience of administering a single dose of a medication which releases active ingredients in a controlled fashion over an extended period of time as opposed to the administration of a number of single doses at regular intervals has long been recognized in the pharmaceutical arts. The advantage to the patient and clinician in having consistent and uniform blood levels of medication over an extended period of time are likewise recognized. The advantages of a variety of sustained release dosage forms are well known. However, the preparation of a film that provides the controlled release of an active has advantages in addition to those well-known for controlled release tablets. For example, thin films are difficult to inadvertently aspirate and provide an increased patient compliance because they need not be swallowed like a tablet. Moreover, certain embodiments of the inventive films are designed to adhere to the buccal cavity and tongue, where they controllably dissolve. Furthermore, thin films may not be crushed in the manner of controlled release tablets which is a problem leading to abuse of drugs such as Oxycontin.

[0117] The actives employed in the present invention may be incorporated into the film compositions of the present invention in a controlled release form. For example, particles of drug may be coated with polymers such as ethyl cellulose or polymethacrylate, commercially available under brand names such as Aquacoat ECD and Eudragit E-100, respectively. Solutions of drug may also be absorbed on such polymer materials and incorporated into the inventive film compositions. Other components such as fats and waxes, as well as sweeteners and/or flavors may also be employed in such controlled release compositions.

[0118] The actives may be taste-masked prior to incorporation into the film composition, as set forth in co-pending PCT application titled, Uniform Films For Rapid Dissolve Dosage Form Incorporating Taste-Masking Compositions, (based on U.S. Provisional Application No. Express Mail Label No.: EU552991605 US of the same title, filed September 27, 2003, attorney docket No. 1199-15P) the entire subject matter of which is incorporated by reference herein.

Actives

[0119] When an active is introduced to the film, the amount of active per unit area is determined by the uniform distribution of the film. For example, when the films are cut into individual dosage forms, the amount of the active in the dosage form can be known with a great deal of accuracy. This is achieved because the amount of the active in a given area is substantially identical to the amount of active in an area of the same dimensions in another part of the film. The accuracy in dosage is particularly advantageous when the active is a medicament, i.e. a drug.

[0120] The active components that may be incorporated into the films of the present invention include, without limitation pharmaceutical and cosmetic actives, drugs, medicaments, proteins, antigens or allergens such as ragweed pollen, spores, microorganisms, seeds, mouthwash components, flavors, fragrances, enzymes, preservatives, sweetening agents, colorants, spices, vitamins and combinations thereof.

[0121] A wide variety of medicaments, bioactive active substances and pharmaceutical compositions may be included in the dosage forms of the present invention. Examples of useful

drugs include ace-inhibitors, antianginal drugs, anti-arrhythmias, anti-asthmatics, anti-cholesterolemics, analgesics, anesthetics, anti-convulsants, anti-depressants, anti-diabetic agents, anti-diarrhea preparations, antidotes, anti-histamines, anti-hypertensive drugs, anti-inflammatory agents, anti-lipid agents, anti-manics, anti-nauseants, anti-stroke agents, anti-thyroid preparations, anti-tumor drugs, anti-viral agents, acne drugs, alkaloids, amino acid preparations, anti-tussives, anti-uricemic drugs, anti-viral drugs, anabolic preparations, systemic and non-systemic anti-infective agents, anti-neoplastics, anti-parkinsonian agents, anti-rheumatic agents, appetite stimulants, biological response modifiers, blood modifiers, bone metabolism regulators, cardiovascular agents, central nervous system stimulates, cholinesterase inhibitors, contraceptives, decongestants, dietary supplements, dopamine receptor agonists, endometriosis management agents, enzymes, erectile dysfunction therapies, fertility agents, gastrointestinal agents, homeopathic remedies, hormones, hypercalcemia and hypocalcemia management agents, immunomodulators, immunosuppressives, migraine preparations, motion sickness treatments, muscle relaxants, obesity management agents, osteoporosis preparations, oxytocics, parasympatholytics, parasympathomimetics, prostaglandins, psychotherapeutic agents, respiratory agents, sedatives, smoking cessation aids, sympatholytics, tremor preparations, urinary tract agents, vasodilators, laxatives, antacids, ion exchange resins, anti-pyretics, appetite suppressants, expectorants, anti-anxiety agents, anti-ulcer agents, anti-inflammatory substances, coronary dilators, cerebral dilators, peripheral vasodilators, psycho-tropics, stimulants, anti-hypertensive drugs, vasoconstrictors, migraine treatments, antibiotics, tranquilizers, anti-psychotics, anti-tumor drugs, anti-coagulants, anti-thrombotic drugs, hypnotics, anti-emetics, anti-nauseants, anti-convulsants, neuromuscular drugs, hyper- and hypo-glycemic agents, thyroid and anti-thyroid preparations, diuretics, anti-spasmodics, terine relaxants, anti-obesity drugs, erythropoietic drugs, anti-asthmatics, cough suppressants, mucolytics, DNA and genetic modifying drugs, and combinations thereof.

[0122] Examples of medicating active ingredients contemplated for use in the present invention include antacids, H_2-antagonists, and analgesics. For example, antacid dosages can be prepared using the ingredients calcium carbonate alone or in combination with magnesium hydroxide, and/or aluminum hydroxide. Moreover, antacids can be used in combination with H_2-antagonists.

[0123] Analgesics include opiates and opiate derivatives, such as oxycodone (available as Oxycontin®), ibuprofen, aspirin, acetaminophen, and combinations thereof that may optionally include caffeine.

[0124] Other preferred drugs for other preferred active ingredients for use in the present invention include anti-diarrheals such as immodium AD, anti-histamines, anti-tussives, decongestants, vitamins, and breath fresheners. Common drugs used alone or in combination for colds, pain, fever, cough, congestion, runny nose and allergies, such as acetaminophen, chlorpheniramine maleate, dextromethorphan, pseudoephedrine HCl and diphenhydramine may be included in the film compositions of the present invention.

[0125] Also contemplated for use herein are anxiolytics such as alprazolam (available as Xanax®); anti-psychotics such as clozopin (available as Clozaril®) and haloperidol (available as Haldol®); non-steroidal anti-inflammatories (NSAID's) such as dicyclofenacs (available as Voltaren®) and etodolac (available as Lodine®), anti-histamines such as loratadine (available as Claritin®), astemizole (available as Hismanal™), nabumetone (available as Relafen®), and Clemastine (available as Tavist®); anti-emetics such as granisetron hydrochloride (available as Kytril®) and nabilone (available as Cesamet™); bronchodilators such as Bentolin®, albuterol sulfate (available as Proventil®); anti-depressants such as fluoxetine hydrochloride (available as Prozac®), sertraline hydrochloride (available as Zoloft®), and paroxtine hydrochloride (available as Paxil®); anti-migraines such as Imigra®, ACE-inhibitors such as enalaprilat (available as Vasotec®), captopril (available as Capoten®) and lisinopril (available as Zestril®); anti-Alzheimer's agents, such as nicergoline; and Ca^{H}-antagonists such as nifedipine (available as Procardia® and Adalat®), and verapamil hydrochloride (available as Calan®).

[0126] Erectile dysfunction therapies include, but are not limited to, drugs for facilitating blood flow to the penis, and for effecting autonomic nervous activities, such as increasing parasympathetic (cholinergic) and decreasing sympathetic (adrenersic) activities. Useful non-limiting drugs include sildenafils, such as Viagra®, tadalafils, such as Cialis®, vardenafils, apomorphines, such as Uprima®, yohimbine hydrochlorides such as Aphrodyne®, and alprostadils such as Caverject®.

[0127] The popular H_2-antagonists which are contemplated for use in the present invention include cimetidine, ranitidine hydrochloride, famotidine, nizatidien, ebrotidine, mifentidine, roxatidine, pisatidine and aceroxatidine.

[0128] Active antacid ingredients include, but are not limited to, the following: aluminum hydroxide, dihydroxyaluminum aminoacetate, aminoacetic acid, aluminum phosphate, dihydroxyaluminum sodium carbonate, bicarbonate, bismuth aluminate, bismuth carbonate, bismuth subcarbonate, bismuth subgallate, bismuth subnitrate, bismuth subsilysilate, calcium carbonate, calcium phosphate, citrate ion (acid or salt), amino acetic acid, hydrate magnesium aluminate sulfate, magaldrate, magnesium aluminosilicate, magnesium carbonate, magnesium glycinate, magnesium hydroxide, magnesium oxide, magnesium trisilicate, milk solids, aluminum mono-ordibasic calcium phosphate, tricalcium phosphate, potassium bicarbonate, sodium tartrate, sodium bicarbonate, magnesium aluminosilicates, tartaric acids and salts.

[0129] The pharmaceutically active agents employed in the present invention may include allergens or antigens, such as , but not limited to, plant pollens from grasses, trees, or ragweed; animal danders, which are tiny scales shed from the skin and hair of cats and other furred animals; insects, such as house dust mites, bees, and wasps; and drugs, such as penicillin.

[0130] An anti-oxidant may also be added to the film to prevent the degradation of an active, especially where the active is photosensitive.

[0131] Cosmetic active agents may include breath freshening compounds like menthol, other flavors or fragrances, especially those used for oral hygiene, as well as actives used in dental and oral cleansing such as quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

[0132] Also color additives can be used in preparing the films. Such color additives include food, drug and cosmetic colors (FD&C), drug and cosmetic colors (D&C), or external drug and cosmetic colors (Ext. D&C). These colors are dyes, their corresponding lakes, and certain natural and derived colorants. Lakes are dyes absorbed on aluminum hydroxide.

[0133] Other examples of coloring agents include known azo dyes, organic or inorganic pigments, or coloring agents of natural origin. Inorganic pigments are preferred, such as the oxides or iron or titanium, these oxides, being added in concentrations ranging from about 0.001 to about 10%, and preferably about 0.5 to about 3%, based on the weight of all the components.

[0134] Flavors may be chosen from natural and synthetic flavoring liquids. An illustrative list of such agents includes volatile oils, synthetic flavor oils, flavoring aromatics, oils, liquids, oleoresins or extracts derived from plants, leaves, flowers, fruits, stems and combinations thereof. A non-limiting representative list of examples includes mint oils, cocoa, and citrus oils such as lemon, orange, grape, lime and grapefruit and fruit essences including apple, pear, peach, grape, strawberry, raspberry, cherry, plum, pineapple, apricot or other fruit flavors.

[0135] The films containing flavorings may be added to provide a hot or cold flavored drink or soup. These flavorings include, without limitation, tea and soup flavorings such as beef and chicken.

[0136] Other useful flavorings include aldehydes and esters such as benzaldehyde (cherry, almond), citral i.e., alphacitral (lemon, lime), neral, i.e., beta-citral (lemon, lime), decanal (orange, lemon), aldehyde C-8 (citrus fruits), aldehyde C-9 (citrus fruits), aldehyde C-12 (citrus fruits), tolyl aldehyde (cherry, almond), 2,6-dimethyloctanol (green fruit), and 2-dodecenal (citrus, mandarin), combinations thereof and the like.

[0137] The sweeteners may be chosen from the following non-limiting list: glucose (corn syrup), dextrose, invert sugar, fructose, and combinations thereof; saccharin and its various salts such as the sodium salt; dipeptide sweeteners such as aspartame; dihydrochalcone compounds, glycyrrhizin; Stevia Rebaudiana (Stevioside); chloro derivatives of sucrose such as sucralose; sugar alcohols such as sorbitol, mannitol, xylitol, and the like. Also contemplated are hydrogenated starch hydrolysates and the synthetic sweetener 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide, particularly the potassium salt (acesulfame-K), and sodium and

calcium salts thereof, and natural intensive sweeteners, such as Lo Han Kuo. Other sweeteners may also be used.

[0138] When the active is combined with the polymer in the solvent, the type of matrix that is formed depends on the solubilities of the active and the polymer. If the active and/or polymer are soluble in the selected solvent, this may form a solution. However, if the components are not soluble, the matrix may be classified as an emulsion, a colloid, or a suspension.

Dosages

[0139] The film products of the present invention are capable of accommodating a wide range of amounts of the active ingredient. The films are capable of providing an accurate dosage amount (determined by the size of the film and concentration of the active in the original polymer/water combination) regardless of whether the required dosage is high or extremely low. Therefore, depending on the type of active or pharmaceutical composition that is incorporated into the film, the active amount may be as high as about 300mg, desirably up to about 150mg or as low as the microgram range, or any amount therebetween.

[0140] The film products and methods of the present invention are well suited for high potency, low dosage drugs. This is accomplished through the high degree of uniformity of the films. Therefore, low dosage drugs, particularly more potent racemic mixtures of actives are desirable.

Anti-foaming and De-foaming Compositions

[0141] Anti-foaming and/or de-foaming components may also be used with the films of the present invention. These components aid in the removal of air, such as entrapped air, from the film-forming compositions. As described above, such entrapped air may lead to non-uniform films. Simethicone is one particularly useful anti-foaming and/or de-foaming agent. The present invention, however, is not so limited and other anti-foam and/or de-foaming agents may suitable be used.

[0142] As a related matter, simethicone and related agents may be employed for densification purposes. More specifically, such agents may facilitate the removal of voids, air, moisture, and similar undesired components, thereby providing denser, and thus more uniform films. Agents or components which perform this function can be referred to as densification or densifying agents. As described above, entrapped air or undesired components may lead to non-uniform films.

[0143] Simethicone is generally used in the medical field as a treatment for gas or colic in babies. Simethicone is a mixture of fully methylated linear siloxane polymers containing repeating units of polydimethylsiloxane which is stabilized with trimethylsiloxy end-blocking unites, and silicon dioxide. It usually contains 90.5-99% polymethylsiloxane and 4-7% silicon dioxide. The mixture is a gray, translucent, viscous fluid which is insoluble in water.

[0144] When dispersed in water, simethicone will spread across the surface, forming a thin film of low surface tension. In this way, simethicone reduces the surface tension of bubbles air located in the solution, such as foam bubbles, causing their collapse. The function of simethicone mimics the dual action of oil and alcohol in water. For example, in an oily solution any trapped air bubbles will ascend to the surface and dissipate more quickly and easily, because an oily liquid has a lighter density compared to a water solution. On the other hand, an alcohol/water mixture is known to lower water density as well as lower the water's surface tension. So, any air bubbles trapped inside this mixture solution will also be easily dissipated. Simethicone solution provides both of these advantages. It lowers the surface energy of any air bubbles that trapped inside the aqueous solution, as well as lowering the surface tension of the aqueous solution. As the result of this unique functionality, simethicone has an excellent anti-foaming property that can be used for physiological processes (anti-gas in stomach) as well as any for external processes that require the removal of air bubbles from a product.

[0145] In order to prevent the formation of air bubbles in the films of the present invention, the mixing step can be performed under vacuum. However, as soon as the mixing step is completed, and the film solution is returned to the normal atmosphere condition, air will be re-introduced into or contacted with the mixture. In many cases, tiny air bubbles will be again

trapped inside this polymeric viscous solution. The incorporation of simethicone into the film-forming composition either substantially reduces or eliminates the formation of air bubbles.

[0146] Simethicone may be added to the film-forming mixture as an anti-foaming agent in an amount from about 0.01 weight percent to about 5.0 weight percent, more desirably from about 0. 05 weight percent to about 2.5 weight percent, and most desirably from about 0. 1 weight percent to about 1.0 weight percent.

Optional Components

[0147] A variety of other components and fillers may also be added to the films of the present invention. These may include, without limitation, surfactants; plasticizers which assist in compatibilizing the components within the mixture; polyalcohols; anti-foaming agents, such as silicone-containing compounds, which promote a smoother film surface by releasing oxygen from the film; thermo-setting gels such as pectin, carageenan, and gelatin, which help in maintaining the dispersion of components; and inclusion compounds, such as cyclodextrins and caged molecules, which improve the solubility and/or stability of certain active components.

[0148] The variety of additives that can be incorporated into the inventive compositions may provide a variety of different functions. Examples of classes of additives include excipients, lubricants, buffering agents, stabilizers, blowing agents, pigments, coloring agents, fillers, bulking agents, sweetening agents, flavoring agents, fragrances, release modifiers, adjuvants, plasticizers, flow accelerators, mold release agents, polyols, granulating agents, diluents, binders, buffers, absorbents, glidants, adhesives, anti-adherents, acidulants, softeners, resins, demulcents, solvents, surfactants, emulsifiers, elastomers and mixtures thereof. These additives may be added with the active ingredient(s).

[0149] Useful additives include, for example, gelatin, vegetable proteins such as sunflower protein, soybean proteins, cotton seed proteins, peanut proteins, grape seed proteins, whey proteins, whey protein isolates, blood proteins, egg proteins, acrylated proteins, water-soluble polysaccharides such as alginates, carrageenans, guar gum, agar-agar, xanthan gum, gellan gum, gum arabic and related gums (gum ghatti, gum karaya, gum tragancanth), pectin,

water-soluble derivatives of cellulose: alkylcelluloses hydroxyalkylcelluloses and hydroxyalkylalkylcelluloses, such as methylcelulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxyethylmethylcellulose, hydroxypropylmethylcellulose, hydroxybutylmethylcellulose, cellulose esters and hydroxyalkylcellulose esters such as cellulose acetate phthalate (CAP), hydroxypropylmethylcellulose (HPMC); carboxyalkylcelluloses, carboxyalkylalkylcelluloses, carboxyalkylcellulose esters such as carboxymethylcellulose and their alkali metal salts; water-soluble synthetic polymers such as polyacrylic acids and polyacrylic acid esters, polymethacrylic acids and polymethacrylic acid esters, polyvinylacetates, polyvinylalcohols, polyvinylacetatephthalates (PVAP), polyvinylpyrrolidone (PVP), PVY/vinyl acetate copolymer, and polycrotonic acids; also suitable are phthalated gelatin, gelatin succinate, crosslinked gelatin, shellac, water soluble chemical derivatives of starch, cationically modified acrylates and methacrylates possessing, for example, a tertiary or quaternary amino group, such as the diethylaminoethyl group, which may be quaternized if desired; and other similar polymers.

[0150] Such extenders may optionally be added in any desired amount desirably within the range of up to about 80%, desirably about 3% to 50% and more desirably within the range of 3% to 20% based on the weight of all components.

[0151] Further additives may be inorganic fillers, such as the oxides of magnesium aluminum, silicon, titanium, etc. desirably in a concentration range of about 0.02% to about 3% by weight and desirably about 0.02% to about 1% based on the weight of all components.

[0152] Further examples of additives are plasticizers which include polyalkylene oxides, such as polyethylene glycols, polypropylene glycols, polyethylene-propylene glycols, organic plasticizers with low molecular weights, such as glycerol, glycerol monoacetate, diacetate or triacetate, triacetin, polysorbate, cetyl alcohol, propylene glycol, sorbitol, sodium diethylsulfosuccinate, triethyl citrate, tributyl citrate, and the like, added in concentrations ranging from about 0.5% to about 30%, and desirably ranging from about 0.5% to about 20% based on the weight of the polymer.

[0153] There may further be added compounds to improve the flow properties of the starch material such as animal or vegetable fats, desirably in their hydrogenated form, especially those which are solid at room temperature. These fats desirably have a melting point of 50°C or higher. Preferred are tri-glycerides with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids. These fats can be added alone without adding extenders or plasticizers and can be advantageously added alone or together with mono- and/or di-glycerides or phosphatides, especially lecithin. The mono- and di-glycerides are desirably derived from the types of fats described above, i.e. with C_{12}-, C_{14}-, C_{16}-, C_{18}-, C_{20}- and C_{22}- fatty acids.

[0154] The total amounts used of the fats, mono-, di-glycerides and/or lecithins are up to about 5% and preferably within the range of about 0.5% to about 2% by weight of the total composition

[0155] It is further useful to add silicon dioxide, calcium silicate, or titanium dioxide in a concentration of about 0.02% to about 1% by weight of the total composition. These compounds act as texturizing agents.

[0156] These additives are to be used in amounts sufficient to achieve their intended purpose. Generally, the combination of certain of these additives will alter the overall release profile of the active ingredient and can be used to modify, i.e. impede or accelerate the release.

[0157] Lecithin is one surface active agent for use in the present invention. Lecithin can be included in the feedstock in an amount of from about 0.25% to about 2.00% by weight. Other surface active agents, i.e. surfactants, include, but are not limited to, cetyl alcohol, sodium lauryl sulfate, the Spans™ and Tweens™ which are commercially available from ICI Americas, Inc. Ethoxylated oils, including ethoxylated castor oils, such as Cremophor® EL which is commercially available from BASF, are also useful. Carbowax™ is yet another modifier which is very useful in the present invention. Tweens™ or combinations of surface active agents may be used to achieve the desired hydrophilic-lipophilic balance ("HLB"). The present invention, however, does not require the use of a surfactant and films or film-forming compositions of the

present invention may be essentially free of a surfactant while still providing the desirable uniformity features of the present invention.

[0158] As additional modifiers which enhance the procedure and product of the present invention are identified, Applicants intend to include all such additional modifiers within the scope of the invention claimed herein.

[0159] Other ingredients include binders which contribute to the ease of formation and general quality of the films. Non-limiting examples of binders include starches, pregelatinize starches, gelatin, polyvinylpyrrolidone, methylcellulose, sodium carboxymethylcellulose, ethylcellulose, polyacrylamides, polyvinyloxoazolidone, and polyvinylalcohols.

[0160] Further potential additives include solubility enhancing agents, such as substances that form inclusion compounds with active components. Such agents may be useful in improving the properties of very insoluble and/or unstable actives. In general, these substances are doughnut-shaped molecules with hydrophobic internal cavities and hydrophilic exteriors. Insoluble and/or instable actives may fit within the hydrophobic cavity, thereby producing an inclusion complex, which is soluble in water. Accordingly, the formation of the inclusion complex permits very insoluble and/or instable actives to be dissolved in water. A particularly desirable example of such agents are cyclodextrins, which are cyclic carbohydrates derived from starch. Other similar substances, however, are considered well within the scope of the present invention.

Forming the Film

[0161] 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.

[0162] 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.

[0163] 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.

[0164] 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.

[0165] 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.

[0166] Offset Gravure is common, where the coating is deposited on an intermediate roller before transfer to the substrate.

[0167] 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.

[0168] 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.

[0169] 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.

[0170] It may be particularly desirable to employ extrusion methods for forming film compositions containing PEO polymer components. These compositions contain PEO or PEO blends in the polymer component, and may be essentially free of added plasticizers, and/or surfactants, and polyalcohols. The compositions may be extruded as a sheet at processing temperatures of less than about 90°C. Extrusion may proceed by squeezing the film composition through rollers or a die to obtain a uniform matrix. The extruded film composition then is cooled by any mechanism known to those of ordinary skill in the art. For example, chill rollers, air cooling beds, or water cooling beds may be employed. The cooling step is particularly desirable for these film compositions because PEO tends to hold heat.

[0171] 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.

[0172] 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.

[0173] 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

[0174] The drying step is also a contributing factor with regard to maintaining the uniformity of the film composition. A controlled drying process is particularly important when, in the absence of a viscosity increasing composition or a composition in which the viscosity is controlled, for example by the selection of the polymer, the components within the film may have an increased tendency to aggregate or conglomerate. An alternative method of forming a film with an accurate dosage, that would not necessitate the controlled drying process, would be to cast the films on a predetermined well. With this method, although the components may aggregate, this will not result in the migration of the active to an adjacent dosage form, since each well may define the dosage unit per se.

[0175] 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.

[0176] Desirably, the film is dried from the bottom of the film to the top of the film. Desirably, substantially no air flow is present across the top of the film during its initial setting period, during which a solid, visco-elastic structure is formed. This can take place within the first few minutes, e.g. about the first 0.5 to about 4.0 minutes of the drying process. Controlling the drying in this manner, prevents the destruction and reformation of the film's top surface, which results from conventional drying methods. This is accomplished by forming the film and placing it on the top side of a surface having top and bottom sides. Then, heat is initially applied

to the bottom side of the film to provide the necessary energy to evaporate or otherwise remove the liquid carrier. The films dried in this manner dry more quickly and evenly as compared to air-dried films, or those dried by conventional drying means. In contrast to an air-dried film that dries first at the top and edges, the films dried by applying heat to the bottom dry simultaneously at the center as well as at the edges. This also prevents settling of ingredients that occurs with films dried by conventional means.

[0177] 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.

[0178] 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.

[0179] Additionally, it has also been discovered that the length of drying time can be properly controlled, i.e. balanced with the heat sensitivity and volatility of the components, and particularly the flavor oils and drugs. The amount of energy, temperature and length and speed of the conveyor can be balanced to accommodate such actives and to minimize loss, degradation or ineffectiveness in the final film.

[0180] 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.

[0181] 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.

[0182] Another method of controlling the drying process involves a zone drying procedure. A zone drying apparatus may include a continuous belt drying tunnel having one or more drying zones located within. The conditions of each drying zone may vary, for example, temperature and humidity may be selectively chosen. It may be desirable to sequentially order the zones to provide a stepped up drying effect.

[0183] The speed of the zone drying conveyor desirably is continuous. Alternatively, the speed may be altered at a particular stage of the drying procedure to increase or decrease exposure of the film to the conditions of the desired zone. Whether continuous or modified, the zone drying dries the film without surface skinning.

[0184] According to an embodiment of the zone drying apparatus 100, shown in Fig. 35, the film 110 may be fed onto the continuous belt 120, which carries the film through the different drying zones. The first drying zone that the film travels through 101 may be a warm and humid zone. The second zone 102 may be hotter and drier, and the third zone 103 may also be hot and dry. These different zones may be continuous, or alternatively, they may be separated, as depicted by the zone drying apparatus 200 in Fig. 36. The zone drying apparatus, in accordance with the present invention, is not limited to three drying zones. The film may travel through lesser or additional drying zones of varying heat and humidity levels, if desired, to produce the controlled drying effect of the present invention.

[0185] To further control temperature and humidity, the drying zones may include additional atmospheric conditions, such as inert gases. The zone drying apparatus further may be adapted to include additional processes during the zone drying procedure, such as, for example,

spraying and laminating processes, so long as controlled drying is maintained in accordance with the invention.

[0186] 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.

Testing Films for Uniformity

[0187] It may be desirable to test the films of the present invention for chemical and physical uniformity during the film manufacturing process. In particular, samples of the film may be removed and tested for uniformity in film components between various samples. Film thickness and over all appearance may also be checked for uniformity. Uniform films are desired, particularly for films containing pharmaceutical active components for safety and efficacy reasons.

[0188] A method for testing uniformity in accordance with the present invention includes conveying a film through a manufacturing process. This process may include subjecting the film to drying processes, dividing the film into individual dosage units, and/or packaging the dosages, among others. As the film is conveyed through the manufacturing process, for example on a conveyor belt apparatus, it is cut widthwise into at least one portion. The at least one portion has opposing ends that are separate from any other film portion. For instance, if the film is a roll, it may be cut into separate sub-rolls. Cutting the film may be accomplished by a variety of methods, such as with a knife, razor, laser, or any other suitable means for cutting a film.

[0189] The cut film then may be sampled by removing small pieces from each of the opposed ends of the portion(s), without disrupting the middle of the portion(s). Leaving the middle section intact permits the predominant portion of the film to proceed through the manufacturing process without interrupting the conformity of the film and creating sample-inducted gaps in the film. Accordingly, the concern of missing doses is alleviated as the film is further processed, e.g., packaged. Moreover, maintaining the completeness of cut portions or

sub-rolls throughout the process will help to alleviate the possibility of interruptions in further film processing or packaging due to guilty control issues, for example, alarm stoppage due to notice of missing pieces.

[0190] After the end pieces, or sampling sections, are removed from the film portion(s), they may be tested for uniformity in the content of components between samples. Any conventional means for examining and testing the film pieces may be employed, such as, for example, visual inspection, use of analytical equipment, and any other suitable means known to those skilled in the art. If the testing results show non-uniformity between film samples, the manufacturing process may be altered. This can save time and expense because the process may be altered prior to completing an entire manufacturing run. For example, the drying conditions, mixing conditions, compositional components and/or film viscosity may be changed. Altering the drying conditions may involve changing the temperature, drying time, moisture level, and dryer positioning, among others.

[0191] Moreover, it may be desirable to repeat the steps of sampling and testing throughout the manufacturing process. Testing at multiple intervals may ensure that uniform film dosages are continuously produced. Alterations to the process can be implemented at any stage to minimize non-uniformity between samples.

Uses of Thin Films

[0192] 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.

[0193] 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.

[0194] 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.

[0195] 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.

[0196] 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.

[0197] 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.

[0198] The features and advantages of the present invention are more fully shown by the following examples which are provided for purposes of illustration, and are not to be construed as limiting the invention in any way.

EXAMPLES

Examples A-1:

[0199] Water soluble thin film compositions of the present invention are prepared using the amounts described in Table 1.

TABLE 1

	Weight (g)								
Component	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**
Hydroxypropylmethyl cellulose		1.76		1.63	32.00		3.67		32.00
Peppermint oil		0.90	1.0	1.05		8.0	2.67		
Sweetener	0.15	0.15	0.22	0.10		4.6	1.53	0.15	
Polyvinylpyrrolidone		0.94		1.05		7.0	2.33		
Tween 80[1]	0.5	0.5	2.0	0.65	11.80		1.35	0.5	11.80
Simethicone[2]	0.2	0.2	0.15	0.30	1.80		0.21	0.2	1.80
Listerine[3]	83.35							83.35	
Methylcellulose	6.0								
Cornstarch[4]			1.75						
Agar			1.25						
Water		42.24	93.63	39.22	768.0	280.0	88.24		768.0
Loratadine[5]					19.2				19.2
Pullulan[6]								6.0	
Ibuprofen									38.4

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

[0200] The ingredients of inventive compositions A-I were combined by mixing until a uniform mixture was achieved. The compositions were then formed into a film by reverse roll coating. These films were then dried on the top side of an infrared transparent surface, the bottom side of which was in contact with a heated water bath at approximately 99°C. No external thermal air currents were present above the film. The films were dried to less than about 6% by weight water in about 4 to 6 minutes. The films were flexible, self-supporting and provided a uniform distribution of the components within the film.

[0201] The uniform distribution of the components within the film was apparent by examination by either the naked eye or under slight magnification. By viewing the films it was apparent that they were substantially free of aggregation, i.e. the carrier and the actives remained substantially in place and did not move substantially from one portion of the film to another. Therefore, there was substantially no disparity among the amount of active found in any portion of the film.

[0202] Uniformity was also measured by first cutting the film into individual dosage forms. Twenty-five dosage forms of substantially identical size were cut from the film of inventive composition (E) above from random locations throughout the film. Then eight of these dosage forms were randomly selected and additively weighed. The additive weights of eight randomly selected dosage forms, are as shown in Table 2 below:

TABLE 2

Sample	Additive Weight (g)	
	Trial 1	Trial 2
1	0.04	0.04
2	0.08	0.08
3	0.12	0.12
4	0.16	0.16
5	0.20	0.20
6	0.24	0.24
7	0.28	0.28
8	0.32	0.32

[0203] The individual dosages were consistently 0.04gm, which shows that the distribution of the components within the film was consistent and uniform. This is based on the simple principal that each component has a unique density. Therefore, when the components of different densities are combined in a uniform manner in a film, as in the present invention, individual dosages forms from the same film of substantially equal dimensions, will contain the same mass.

[0204] An alternative method of determining the uniformity of the active is to cut the film into individual doses. The individual doses may then be dissolved and tested for the amount of active in films of particular size. This demonstrates that films of substantially similar size cut from different locations on the same film contain substantially the same amount of active.

[0205] When the films formed from inventive compositions A-H are placed on the tongue, they rapidly dissolve, releasing the active ingredient. Similarly, when they are placed in

water, the films rapidly dissolve which provides a flavored drink when the active is chosen to be a flavoring.

Examples J-L:

[0206] Thin films that have a controlled degradation time and include combinations of water soluble and water insoluble polymers and water soluble films that allow controlled release of an active are prepared using approximately the amounts described in Table 3.

TABLE 3

	Weight (g)		
Component	**J**	**K**	**L**
Hydroxypropylmethyl cellulose		1.0	1.0
Tween 80[1]	0.7	0.7	0.7
Water			5.0
Aquacoat ECD[2]	17.0	17.0	17.5
Peppermint oil	1.0	0.4	1.1

[1] Available from ICI Americas

[2] A 30% by weight aqueous dispersion of ethyl cellulose available from FMC

[0207] The components of inventive compositions J-L were combined and formed into films using the methods for preparing inventive compositions A-I above. These films were also flexible, self-supporting and provided a uniform distribution of active which permits accuracy in dosing.

[0208] The uniformity of the films prepared from inventive compositions J-L may also be tested by either visual means measuring the weights of individual dosage films, or by dissolving the films and testing for the amount of active as described above.

Examples M-O:

[0209] An alternative method of preparing films which provides an accurate dosing may be used for any of inventive compositions A-I. The method begins with first combining the ingredients with mixing. The combination of ingredients is then divided among individual wells or molds. In such a method, aggregation of the components during drying is prevented by the individual wells.

TABLE 4

	Weight %		
Component	**M**	**N**	**O**
5% Methylcellulose Solution[1]	73.22	44.22	74.22
Raspberry Flavor	3.28	3.28	3.28
Sweetener Blends	1.07	1.07	1.07
Tween-80[2]	2.47	2.47	2.47
Polyvinylpyrrolidone	3.30	3.30	3.30
Ethanol 95%	8.24	8.24	8.24
Propylene Glycol	1.65	1.65	1.65
Calcium Carbonate	4.12	4.12	4.12
Cornstarch[3]	1.65	1.65	1.65
Red Dye[4]	1.00		
Corn Syrup[5]		30.00	

[1] Available from Dow Chemical Co. as Methocel K35
[2] Available from ICI Americas
[3] Available from Grain Processing Corporation as Pure Cote B792
[4] Available from McCormick
[5] Available from Bestfoods, Inc. as Karo Syrup

[0210] The ingredients in the above Table 4 were combined and formed into a film by casting the combination of ingredients onto the glass surface and applying heat to the bottom side of the glass. This provided inventive compositions M-O.

[0211] The film of composition M was examined both prior to and after drying for variations in the shading provided by the red dye. The film was examined both under sunlight and by incandescent bulb light. No variations in shade or intensity of color were observed.

[0212] Further testing of the films of composition M included testing of absorption which is directly related to concentration. The film was cut into segments each measuring 1.0 in. by 0.75 in., which were consecutively assigned numbers. Approximately 40 mg of the scrap material from which the segments were cut was dissolved in about 10 ml of distilled water and then quantitatively transferred to a 25 ml volumetric flask and brought to volume. The solution was centrifuged and scanned at 3nm intervals from 203-1200nm. The frequency of maximum absorption was found to be 530nm. The solution was then re-centrifuged at a higher RPM (for

the same length of time) and re-scanned, which demonstrated no change in the % transmission or frequency.

[0213] Each of the segments were weighed to 0.1mg and then dissolved in 10ml distilled water and transferred quantitatively to a 25 ml volumetric flask and brought to volume with distilled water. Each segment solution was then centrifuged as above, and then scanned, at first from 203-1200nm and later from only 500nm to 550nm at a 1nm scanning speed. The value recorded was the % transmission at the lowest wave length, which was most frequently 530nm.

[0214] The absorption values are shown in Table 5 below:

TABLE 5

Segment	mg / % A
1 - 2	1.717
3 - 4	1.700
5 - 6	1.774
7*	1.701
9 - 10	1.721
11 - 12	1.729
13 - 14	1.725
15 - 16	1.713

* segment 8 was lost

[0215] The overall average absorption was 1.724. Of the 15 segments tested, the difference between the highest and lowest values was 0.073 units, or 4% based on the average. This shows excellent control over the uniformity of the dye within the composition because the absorption is directly proportional to the concentration of the dye within each segment.

[0216] The film of inventive composition N provided a very flexible film. This film was able to be stretched and exhibited a very high tensile strength.

[0217] After forming the film of inventive composition O, the film was removed from the glass by very rapidly stripping the length of the glass with a razor. This provided very tightly wound "toothpick-like" dosage forms. Each dosage form consistently weighed 0.02 g. This

demonstrates the uniformity of the dosage forms as well as the superior self-supporting properties of the films.

Examples P-W:

[0218] Compositions P-W were prepared to demonstrate the interaction among various conditions in production of films as they relate to the present invention. The ingredients in the below Table 6 were combined and formed into a film using the process parameters listed in Table 7 below, prepared in a 6m drying tunnel designed to incorporate bottom drying of the films. Each of the examples shows the effect of different ingredient formulations and processing techniques on the resultant film products.

TABLE 6

	Weight (g)							
Component	**P**	**Q**	**R**	**S**	**T**	**U**	**V**	**W**
Hydroxypropylmethyl cellulose	320	320	320	320	320	320	345	345
Water	1440	1440	1440	1440		1440	999	999
Sweetener						60	60	45
Mint Flavor						80	80	
Propylene Glycol	50	50	50	100	100	100	100	69.3
Xanthan	22		11	11.23	10	10	10	6.9
Water/Ethanol(60/40)					1440			
Orange Flavor								42

TABLE 7

	Film Thickness (Micron)	Top[1] v (m/sec)	Bot.[1] v (m/sec)	T[1] (°C)	Top[2] v (m/sec)
P1	100	0	22	75	0
P2	350	0	22	75	0
P3	350	0	40	75	0
P4	350	0	40	75	0
P5	350	10	40	75	10
Q	350	0	40	75	10
R	350	0	40	85	10
S1	250	0	40	100	0
S2	300	0	40	100	0
S3	350	0	40	100	0
T1	250	0	40	100	0
T2	350	0	40	100	0
U1	300	0	40	100	0
U2	250	0	40	100	0
U3	300	0	40	100	0
V1	300	0	40	100	0
V2	300	0	40	100	0
V3	300	0	40	100	0
W1	300	0	40	93	0
W2	250	0	40	90	0
W3	200	0	40	90	0

[1] First Heater Section (3m)
[2] Second Heater Section (3m)

TABLE 7 (continued)

	Bot.[2] v (m/sec)	T[2] (°C)	Film Weight (g)	Coater Speed m/min	% Moisture
P1	23	60	109	5	>20
P2	23	60	n/a	5	>20
P3	40	60	161	3	>20
P4	40	75	191	3	>20
P5	40	75	253	3	>20
Q	40	75	n/a	3	>20
R	0	85		2.5	>20
S1	40	90	163	1.5	<5
S2	40	90	193	1.5	<5
S3	40	90	225	1.5	<5
T1	40	90	64	1.5	<5
T2	40	90	83	1.5	<5
U1	40	90	208	1.5	20
U2	40	90	177	1.5	20
U3	40	90	212	1.3	20
V1	40	90	237	1.3	20
V2	40	100	242	1.3	20
V3	40	100	221	1	6
W1	40	90	220	1.3	5
W2	40	90	199	1.3	5
W3	40	90	169	1.3	5

[1] First Heater Section (3m)
[2] Second Heater Section (3m)

[0219] In Table 7, each of the process parameters contributes to different properties of the films. Film thickness refers to the distance between the blade and the roller in the reverse roll coating apparatus. Bottom velocity and top velocity refer to the speed of air current on the

bottom and top sides of the film, respectively. The film weight is a measure of the weight of a circular section of the substrate and the film of 100 cm^2.

[0220] Compositions P-R show the effects of visco-elastic properties on the ability to coat the film composition mixture onto the substrate for film formation. Composition P displayed a stringy elastic property. The wet film would not stay level, the coating was uneven, and the film did not dry. In Composition Q, substantially the same formulation as P was used however the xanthan was not included. This product coated the substrate but would not stay level due to the change in the visco-elastic properties of the wet foam. Composition R was prepared using substantially the same formulation, but incorporated one-half of the amount of xanthan of Composition P. This formulation provided a composition that could be evenly coated. Compositions P-Q demonstrate the importance of proper formulation on the ability of the film matrix to conform to a particular coating technique.

[0221] The films produced from Composition S contained a large amount of air in the films. This is shown by the dried film thickness which was the same despite that variation in the coated thickness as in Table 7. Microscopic examination of the film revealed a large number of air bubbles in the film. In order to correct for the addition of air in the films, care must be taken in the mixing process to avoid air inclusion.

[0222] Composition T included a change in the solvent to 60/40 water ethanol. Composition T was stirred slowly for 45min. to deaerate the mixture. The dried weight film products T1 and T2 were consistent with the increase in solids from T1 to T2. The films dried much faster with less than 5% moisture. With the particular combination of ingredients in Composition T, the substitution of part ethanol for part water allowed the film to dry more quickly. The elimination of air from the film as a result of the slow stirring also contributed to the uniformity of the final film product and the faster drying time.

[0223] Only water was used as a solvent in Composition U. The dried weight of the U1-U3 changed consistently in accordance with the change in coating thickness indicating that no air

bubbles were present. However, these films contained 20% moisture upon exit from the oven, unlike the films of Composition T, which included part ethanol and dried completely.

[0224] The amount of solids was increased and the amount of water was decreased in Compositions V1 and V2. The dried weight was greater than U1-U3 due to the increase in solids, however the films still contained 20% moisture upon exit from the oven, similar to Composition U.

[0225] The coating line speed was reduced for Composition V3, to prevent premature drying of the exposed top film surface. This film product dried to 6% moisture.

[0226] While increasing the amount of solids improved the film weight, longer drying times were required. This was due to the surface of the film sealing preventing easy removal of the water. Therefore, for Compositions W1-W3, the temperature in the first 3m section of the dryer was decreased. This prevented the premature drying of the top surface of the films. Even at greater film thicknesses, the films were dried to 5% moisture even at faster coater line speeds.

Examples X-AA:

TABLE 8

	Weight (g)			
Component	**X**	**Y**	**Z**	**AA**
Loratadine	104.69			
Zomig		52.35		
Paxil			104.69	
Hydroxypropyl methylcellulose	320	320	320	150
Sweetener blend	60	60	60	0.4
Simethicone	1.5	1.5	1.5	1.5
Propylene glycol	100	100	100	
Water	1440	1440	1440	790
Cream essence				0.4
Polyvinyl pyrrolidinone				4
Ethanol				40
Cocoa				55.2
Polyoxyl-40-stearate				7

[0227] Compositions X, Y and Z of Table 8 were taste mask coated using a Glatt coater and Eudragit E-100 polymethacrylate polymer as the coating. The coating was spray coated at a 20% level. Therefore 10mg of drug 12.5 mg of the final dry product must be weighed.

[0228] The base formula which excluded the drug additive was mixed with care to not incorporate air. After initial mixing the formula was slowly mixed to deaerate over 30 min. During this time the drug was weighed and prepared for addition to the base mix.

[0229] For Composition X, the Loratadine (80% drug) was added slowly to the mix with stirring. After 5 min. of stirring, the total mix was added to the pan of a three roll coater set (reverse roll coater) at 30 micron coating thickness.

[0230] The process bottom temperature was set at 90°C with no top heat or air, the bottom air velocity was set at 40 m/sec., and the line speed was set at 1.3 m/min. Total drying time for the film was 4.6 min.

[0231] The liquid was coated at 30 microns and dried in the oven in less than 5 min. The film was flexible and a 1" x .75" piece weighed 70 mg and contained 10 mg of Loratadine.

[0232] The experiment was repeated for Compositions Y and Z, Zomig and Paxil, respectively. Both produced flexible films with the target weight of 70 mg containing 5 mg of Zomig and 70 mg containing 10 mg of Paxil, respectively.

[0233] The products were sweet without any noticeable drug aftertaste.

[0234] The ingredients of Composition AA were mixed in order to reduce air captured in the fluid matrix. After mixing 45 g of loratadine coated at a 80% active level and 20% coating using Eudragit E-100, this mixture was added slowing with mixing until the drug was evenly dispersed, approximately 5 min. The liquid was then deposited into the 3 roll coater (reverse roll coater) and coated at 30 microns at a line speed of 1.3 m/min. The oven temperature was set at 90°C to apply air and heat to the bottom only, with an air velocity set at 40 m/sec. The dried film

was 0.005 inch. thick (5 mil) and was cut into 1 in. x 0.75 in. pieces weighing 70 mg +/- 0.7 mg, demonstrating the uniformity of the composition of the film. The film was flexible with 5% moisture, free of air bubbles, and had uniform drug distribution as seen under the light microscope, as well as shown by the substantially identical weight measurements of the film pieces.

Examples BA-BI:

[0235] The incorporation of the anti-foaming/de-foaming agent (i.e., simethicone) provided a film that not only provided a uniform film that substantially reduced or eliminated air bubbles in the film product, but also provided other benefits. The films displayed more desirable organoleptic properties. The films had an improved texture that was less "paper-like" provided a better mouth-feel to the consumer.

[0236] The compositions in Table 9 were prepared (including the addition of simethicone in inventive compositions BA-BG) and mixed under vacuum to remove air bubbles.

[0237] The resultant uncut films of inventive compositions BA-BG exhibited uniformity in content particularly with respect to the insoluble active, as well as unit doses of ¾" by 1" by 5 mils cut therefrom. The inventive compositions also were observed to have a smooth surface, absent of air bubbles. The significantly higher amounts of simethicone present in inventive compositions BF-BG also provided a very uniform film, but not significantly improved from that of inventive compositions BA-BE.

[0238] By contrast, comparative examples BH-BI were observed to have a rougher surface, exhibiting the inclusion of air bubbles in the resultant film which provided a less uniform texture and distribution of the ingredients.

TABLE 9

Component	BA	BB	BC	BD	BE	BF	BG	BH	BI
Hydroxypropylmethyl cellulose	0	3.77	3.70	3.84	0	3.67	0	0	3.84
Peppermint oil	2.94	1.93	2.39	0	0	2.67	2.94	2.67	0
Sweetener	2.20	0.32	0.23	0	0.17	1.53	2.20	1.54	0
Polyvinylpyrrolidone	2.68	2.01	2.39	0	0	2.33	2.68	2.34	0
Tween 80[1]	2.24	1.07	1.48	1.42	0.55	1.35	2.24	0	1.42
Simethicone[2]	0.66	0.42	0.68	0.22	0.22	5.00	2.00	0	0
Listerine[3]	0	0	0	0	92.41	0	0	0	0
Methylcellulose	4.03	0	0	0	0	0	4.03	0	0
Cornstarch[4]	2.68	0	0	0	0	0	2.68	0	0
Water	73.53	90.47	89.14	92.22	0	83.45	72.19	93.46	92.44
Loratadine[5]	4.29	0	0	2.31	0	0	4.29	0	2.31
Pullulan[6]	0	0	0	0	6.65	0	0	0	0
Calcium Carbonate	1.43	0	0	0	0	0	1.43	0	0
Xanthan Gum	0.30	0	0	0	0	0	0.30	0	0
Propylene Glycol	3.02	0	0	0	0	0	3.02	0	0

[1]Available from ICI Americas
[2]Available from OSI
[3]Available from Pfizer, Inc. including thymol (0.064%), eucalyptol (0.092%), methyl salicylate (0.060%), menthol (0.042%), water (up to 72.8%), alcohol (26.9%), benzoic acid, poloxamer 407, sodium benzoate, and caramel color
[4]Available from Grain Processing Corporation as Pure Cote B792
[5]Available from Schering Corporation as Claritin
[6]Available from Hayashibara Biochemical Laboratories, Inc., Japan

Examples CA-CC:

[0239] The following examples of the present invention describe films and film-forming compositions that use an ethoxylated caster oil as a surfactant, or alternatively are free of surfactants, plasticizers and/or polyalcohols. Desirably, the films or film-forming compositions of the present invention are essentially free of surfactants. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of plasticizers. Still furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of polyalcohols. Moreover, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants and plasticizers. Furthermore, the films or film-forming compositions of the present invention are desirably formulated to be essentially free of surfactants, plasticizers and polyalcohols.

TABLE 10

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

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

[0240] 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.

[0241] After release of the vacuum, 6 grams of the liquid was added to a coating paper using a 200 micron spiral wound rod and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 5% moisture remained. The formula coated and dried to a film thickness of approx. 60 microns and quickly dissolved in the mouth.

TABLE 11

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

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

[0242] The above ingredients were added to water at 40% until a homogeneous suspension was made. Vacuum was added over 20 min. starting at 500 mm Hg. and ending at 660 mm Hg. until all air was removed from suspension. Film was made as described in prior experiments. The liquid coated the silicone release substrate and dried to a uniform flexible film. The film passed the 180° bend test without cracking and dissolved in the mouth.

TABLE 12

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

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

[0243] 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.

[0244] After release of the vacuum, the liquid was added to a coating paper using a 350 micron smooth bar and a K Control Coater Model 101 (RK Print Coat Inst. Ltd.). The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C until about 4% moisture remained. The formula coated and dried to a film. The film had an acceptable taste and quickly dissolved in the mouth. The taste-masking flavor is an ingredient that affects the taste receptors to mask the receptors from registering a different, typical undesirable, taste. The film passed the 180° bend test without cracking and dissolved in the mouth.

Example CD:

[0245] The following example of the present invention describes films and film-forming compositions that use a taste-masked, pharmaceutically active agent which also contains flavors and taste-masking aids. A taste-masking flavor is an ingredient that effects taste receptors to mask the receptors from registering a different, typically undesirable, taste.

TABLE 13

Component	(grams) CD
Hydroxypropylmethyl cellulose	4.26
Hydroxypropyl cellulose	1.42
Precipitated calcium Carbonate	1.22
Sweetner[1]	0.6
Taste-Masking flavor[2]	0.08
Taste-masked Acetaminophen[3]	5.86
Cinnamon Flavor	0.9
Spearmint Flavor	0.43
Polydimethylsiloxane emulsion	0.23

[1] Sucralose, available from McNeil Nutritionals
[2] Magna Sweet, available from Mafco Worldwide Corp.
[3] Gutte Enteric, coated acetaminophen, Gatte, LLC

[0246] The above ingredients, except for the pharmaceutically active agent and flavors, were added at 35 grams water and stirred until polymers were fully hydrated which took about 20 min. Food coloring (7 drops of red food coloring and 1 drop of yellow fool coloring) was also added. The mix was then put under vacuum to eliminate entrapped air. Vacuum was added in a steady manner starting at 500 mm and progressing up to 760 mm over about 10 to 20 minutes. The taste-masked Acetaminophen was added to the mix in about 4 minutes was stirring under vacuum. The flavors were then added to the mix in about 4 minutes was stirring under vacuum.

[0247] After release of the vacuum, the liquid solution was added to a coating paper using a 350 micron smooth bar. The paper substrate onto which the coating was added was a silicone coated paper. The coated paper was then dried at 90°C for about 11 minutes until about 3% moisture remained.

[0248] The formula coated and dried to a film. The film had an acceptable taste and moderately quickly dissolved in the mouth. The film did not curl on standing. The film passed the 180° bend test without cracking and dissolved in the mouth.

Examples CE-CF:

[0249] Thin film compositions of the present invention were prepared using the amounts described in Table 14.

TABLE 14

Component	Weight (g)
Hydroxypropylmethyl cellulose	3.92
Pullulan	3.92
Trehalose[1]	3.5
Precipitated Calcium Carbonate	3.85
Propylene Glycol	1.96
Simethicone[2]	0.35
Bovine Extract[3]	32.5
Water	q.s.

[1] Available from Cargill Inc.
[2] Available from Sentry
[3] Available from Amarillo Biosciences Inc.

[0250] The above ingredients were combined by mixing until a uniform mixture was achieved. A sufficient amount of water was present in the film compositions prior to drying, *i.e.*, q.s., which may range between about 200g to about 1000g. The bovine extract protein contained in the compositions is a heat sensitive protein. After mixing, the compositions were cast into films on release paper using a K-Control Coater with a 250 micron smooth bar.

[0251] In Example CE, the films subsequently were dried in an oven at approximately 80°C for about 6 minutes. The films were dried to about 4.3 percent moisture. In Example CF, the films were dried in an oven at approximately 60°C for about 10 minutes. The films were dried to about 5.06 percent moisture. After drying, the protein derived from bovine extract, which was contained in the films, was tested to determine whether or not it remained substantially active. To test the activity, a film dosage unit of this example was administered to a human. After ingesting the dosage, a microarray on the human's blood was conducted. The results, listed in Appendix A which is incorporated by reference herein, and graphically represented in Fig. 32, demonstrate that the protein was approximately 100 percent active in the final, dried film products of both Examples CE and CF. Therefore, the heat sensitive active did not substantially degrade or denaturize during the drying process.

Example CG:

[0252] Thin film compositions of the present invention were prepared using the amounts described in Table 15.

TABLE 15

Component	Weight (g unless otherwise indicated)	
	CG	CH
Hydroxypropylmethyl cellulose	4.59	9.18
Hydroxypropyl cellulose	1.53	3.06
Sucralose[1]	0.7	1.4
Magna Sweet[2]	0.09	0.18
Precipitated calcium carbonate	2.0	4
Fat-coated dextromethorphan hydrobromide	5.96	11.93
Orange concentrate flavor	1.05	2.1
Prosweet MM24[3]	0.18	0.35
Propylene glycol	1.22	2.45
Simethicone[4]	0.18	0.35
Water	32.5	65
Red food color		4 drops
Yellow food color		6 drops

[1] Available from McNeil Nutritional

[2] Taste-masking flavor, available from Mafco Worldwide Corp.

[3] Taste-masking flavor, available from Virginia Dare

[4] Available from Sentry

[0253] The above ingredients in the amounts listed for CG were combined by mixing, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were subsequently dried according to conventional drying techniques, rather than via the uniform drying process of the present invention. One film was dried in an oven at 80°C for 9 minutes on a wire rack. The second film was dried in an oven at 80°C for 9 minutes on a wire screen. Both films were dried to about 2.4 percent moisture.

[0254] The resulting dried films showed imprints of the wire rack and screen after drying. These configurations comprise imprints of wire supports typically used in the drying process. Without uniform heat diffusion, the wire supports conducted heat more intensely at the

points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The result is increased particle density seen as aggregations at the contact points.

[0255] The solution was cast into two more films on release paper using the K-Control Coater with a 350 micron smooth bar. These films were dried by the process of the present invention, under the same time and temperature conditions as above. In particular, the films were dried in an 80°C air oven for 9 minutes on trays lined with furnace filters, which uniformly disperse heat. The films were dried to about 1.89 percent moisture. The resulting films had no streaks, and were homogenous. Due to uniform heat diffusion throughout the film, no particle aggregations developed.

Example CH:

[0256] The ingredients in Table 15, in the amounts listed for CH, were combined by mixing, and then cast into three films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for 9 minutes in an 80°C air oven on trays lined with furnace filters, which uniformly distribute heat. The films were dried to about 2.20 percent moisture. As depicted in Fig. 17, the dried films 200 had no streaks, and were homogenous, i.e., no particle aggregations developed. The active particles appeared intact in the dried films. The films exhibited adequate strength and passed the 180° bend test without cracking, in which the films are bent in half with pressure.

[0257] The mixed solution was cast into three more films on release paper using a K-Control Coater with a 350 micron smooth bar. These films similarly were dried for 9 minutes in an 80°C air oven, but by conventional top and bottom drying means. Two of the films were dried on wire racks, while the third was dried on a wire screen. All three films were dried to about 2.65 percent moisture. The dried films showed the imprints of the wire racks and screen, for the reasons described above in Example CG.

[0258] More particularly, the dried films 100 exhibited aggregations 110 of particles in both line and diamond configurations, as shown in Figs. 9-16. These configurations comprise

imprints of wire supports used in the drying process to display the disuniformity in heat transfer which occurs in conventional top and bottom drying. As discussed above, the wire supports conducted heat more intensely at the points of contact with the substrate, leading to increased evaporation at these points. This caused more vigorous mixing, thereby pulling more particles to the contact points. The resulting increased particle density at the contact points is depicted in Figs. 9-16.

[0259] Moreover, the fat-coated dextromethorphan particles contained within the films of this example were not destroyed by the drying processes. Figs. 28-31 depict fat-coated dextromethorphan particles 500 prior to any processing, and particularly, their substantially spherical shape. After exposure to drying conditions of 80°C for 9 minutes, the fat-coated drug particles 500 were found to have remained intact within the films, i.e., maintained their spherical shape, as shown in Figs. 18-25. Although the active particles were exposed to potentially deleterious temperatures, they did not degrade. In contrast, fat-coated dextromethorphan particles placed in an evaporating dish and heated in an air oven at 80°C for 9 minutes substantially degrade. As seen in Figs. 26 and 27, the fat-coated dextromethorphan particles appear completely melted after the exposure.

Example CI:

[0260] Thin film compositions of the present invention were prepared using the amounts described in Table 16.

TABLE 16

Component	Weight (g unless otherwise indicated)
Hydroxypropylcellulose	6.00
Polyethylene oxide	2.00
Sucralose[1]	0.84
Magna sweet[2]	0.09
Mixture of microcrystalline cellulose and sodium carboxymethylcellulose[3]	0.18
Precipitated calcium carbonate	1.55
Sildenafil[4]	2.91
Peppermint & bittermint flavor	1.75
Prosweet[5]	0.44
Masking flavor[6]	1.31
N,2,3-trimethyl-2-isopropylbutanamide[7]	0.075
Simethicone[8]	0.035
Water	32.5
Blue food coloring	3 drops

[1] Available from McNeil Nutritional
[2] Taste-masking flavor, available from Mafco Worldwide Corp.
[3] Avicel CL-611, available from FMC Biopolymer
[4] Available from Pfizer, Inc. as Viagra®
[5] Taste-masking flavor, available from Virginia Dare
[6] Available from Ungerer and Co.
[7] Cooling agent
[8] Available from Sentry

[0261] The above ingredients were combined by mixing until a uniform mixture was achieved, and then cast into two films on release paper using a K-Control Coater with a 350 micron smooth bar. One film was dried for 10 minutes in an 80°C air oven to a moisture level of 3.52%, while the second film was dried for 10 minutes in an 80°C air oven to a moisture level of 3.95%. The dried films had adequate strength and tear resistance. The films passed the 180° bend test without breaking. The films also dissolved at a moderately fast rate in the mouth and exhibited an acceptable flavor.

[0262] As mentioned above, the controlled drying process of the present invention allows for uniform drying to occur, whereby evaporative cooling and thermal mixing contribute to the rapid formation of viscoelastic film and the "locking-in" of uniformity of content throughout the

film. One of the additional advantages of the present invention is that the film composition reaches its viscoelastic state, and even the fully dried state, without exposing the components of the composition to temperatures which will cause them to be altered or unusable for their intended purpose. For example, heat sensitive drugs, proteins, flavors, sweeteners, volatile components, antigens, antibodies and the like, readily decompose at certain temperatures become inactive or denature, making them ineffective for their intended use. In the present invention, due to the combination of a short heat history required to dry, and the controlled non-top-skinning drying process, the film composition never need to attain the oven temperature (or other heat source) to reach the dried state. To demonstrate this, films were made in accordance with the present invention and dried as discussed below. A first thermocouple was placed within the film and a second thermocouple was suspended in the oven in order to measure the temperature differential between the oven environment and the film composition during the drying process.

[0263] To measure the temperature differentials, a thermocouple, which was connected to a Microtherma 1 thermometer, was placed within the films, and another thermocouple was suspended in the drying oven. Temperature readings in the films and oven were recorded every 30 seconds during the drying of the films.

[0264] The thermocouple results for the first film are listed in Table 17 below, and graphically represented in Fig. 33. The results for the second film are listed in Table 18 below, and graphically represented in Fig. 34. The results show that even after 10 minutes of drying, the temperatures of the film were substantially below (at least about 5°C) the oven environment. Films dried for less than 10 minutes may experience significantly greater temperature differentials. For example, drying for 4 to 6 minutes, which is a particularly desirable time frame for many films of the present invention, produces differentials of about 25°C to about 30°C. Accordingly, films may be dried at high, potentially deleterious temperatures without harming heat sensitive actives contained within the films.

TABLE 17

Time (Min.)	Probe Temp (°C)	Oven Temp (°C)
0	42.7	78
1	48.1	80
2	48.8	81
3	50	80
4	51.6	80
5	53.6	80
6	56.8	80
7	61.4	80
8	66.8	80
9	72.7	80
10	76.1	80

TABLE 18

Time (Min.)	Probe Temp (°C)	Oven Temp (°C)
0	44.4	77
1	49.8	81
2	49.2	81
3	49.4	80
4	51	80
5	52	80
6	55	80
7	58.9	80
8	64.5	80
9	69.8	80
10	74.4	80

Examples CJ-DB:

[0265] The following examples describe film compositions of the present invention, which contain water-soluble polymers including polyethylene oxide (PEO) alone or in combination with hydroxypropyl cellulose (HPC) or hydroxypropylmethyl cellulose (HPMC). Thin film compositions were prepared using the polymer amounts listed in Table 19.

TABLE 19

Composition	PEO (g)	HPC (g)	HPMC (g)
CJ		32	8
CK		24	16
CL		16	24
CM		8	32
CN			40
CO	8		32
CP	16		24
CQ	24		16
CR	32		8
CS	40		
CT	4		36
CV	6		34
CV	32	8	
CW	24	16	
CX	16	24	
CY	8	32	
CZ		40	
DA	4	36	
DB	6	34	

[0266] The above polymer components were combined with equal amounts of precipitated calcium carbonate (mimics drug loading), simethicone emulsion, and water to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films then were dried for about 9 minutes at 80°C in accordance with the present invention. The film compositions were tested for various properties, the results of which are described in Table 20 below.

TABLE 20

Composition	Composition of Polymer in Film	Solution Coating Rating	Solution Leveling Rating	% Moisture in Film	180° Bend Test	Dissolution Test (seconds)	Curl Test
CJ	20% HPMC/ 80% HPC	well	well	2.9	Failed at crease	12, 15	Curl
CK	40% HPMC/ 60% HPC	well	well	1.70	Failed at crease	21, 22	Curl
CL	60% HPMC/ 40% HPC	well	well	2.40	Failed at crease	24, 27	Curl
CM	80% HPMC/ 20% HPC	well	well	2.76	Failed at crease	31, 31	Curl
CN	100% HPMC	reasonably well	well	2.66	Failed at crease	35, 38	Curl
CO	10% PEO/ 90% HPMC	some streaking	well	2.27	Failed at crease	31, 32	Curl
CP	15% PEO/ 85% HPMC	well	well	3.31	Failed	24, 27	Curl
CQ	20% PEO/ 80% HPMC	well	well	2.06	Passed	22, 31	Slight curl
CR	40% PEO/ 60% HPMC	well	well	2.01	Passed	13, 12	Slight curl
CS	60% PEO/ 40% HPMC	well	well	1.40	Passed	5, 6	Very slight curl
CT	80% PEO/ 20% HPMC	well	well	1.35	Passed	5, 6	Very slight curl
CU	100% PEO	well	well	0.98	Passed	5, 5	No curl
CV	20% HPC/ 80% PEO	well	well	1.01	Passed	5, 5	No curl
CW	40% HPC/ 60% PEO	well	well	2.00	Passed	6, 6	No curl
CX	60% HPC/ 40% PEO	well	well	0.97	Passed	7, 7	Slight curl
CY	80% HPC/ 20% PEO	well	well	1.41	Passed	12, 12	Very slight curl
CZ	85% HPC/ 15% PEO	well	well	1.86	Failed at crease	13, 14	Curl
DA	90% HPC/ 10% PEO	well	well	1.62	Failed at crease	14, 13	Curl
DB	100% HPC	well	well	2.01	Failed at crease	16, 17	Curl

[0267] The solution coating rating and solution leveling rating were both based upon panel observations made during casting of the film compositions.

[0268] For the 180° bend test, the dried films were placed in a moisture analyzer (HR73 Moisture Analyzer from Mettler Toledo) to obtain percent moisture and to remove any solvent (e.g. water) remaining in the films after drying at 80°C in accordance with the present invention.

The films then were creased to about 180° and observed for break. Films that broke during creasing were considered a failure. If the film did not break during creasing, a 200 g weight was dropped onto the creased film from a height of about 8.5 mm. Films that broke were considered a failure, and those that did not break were considered a pass. It should be noted, however, that this flexibility test is an extreme test. Films that failed this test are still considered operable within the scope of the present invention. More specifically, there may be certain applications that do not require such extreme flexibility properties.

[0269] The films also were tested for dissolution rate. An approximately 20 mm by 100 mm piece of film, having a 2.85 g weight attached, was lowered into a 32.5°C water bath to a depth of about 50 mm. The time required for the film to dissolve and separate into two pieces was determined (in seconds).

[0270] For the curl test, samples of film (about 35mm by 35mm) were placed on a glass plate in a laboratory window ledge. The film samples were allowed to stand in the window ledge at room conditions for two to three days and then were observed for curling.

[0271] In accordance with the present invention, desirable film compositions are flexible, fast dissolving, and not likely to substantially curl. As indicated by the results in Table 20, Compositions CQ-CY performed best, exhibiting good flexibility, dissolution, and curling properties. In particular, Compositions CQ-CY passed the 180° bend test and dissolved at moderate to fast rates. These compositions also exhibited no or only slight curl. Accordingly, it may be desirable to employ polymer components as in Compositions CQ-CY, particularly about 20% to 100% PEO in the polymer component optionally combined with about 0% to 80% HPC or HPMC.

Examples DC-DG:

[0272] The following examples of the present invention describe films that include PEO or PEO-polymeric blends and an active component. Thin film compositions with these components were prepared using the amounts described in Table 21.

TABLE 21

	Weight (g unless otherwise indicated)				
Component	**DC**	**DD**	**DE**	**DF**	**DG**
PEO[1]	8.75	7	1.75	7	1.75
Sucralose	0.7	0.7	0.7	0.7	0.7
Precipitated calcium carbonate	3.65	3.65	3.65	3.65	3.65
Orange concentrate flavor	1.05	1.05	1.05	1.05	1.05
Vanilla	0.5	0.5	0.5	0.5	0.5
HPMC		1.75	7.0		
HPC				1.75	7.0
Simethicone[2]	0.35	0.35	0.35	0.35	0.35
Water	32.5	32.5	32.5	32.5	32.5
Loratadine[3]	2.5	2.5	2.5	2.5	2.5
Yellow food coloring	3 drops	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops	2 drops

[1] Available from the Dow Chemical Company
[2] Available from Sentry
[3] Available from Schering Corporation as Claritin

[0273] The above components for each of Compositions DC through DG were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80°C in accordance with the method of the present invention to varying moisture levels.

[0274] After drying, the films were tested for various properties, including the 180° bend test, dissolution test, and curl test, as described above in Examples CJ-DB. The films also were tested for resistance to tearing. Tear resistance was measured by a panel test in which members tried to tear the film apart by pulling on opposing ends of the film. Films that tore cleanly received a low grade. Films that stretched a little and began to break received a moderate grade, and films that stretched and were difficult to tear received a high grade.

[0275] Composition DC, which included a 100% PEO film base, was dried in accordance with the method of the present invention to about 1.30 percent moisture. The dried film had good strength, and passed the 180° bend test. The film also exhibited good resistance to tearing (high grade). The film dissolved at a fast rate on the tongue, and had a dissolution testing rate of about 3.5 to 4 seconds. The film exhibited no curling.

[0276] Composition DD, which included an 80%/20% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 2.30 percent moisture. The dried film exhibited adequate strength, and passed the 180° bend test. The film also exhibited good resistance to tearing. It dissolved at a moderate to fast rate on the tongue, and had a dissolution testing rate of about 5 seconds. The film exhibited slight curling.

[0277] Composition DE, which included a 20%/80% PEO/HPMC film base, was dried in accordance with the method of the present invention to about 3.0 percent moisture. The film had good strength, and passed the 180° bend test. The film exhibited moderate tear resistance, dissolved on the tongue at a slow rate, and had a dissolution testing rate of 16 seconds. The film exhibited some curling.

[0278] Composition DF, which included an 80%/20% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.52 percent moisture. The film exhibited good strength, passed the 180° bend test, and exhibited high tear resistance. The film also dissolved at a fast rate on the tongue, and had a dissolution rating of 4 seconds. The film exhibited very slight curling.

[0279] Composition DG, which included a 20%/80% PEO/HPC film base, was dried in accordance with the method of the present invention to about 2.81 percent moisture. The film had adequate strength, passed the 180° bend test, and exhibited moderate tear resistance. The film dissolved on the tongue at a fast rate, and had a 10 second dissolution testing rate. The film exhibited no curling.

[0280] As indicated above, each of Compositions DC-DG contained about 20% to 100% PEO in the polymer component, optionally in combination with varying levels of HPC or HPMC. The results indicate that varying the polymer component achieved different film properties.

Examples DH-DZ:

[0281] The following examples of the present invention describe films that include PEO or PEO-HPC polymer blends. The film compositions include PEO of varying molecular weights. Thin film compositions with these components were prepared using the amounts described in Table 22 (listed by weight percent of the polymer component).

TABLE 22

Composition	100,000 PEO (wt.%)	200,000 PEO (wt.%)	300,000 PEO (wt.%)	900,000 PEO (wt.%)	HPC (wt.%)
DH			20		80
DI			50		50
DJ			80		20
DK		50			50
DL		67.5			32.5
DM		70			30
DN		75			25
DO		100			
DP	50				50
DQ	100				
DR				10	90
DS				20	80
DT		40		10	50
DU	25			15	60
DV	20	80			
DW		80		20	
DX		80	20		
DY		50	50		
DZ		20	80		

[0282] The above polymer components were combined with sucralose, precipitated calcium carbonate (mimics drug loading), orange concentrate flavor, Tween 80 (available from ICI Americas), vanilla flavor, simethicone emulsion, water, and yellow and red food coloring to form the film compositions. The components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The solution coating and leveling properties were observed. The films then were dried for about 9 minutes at 80°C in accordance with the method of the present invention. The film compositions were tested for various properties to determine the effect of varying the

PEO molecular weight and level in the polymer component, the results of which are described in Table 23 below.

TABLE 23

Composition	Film thickness (mils)	% Moisture	Roof of Mouth Tendency	180° Bend Test	Dissolution Test (seconds)	Tear Resistance
DH	3.5	2.5	low	passed	8	poor
DI	3.8	2.01	low	passed	7	moderate
DJ	2.6	2.63	high	passed	3	excellent
DK	3.4	2.35	low	passed	4	poor
DL	3.5	1.74	low	passed	4	good to excellent
DM	3.5	1.68	low	passed	4	good to excellent
DN	3.3	2.33	moderate	passed	3	good to excellent
DO	3.1	2.14	high	passed	4	excellent
DP	4.1	1.33	high	passed	3.5	poor
DQ	3.2	2.07	high	passed	4	good
DR	3.4	1.90	low	passed	10	poor
DS	3.5	2.04	low	passed	10	poor
DT	3.3	2.25	moderate	passed	5	good
DU	3.6	2.84	low to moderate	passed	6	moderate
DV	2.5	3.45	high	passed	2	excellent
DW	2.5	2.83/1.68	high	passed	3-4	excellent
DX	3.5	2.08	high	passed	5	excellent
DY	2.8	1.67	high	passed	3	excellent
DZ	2.5	1.89/0.93	high	passed	3	excellent

[0283] The films were tested for various properties, including the 180° bend test, dissolution test, and tear resistance, as described above. The films also were tested for adhesion, i.e., tendency to go to the roof of the mouth. Adhesion was rated by a panel test in which films that did not stick to the roof of the mouth received a low grade, films that stuck somewhat received a moderate grade, and films that stuck completely received a high grade.

[0284] As indicated above, the level and molecular weight of PEO in the polymer component were varied to achieve different film properties. In general, the higher the level of PEO in the polymer component, the greater the adhesiveness and tear resistance exhibited by the

film. Film compositions containing about 50% or greater levels of PEO attained higher tear resistance ratings than those with less than 50% PEO. The tear resistance of lower levels of PEO, however, was shown to be improved by combining small amounts of higher molecular weight PEOs with the lower molecular weight PEOs (e.g. Compositions DT and DU).

[0285] Compositions containing about 20% to 75% PEO performed best with respect to adhesion prevention (lower tendencies to go to the roof of the mouth). Compositions containing higher levels of PEO performed well when adhesion was desired.

[0286] As regards dissolution rate, polymer components containing about 50% or higher levels of PEO performed best, providing faster dissolving film compositions. In those films containing combinations of varying molecular weight PEOs, those with about 60% or higher of the lower molecular weight PEOs (100,000 to 300,000) in the PEO combination dissolved faster.

Example EA:

[0287] The following example of the present invention describes films that include PEO and polyvinyl pyrrolidone (PVP) polymeric blends. Thin film compositions with these components were prepared using the amounts described in Table 24. In particular, the polymer component of the films contained about 80% PEO and 20% PVP, or a ratio of 4:1 PEO to PVP.

TABLE 24

Component	Weight (g unless otherwise noted)
PVP	3.75
PEO	15
Sucralose[1]	1.5
Precipitated calcium carbonate	14.57
Orange concentrate flavor	2.25
Tween 80[2]	0.056
Simethicone[3]	0.38
Water	62.5
Yellow food color	6 drops
Red food color	4 drops

[1] Available from McNeil Nutritionals
[2] Available from Fisher
[3] Available from Sentry

[0288] The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 350 micron smooth bar. The films were dried for about 9 minutes at 80°C in accordance with the method of the present invention to a moisture level of about 2.19%. The films exhibited good strength, dissolved in the mouth at a moderate to fast rate, had high tear resistance, a thickness of about 4 mils, good flavor, low tendency to adhere to the roof of the mouth, and passed the 180° bend test. The film had a dissolution rate of 4 seconds, according to the test described above. In addition, the film easily released from the release paper.

EXAMPLE EB-ED:

[0289] The following examples of the present invention describe extruded films that include PEO-based polymer components. Film compositions were prepared using the amounts described in Table 25 for Example EC and Table 26 for Example ED.

TABLE 25

COMPONENT	WEIGHT (g unless otherwise noted)
HPC	73.78
Polyethylene oxide	153.22
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

TABLE 26

COMPONENT	WEIGHT (g unless otherwise noted)
Polyethylene oxide	227
Sucralose	18.16
Precipitated calcium carbonate	176.38
Orange concentrated flavor	27.24
Tween 80	0.68
Simethicone	4.54
Yellow food coloring	27 drops
Red food coloring	18 drops

[0290] The films of Examples EB-ED were extruded using a single screw extruder in accordance with the specifications provided in Table 27 below (temperatures are in °F).

TABLE 27

Composition	RPM	Temp. Barrel Zn.1	Temp. Barrel Zn. 2	Temp. Barrel Zn. 3	Temp. Zn. 4	Temp. Die	Temp. Melt	PSI Pressure		Amps
								P1	P2	
EB	73	175	181	185	190	190	194	600	1250	12
EB	153	177	181	199	211	210	217	175	1070	7.8
ED	253	175	181	200	211	210	222	0	761	6.3
ED	109	175	181	200	211	210	207	0	1000	6.0
EC	109	175	181	200	211	210	217	0	875	12.1
EC	149	175	200	226	248	239	258	0	583	7.3

[0291] More specifically, for Example EB, two pounds of PEO having a molecular weight of about 200,000 were weighed and placed in a polyethylene plastic bag. This PEO flush was then extruded according to the specifications in Table 27.

[0292] For Example EC, a blend of the components listed in Table 25 was prepared. The HPC, PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

[0293] For Example ED, a blend of the components listed in Table 26 was prepared. The PEO, sucralose, and precipitated calcium carbonate were placed in a large electric blender and allowed to mix. A solution of orange concentrate flavor and Tween 80 was added to the blender while mixing, after which a solution of simethicone and the food colors was added to the blender while mixing. The blended composition was extruded in accordance with the specifications in Table 27.

[0294] The extruded films did not exhibit stickiness to each other during processing. As such, the resulting film could be rolled or wound onto itself without the need for a backing material.

Examples EE-EH:

[0295] The following examples of the present invention describe films that include a densifying agent. A thin film composition including PEO-polymeric blends and a densifying agent (simethicone) were prepared using the amounts described in Table 28.

TABLE 28

Component	Weight (g unless otherwise indicated)			
	EE	EF	EG	EH
Hydroxypropylcellulose	3.05	3.05	3.05	3.05
Polyethylene oxide	6.33	6.33	6.33	6.33
Sucralose	0.75	0.75	0.75	0.75
Precipitated calcium carbonate	7.47	7.47	7.09	7.09
Orange concentrate flavor	1.12	1.12	1.12	1.12
Tween 80	0.028	0.028	0.028	0.028
Simethicone	0	0	0.38	0.38
Water	31.25	31.25	31.25	31.25
Yellow food coloring	3 drops	3 drops	3 drops	3 drops
Red food coloring	2 drops	2 drops	2 drops	2 drops

[0296] The densities of these thin film compositions were measured, the results of which are shown in Table 29.

TABLE 29

Composition	Average Weight of Film/Density
EE	146.5mg/1.123
EF	126.5mg/0.969
EG	137mg/1.057
EH	146mg/1.119

[0297] Vacuum conditions were added to two of the film compositions (EE and EH). Composition EE contained 0% simethicone and vacuum was applied. Composition EF contained 0% simethicone and no vacuum applied. As shown in Table 29 above, the density increased with the addition of vacuum conditions from 0.969 (EF) to 1.123 (EE). Composition EG contained 2% simethicone and no vacuum applied. Composition EH contained 2% simethicone and vacuum was applied. Again, density increased from 1.057 (EG) to 1.119 (EH). Overall, the density of the films increased from 0.969 (EF: no simethicone and no vacuum) to 1.057 (EG: simethicone but no vacuum) to 1.119 (EH: simethicone and vacuum).

Examples EI-EW:

[0298] The following examples of the present invention describe films that include PEO or PEO-polymeric blends. In particular, PEO was combined with polyvinylpyrrolidone (PVP), starch (pregelatinized modified corn starch), sodium carboxymethyl cellulose (CMC), hydroxypropylcellulose (HPC), hydroxypropylmethyl cellulose (HPMC) or polyvinyl alcohol (PVA) to form the polymer components of the films. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Fig. 38.

[0299] In addition to the polymer components listed in Fig. 38, each of these film compositions included: about 4% sucralose, about 38.85% calcium carbonate, about 6% orange flavor, about 0.15% Tween 80, about 1% simethicone, and food coloring. The PEO included in the polymer component of these examples had a molecular weight of about 200,000.

[0300] Fig. 38 also displays certain properties of these films, including: percent solids of solution; viscosity; percent moisture; film thickness; film strength; tear resistance of the film;

tendency of the film to go to the roof of the mouth; the 180° bend test; whether molding, or aggregations, are present in the film; dissolution times of the film; rating of dissolution in the mouth; and time in drying oven. Each of these film property tests is described in detail above. The results of these various tests are indicated in Fig. 38.

Examples EX-FK:

[0301] The following examples of the present invention describe films that include PEO or PEO-polymeric blends (with HPC) and different active components. Thin film compositions with these components were prepared in accordance with the method of the present invention using the amounts described in Tables 30 and 31.

TABLE 30

Component	Weight (in g, unless otherwise indicated)						
	EX	EY	EZ	FA	FB	FC	FD
HPC	5.68	5.64	6	6.73	6.22	6.22	
PEO	1.89	1.88	2	2.25	1.78	1.78	9.04
Sucralose	0.84	0.84	0.44	0.66	0.84	0.84	0.44
Magna Sweet	0.08	0.08	0.09	0.10	0.09	0.09	
Avicel CL 611[1]	0.18	0.18	0.18	0.20	0.18	0.18	
Precipitated calcium carbonate	0.67		2.2		0.71	3.07	
Dextromethorphan	5.83	6.94					
Caffeine			3.28				
Tadalafil[2]				4.92			
Sildenafil[3]					4.38		
Loperamide[4]						2.8	
Prosweet	0.18	0.18		0.20	0.61	0.18	
Taste Masking Flavor			0.87		1.31	0.89	
Peppermint			0.87				
Peppermint Bittermask flavor			1.07				
Vanilla flavor				0.56			
Watermelon artificial flavor	1.23	1.23			1.22		
Orange flavor				1.18			
Hawaiian punch flavor						1.22	
Strawberry & cream flavor							1.11
WS-23[5]	0.075	0.075	0.075	0.084	0.075	0.075	
WS-3[6]							0.025
Simethicone	0.08	0.08	0.18	0.39	0.09	0.18	46.43
Propylene glycol	0.76	0.38	0.25	0.22			
Water	32.5	32.5	32.5	32.5	32.5	32.5	
Green color	5 drop	5 drop			5 drop		
Red color				2 drop		5 drop	7 drop
Blue color			3 drop				
Yellow color				3 drop			

[1] Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer

[2] Available from Lilly ICOS, LLC, as Cialis®

[3] Available from Pfizer, Inc. as Viagra®

[4] Available as Imodium

[5] N-2,3-trimethyl-2-isopropyl butanamide

[6] N-Ethyl-p-menthane-3-carboxamide

TABLE 31

Component	Weight (in g, unless otherwise indicated)						
	FE	FF	FG	FH	FI	FJ	FK
HPC	1.28	3.05	4.5	3.29	2.6	2.92	3.29
PEO	2.66	6.33	3	6.83	5.4	6.08	6.83
Sucralose	0.31	0.9	0.6		0.64		
Magna Sweet		0.09					
Avicel CL 611[1]		0.56	0.45				
Precipitated calcium carbonate	1.07	2.02	0.99	6.05	0.90	2.67	1.39
Meloxicam[2]	1.97						
Risperidone[3]		0.62					
Zyrtec®[4]			3.75				
Five Grass Powder[5]				2.207			
Tea Tree Oil[6]					4		
Antibacterial concentrate[7]						6.12	
Mite extract[8]							6.87
Prosweet		0.66					
Taste Masking Flavor		1.41					
Peppermint Bittermask flavor		2.81			2.24		
Orange flavor	0.47						
Strawberry & cream flavor			1.5				
WS-3[9]	0.020	0.081	0.038		0.04		
Tween 80	0.012	0.028	0.022		0.024	0.027	
Simethicone	0.08	0.19	0.15	0.37	0.16	0.18	0.37
Water	14.63	31.25	25	31.25	24	22	31.25
Red color	2 drop		5 drop				
Blue color		3 drop			3 drop		
Yellow color	3 drop						

[1] Mixture of microcrystalline cellulose and sodium carboxymethylcellulose, available from FMC Biopolymer
[2] Available as Mobic®
[3] Available as Risperdal®
[4] Available from Pfizer, Inc.
[5] Allergy treatment
[6] Antibiotic
[7] MegaBac™, available from Nicrosol Technologies
[8] Allergy treatment
[9] N-Ethyl-p-menthane-3-carboxamide

[0302] The above components were combined by mixing until a uniform mixture was achieved, and then cast into films on release paper using a K-Control Coater with a 250 or 350 micron smooth bar. The films were dried for about 9 to 10 minutes at 80°C in accordance with the method of the present invention resulting in dried films having adequate to good strength.

[0303] While there have been described what are presently believed to be the preferred embodiments of the invention, those skilled in the art will realize that changes and modifications may be made thereto without departing from the spirit of the invention, and it is intended to include all such changes and modifications as fall within the true scope of the invention.

WHAT IS CLAIMED IS:

1. A mucosally-adhesive water-soluble film product comprising:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component comprises greater than 75% polyethylene oxide and up to 25% hydrophilic cellulosic polymer;

the polyethylene oxide comprises one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight comprises about 60% or more in the polymer component.

2. The film product according to claim 1, wherein said film product has a viscosity of about 1,000 cps to about 40,000 cps.

3. The film product according to claim 1, wherein said film product has a thickness of about 3 mils to about 6 mils.

4. The film product according to claim 1, further comprising an additional pharmaceutical active.

5. The film product according to claim 1, further comprising one or more sweeteners.

6. The film product according to claim 5, wherein said one or more sweeteners comprise a hydrogenated starch hydrolysate.

7. The film product according to claim 5, wherein said one or more sweeteners comprise the potassium salt of 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide.

8. The film product according to claim 1, further comprising one or more flavors.

9. The film product according to claim 1, further comprising one or more buffers.

10. A mucosally-adhesive water-soluble film product comprising:

an analgesic opiate pharmaceutical active; and

at least one water-soluble polymer component consisting of polyethylene oxide in combination with a hydrophilic cellulosic polymer;

wherein:

the water-soluble polymer component comprises the hydrophilic cellulosic polymer in a ratio of up to about 4:1 with the polyethylene oxide;

the polyethylene oxide comprises one or more low molecular weight polyethylene oxides and one or more higher molecular weight polyethylene oxides, the molecular weight of the low molecular weight polyethylene oxide being in the range 100,000 to 300,000 and the molecular weight of the higher molecular weight polyethylene oxide being in the range 600,000 to 900,000; and

the polyethylene oxide of low molecular weight comprises about 60% or more in the polymer component.

11. The film product according to claim 10, wherein said film product has a viscosity of about 1,000 cps to about 40,000 cps.

12. The film product according to claim 10, wherein said film product has a thickness of about 3 mils to about 6 mils.

13. The film product according to claim 10, further comprising an additional pharmaceutical active.

14. The film product according to claim 10, further comprising one or more sweeteners.

15. The film product according to claim 14, wherein said one or more sweeteners comprise a hydrogenated starch hydrolysate.

16. The film product according to claim 14, wherein said one or more sweeteners comprise the potassium salt of 3,6-dihydro-6-methyl-1-1-1,2,3-oxathiazin-4-one-2,2-dioxide.

17. The film product according to claim 10, further comprising one or more flavors.

18. The film product according to claim 10, further comprising one or more buffers.

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

ABSTRACT

[0304] The invention relates to the film products and methods of their preparation that demonstrate a non-self-aggregating uniform heterogeneity. Desirably, the films disintegrate in water and may be formed by a controlled drying process, or other process that maintains the required uniformity of the film. The films contain a polymer component, which includes polyethylene oxide optionally blended with hydrophilic cellulosic polymers. Desirably, the films also contain a pharmaceutical and/or cosmetic active agent with no more than a 10% variance of the active agent pharmaceutical and/or cosmetic active agent per unit area of the film.

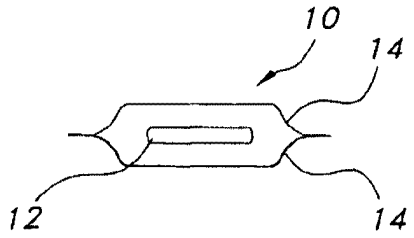


FIG. 1

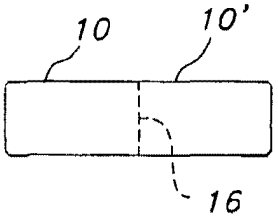


FIG. 2

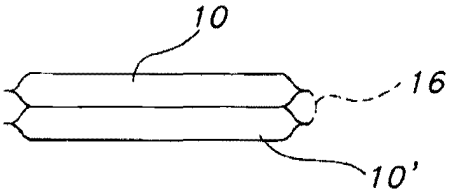


FIG. 3

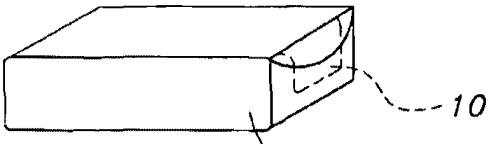


FIG. 4

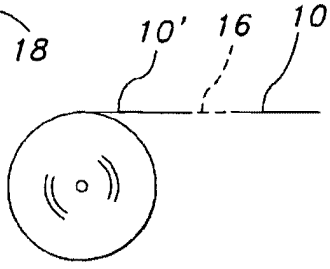


FIG. 5

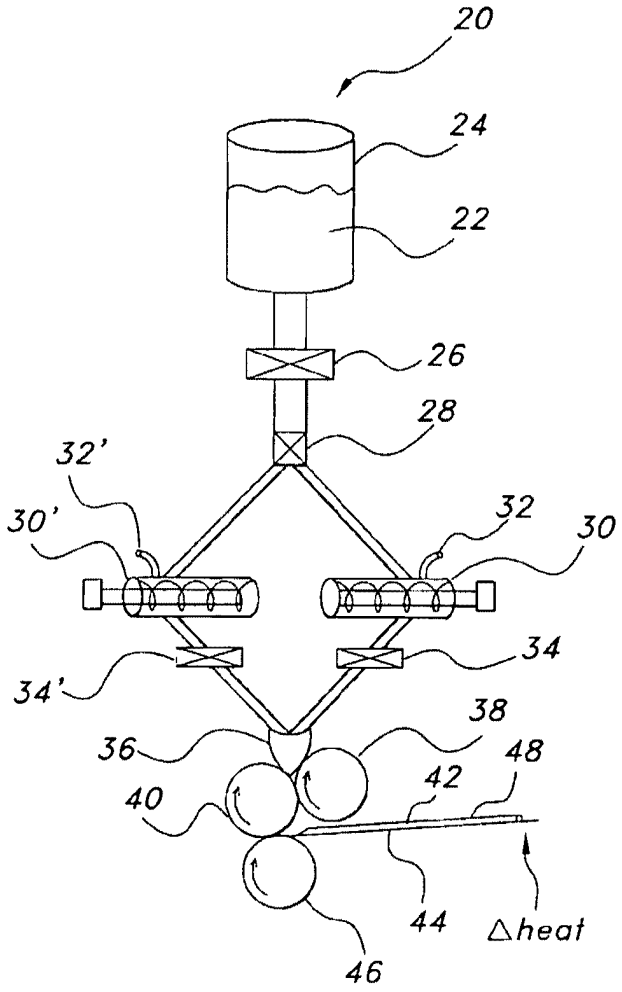


FIG. 6

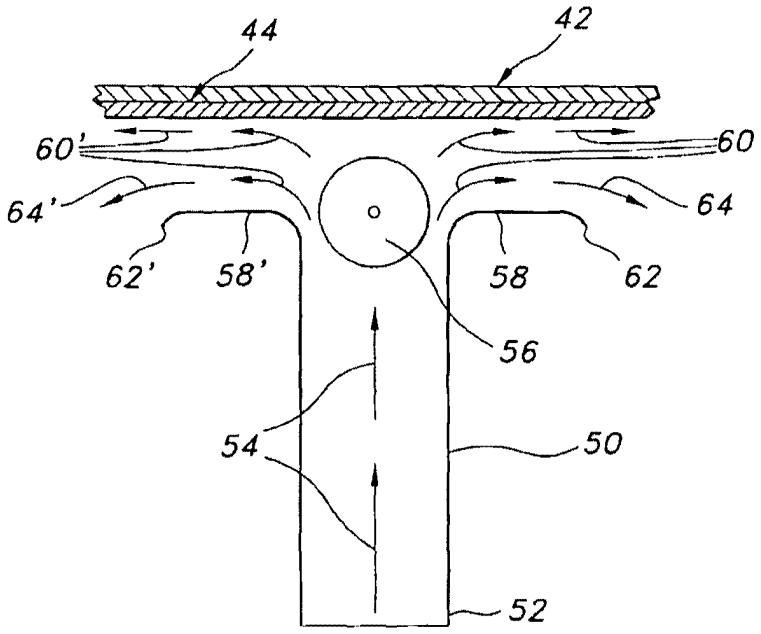


FIG. 7

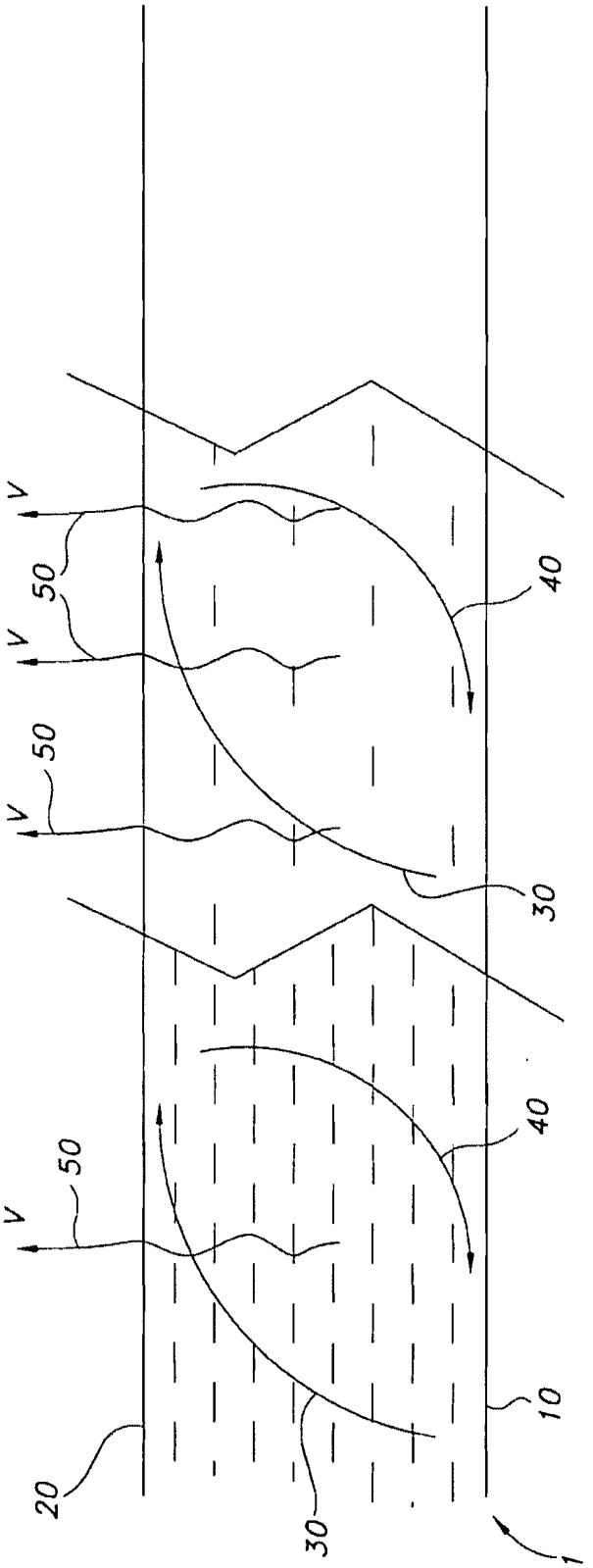


FIG. 8

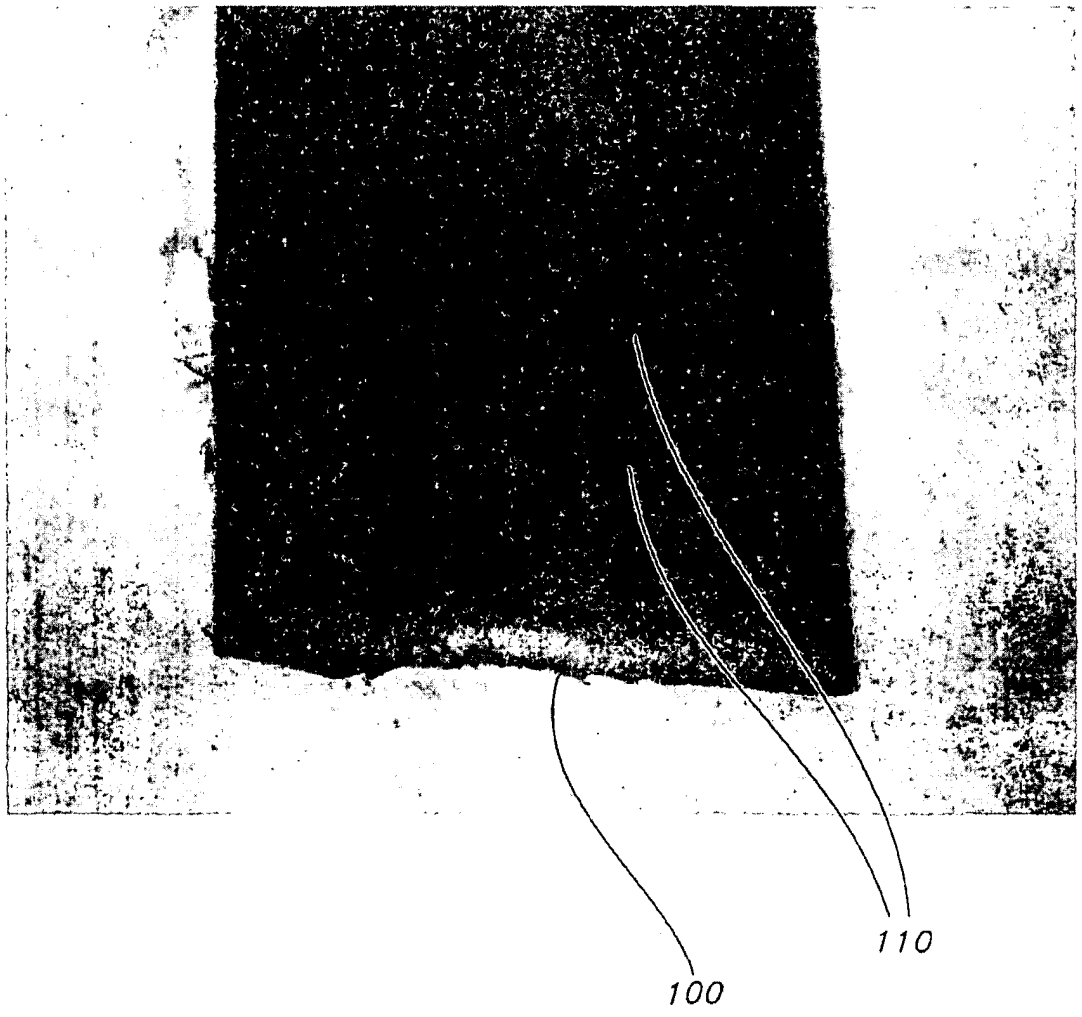


FIG. 9

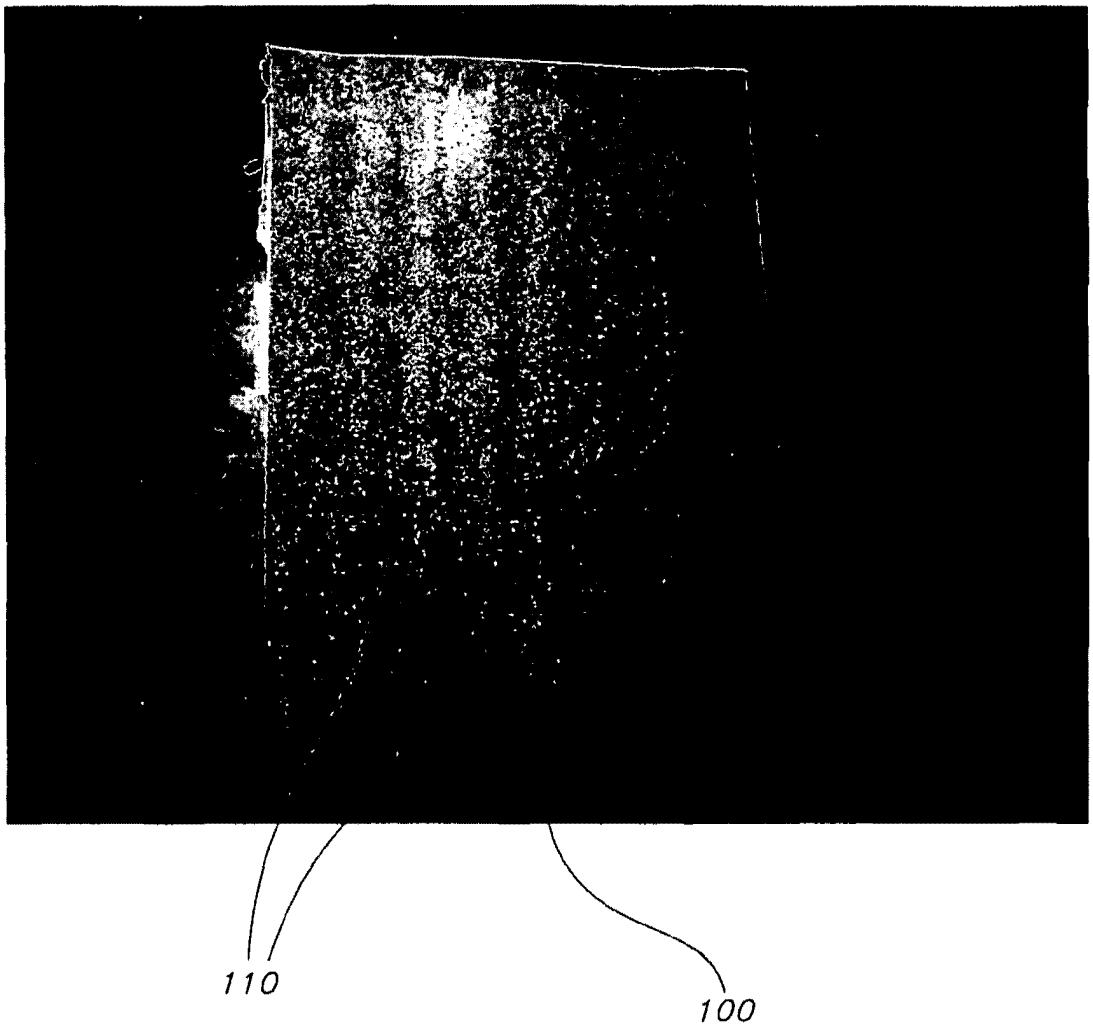


FIG. 10

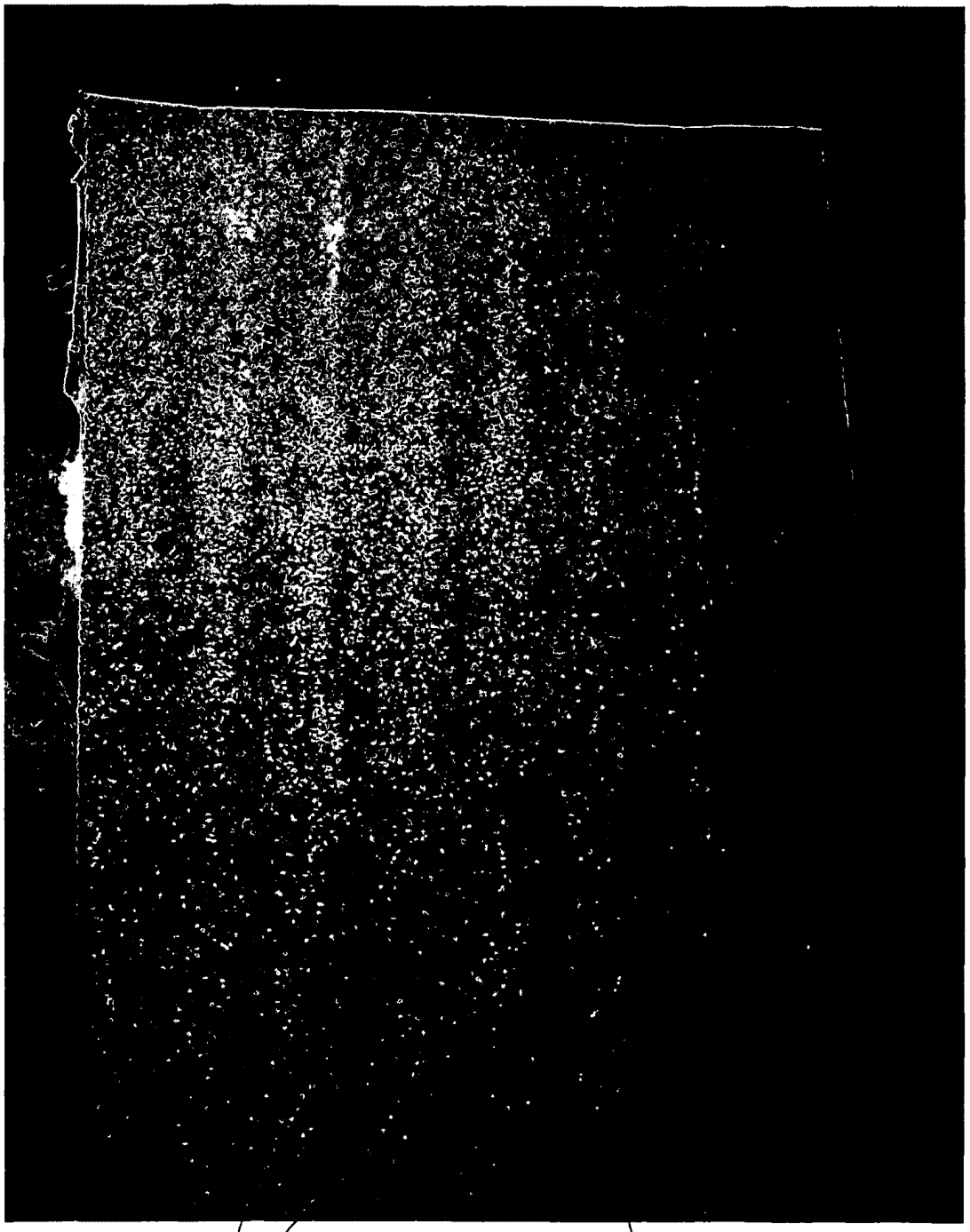


FIG. 11

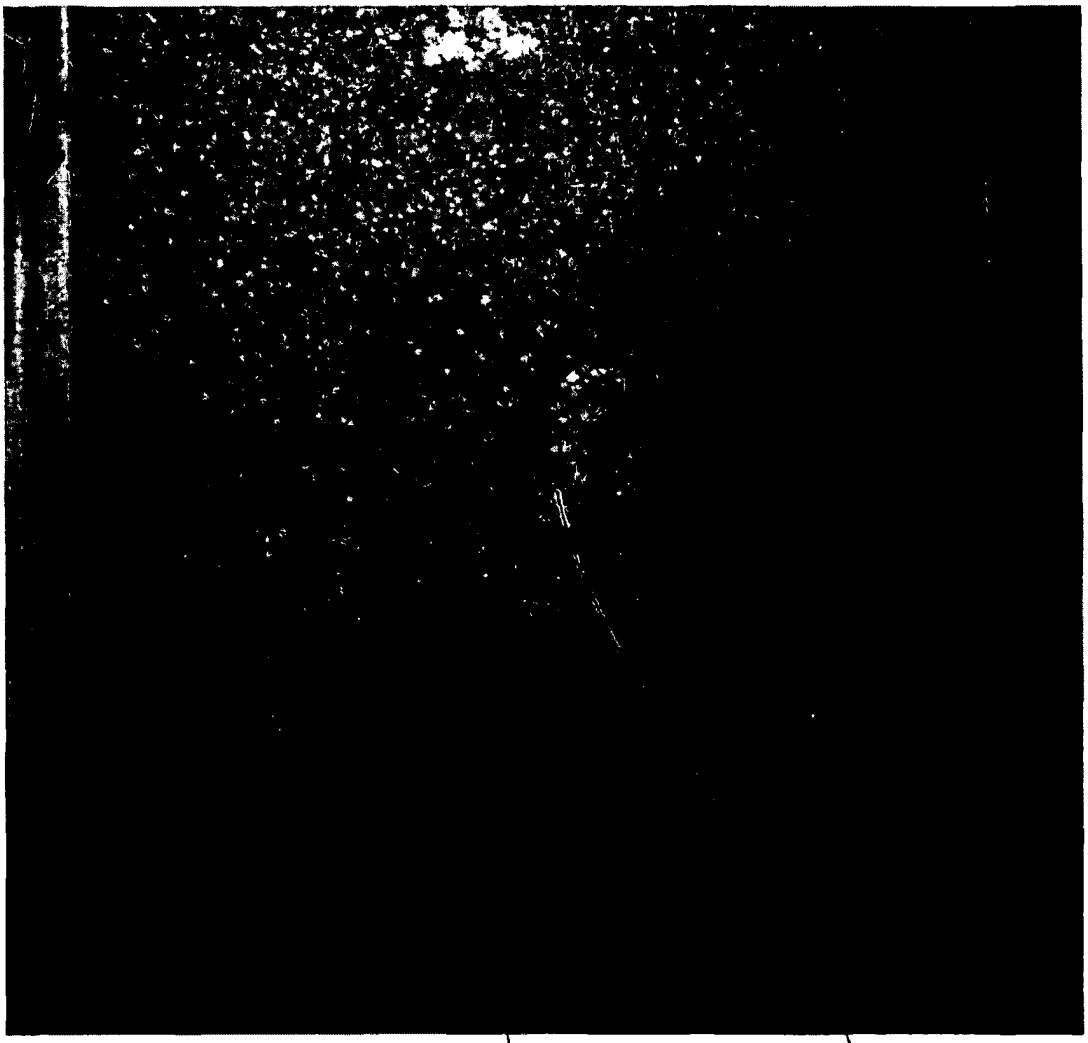


FIG. 12

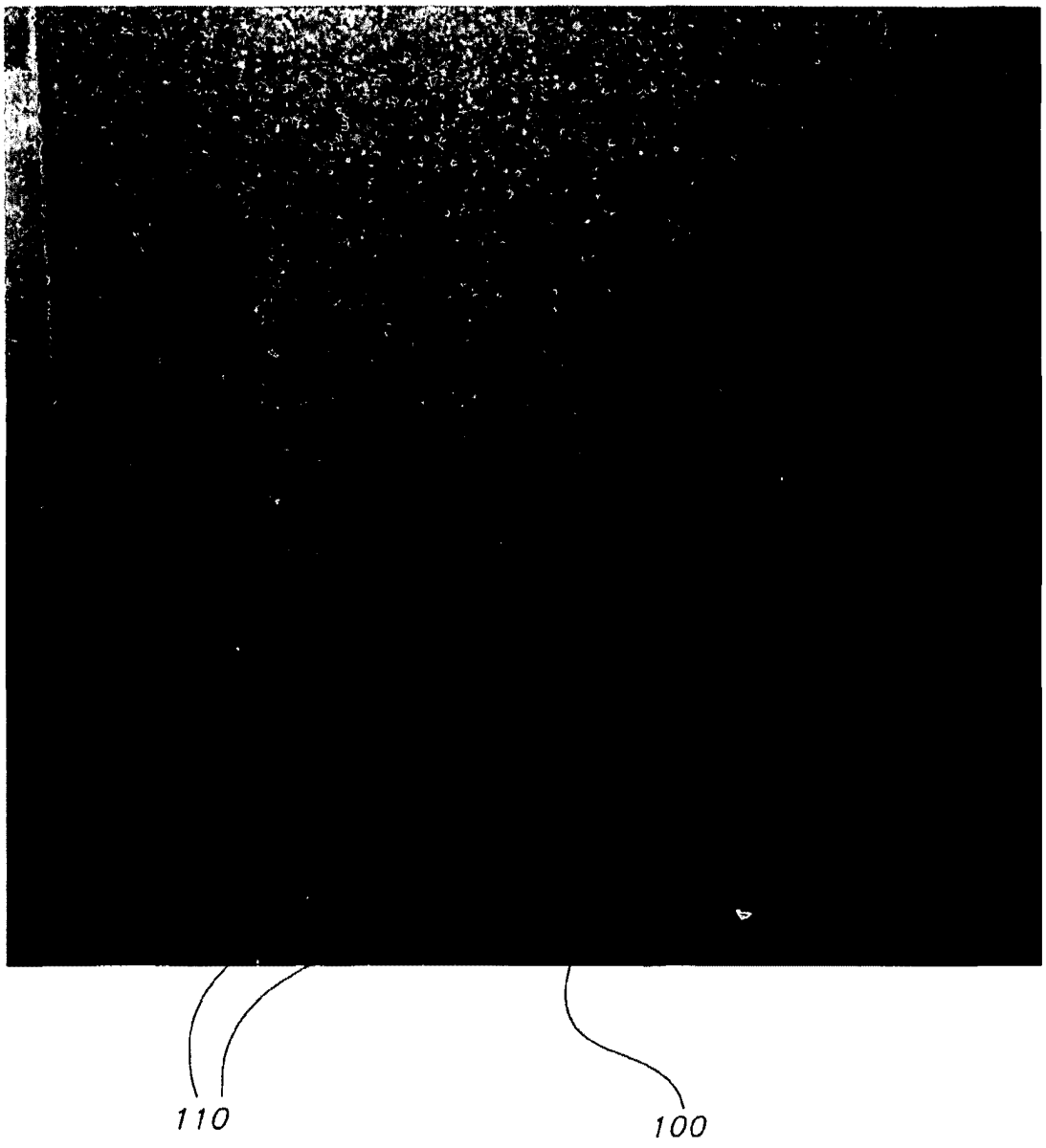


FIG. 13

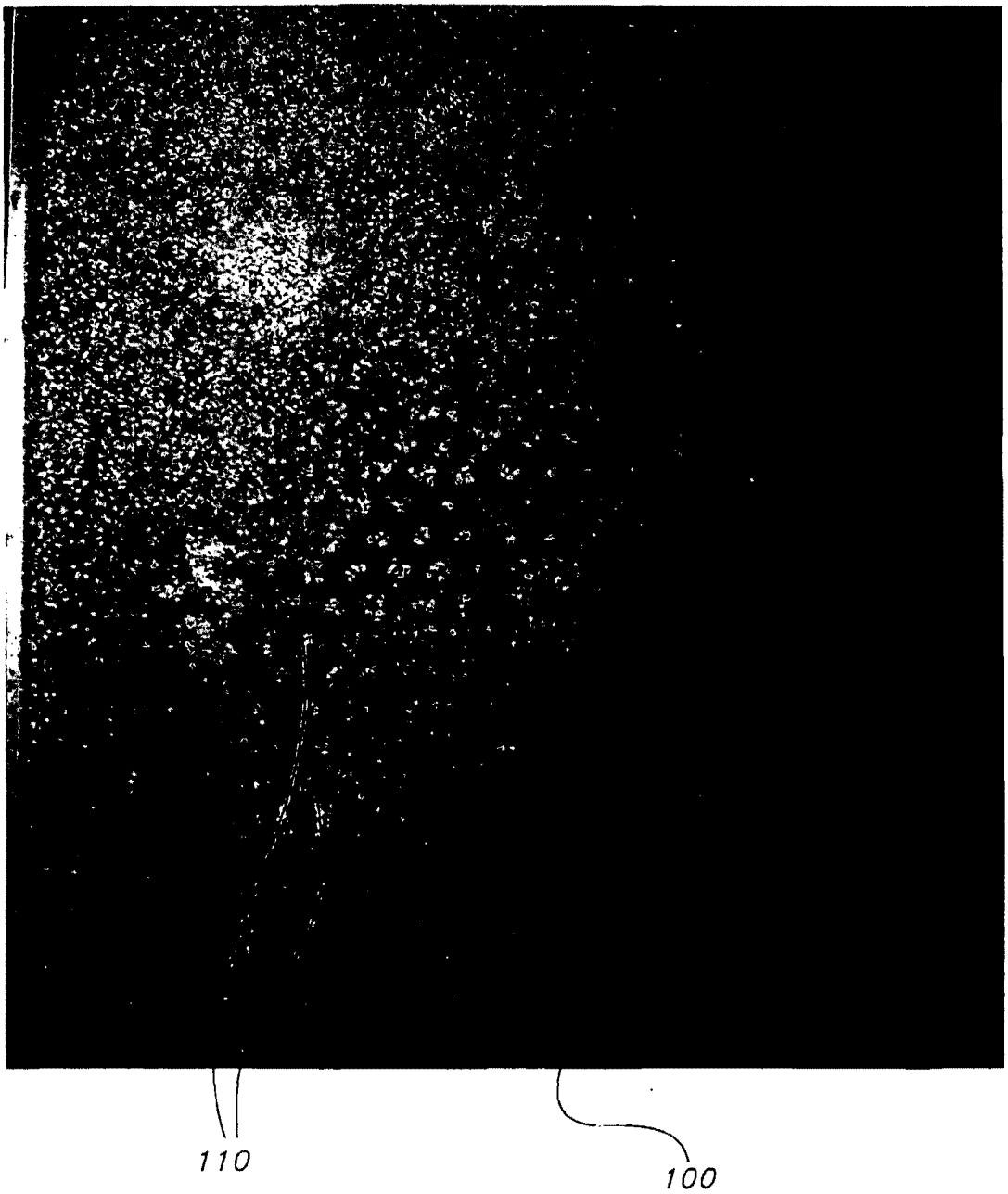


FIG. 14

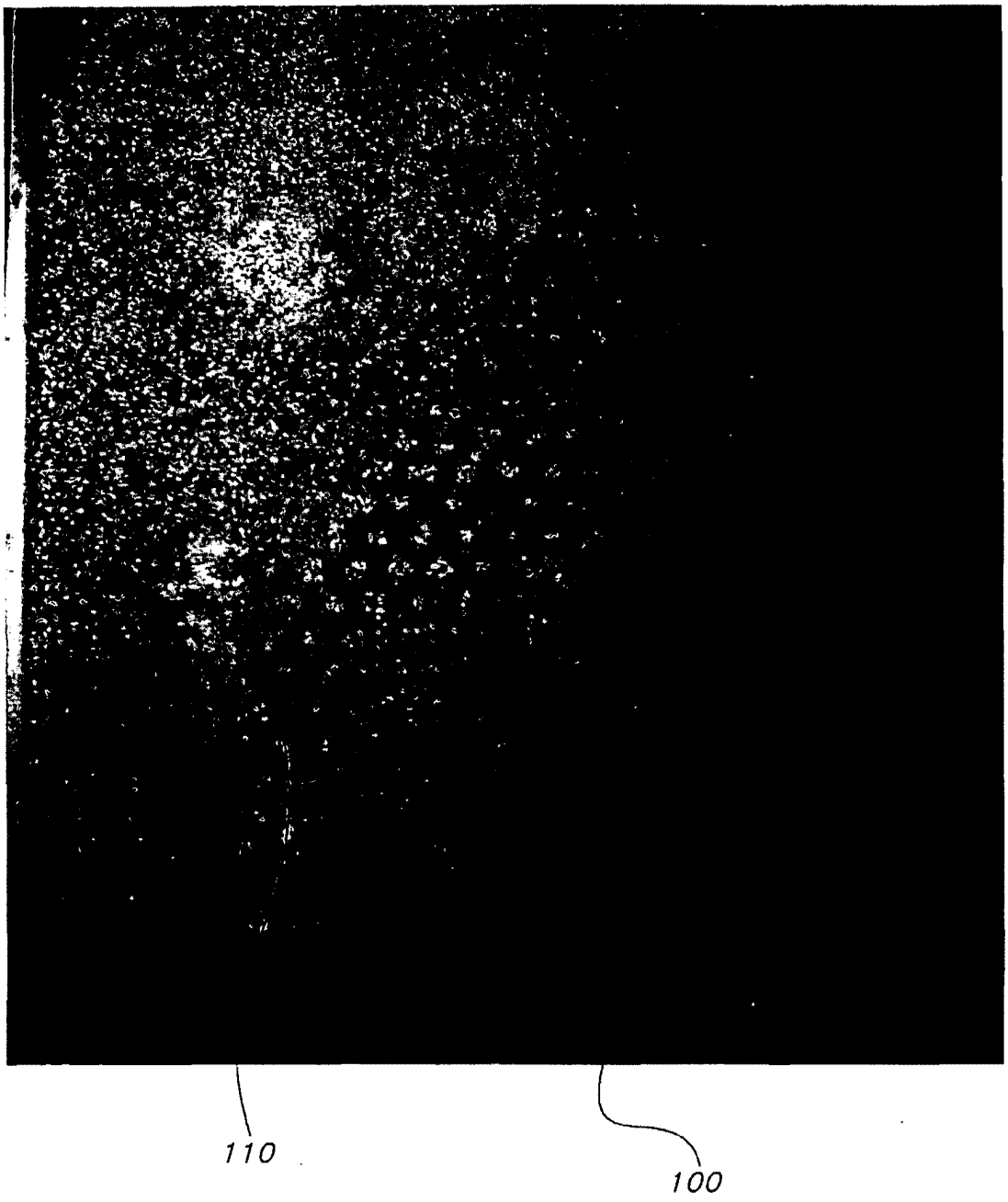


FIG. 15

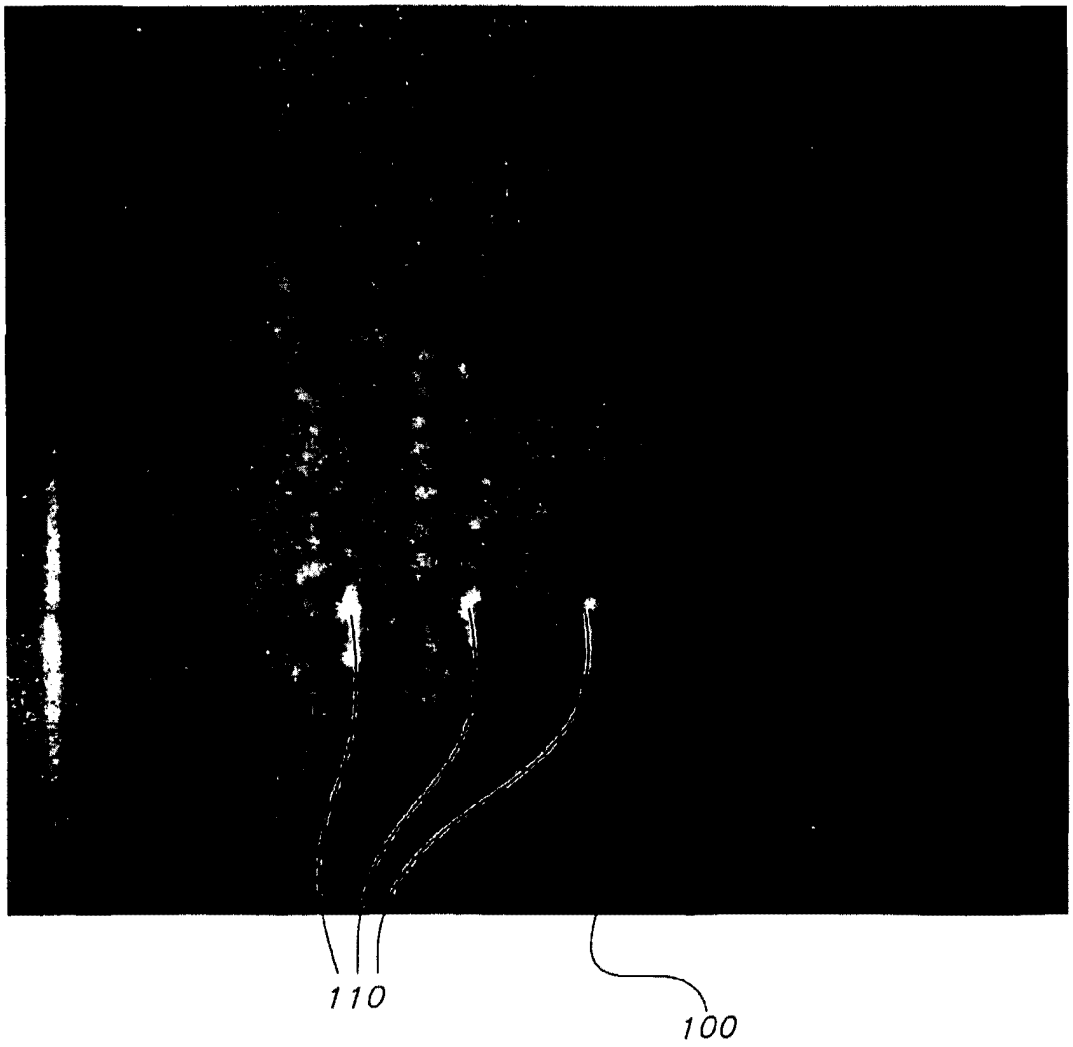


FIG. 16

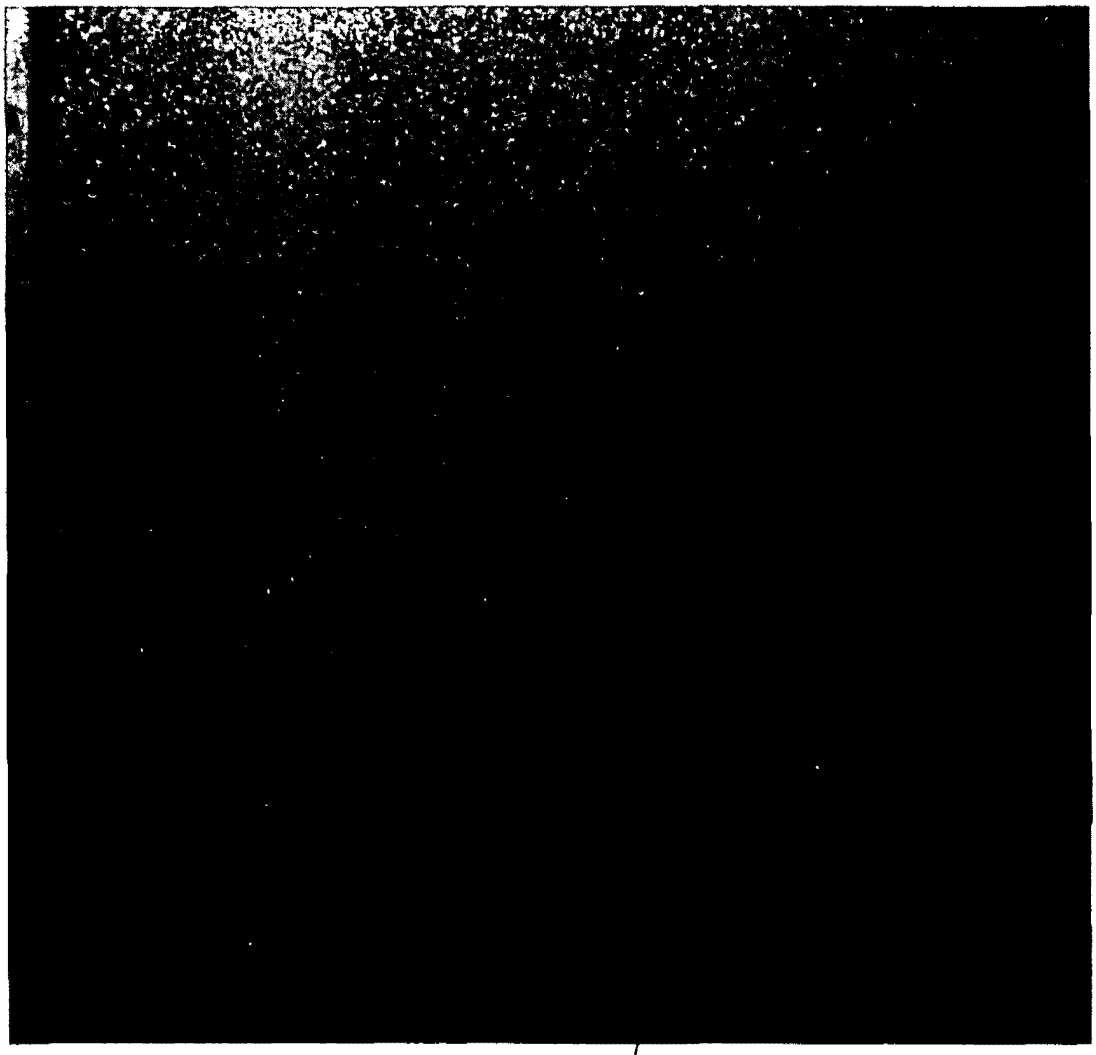


FIG. 17

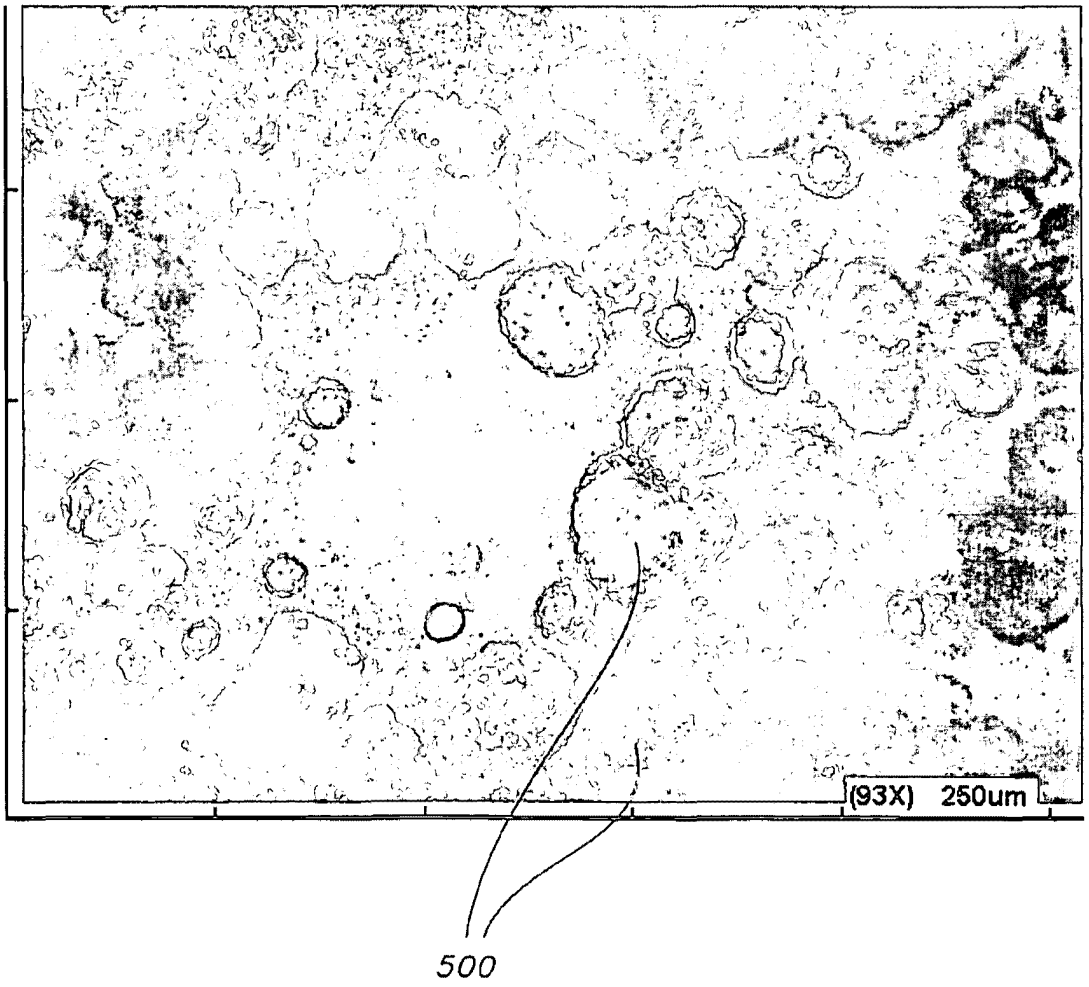


FIG. 18

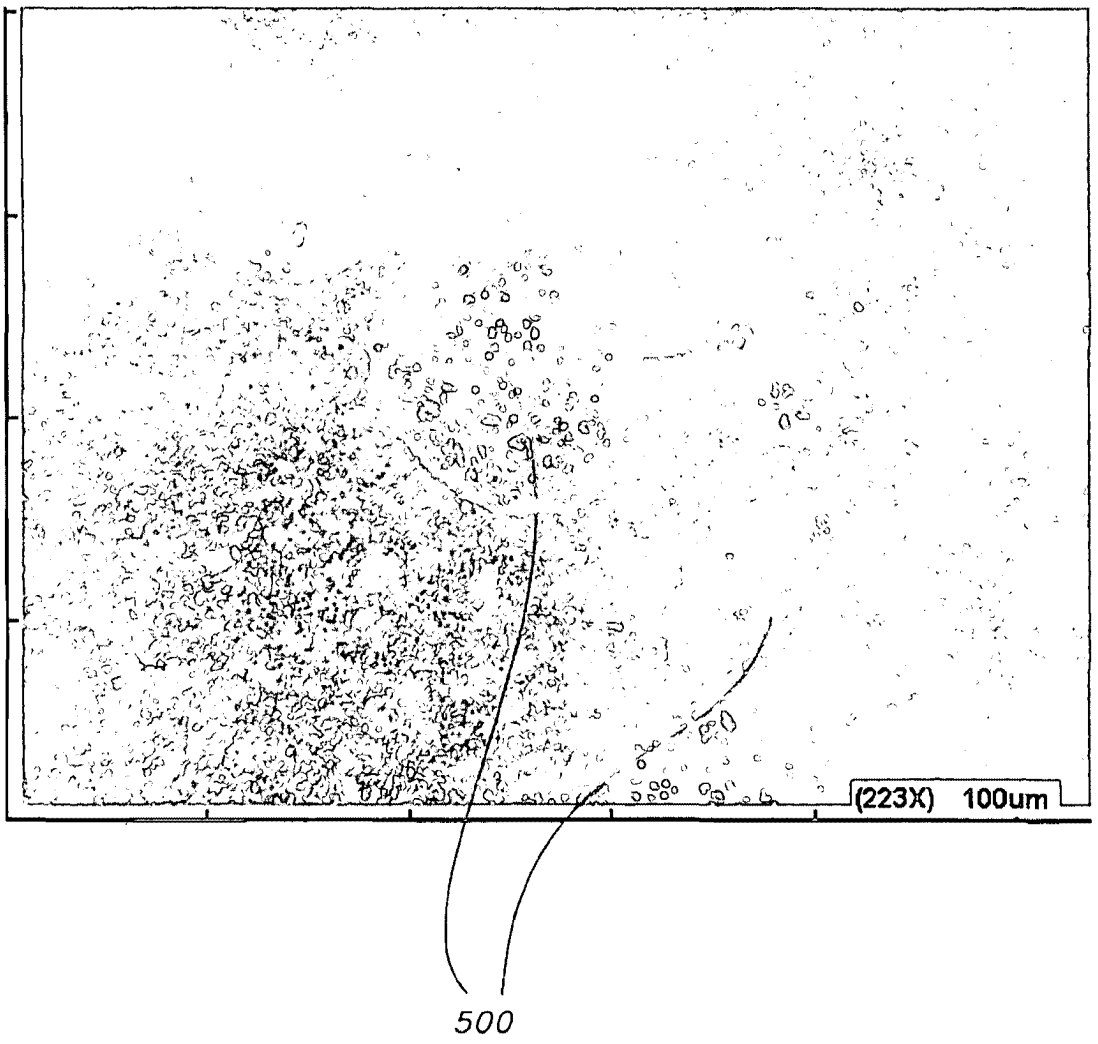


FIG. 19

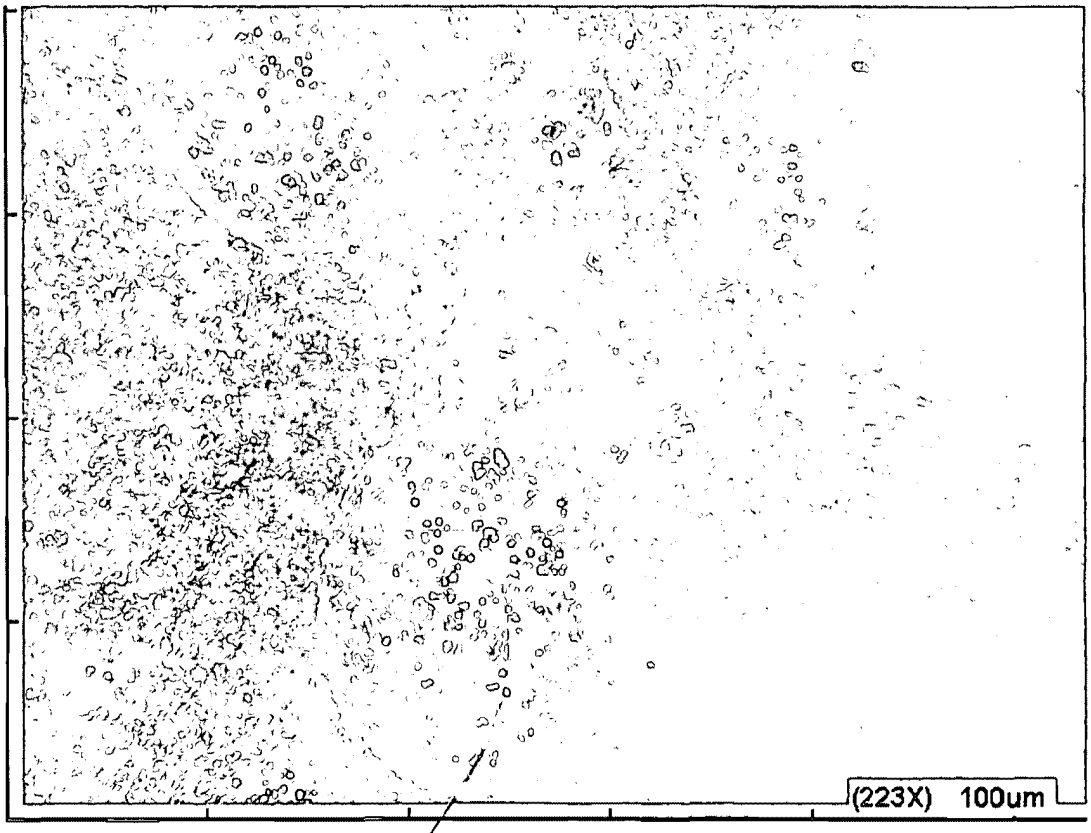


FIG. 20

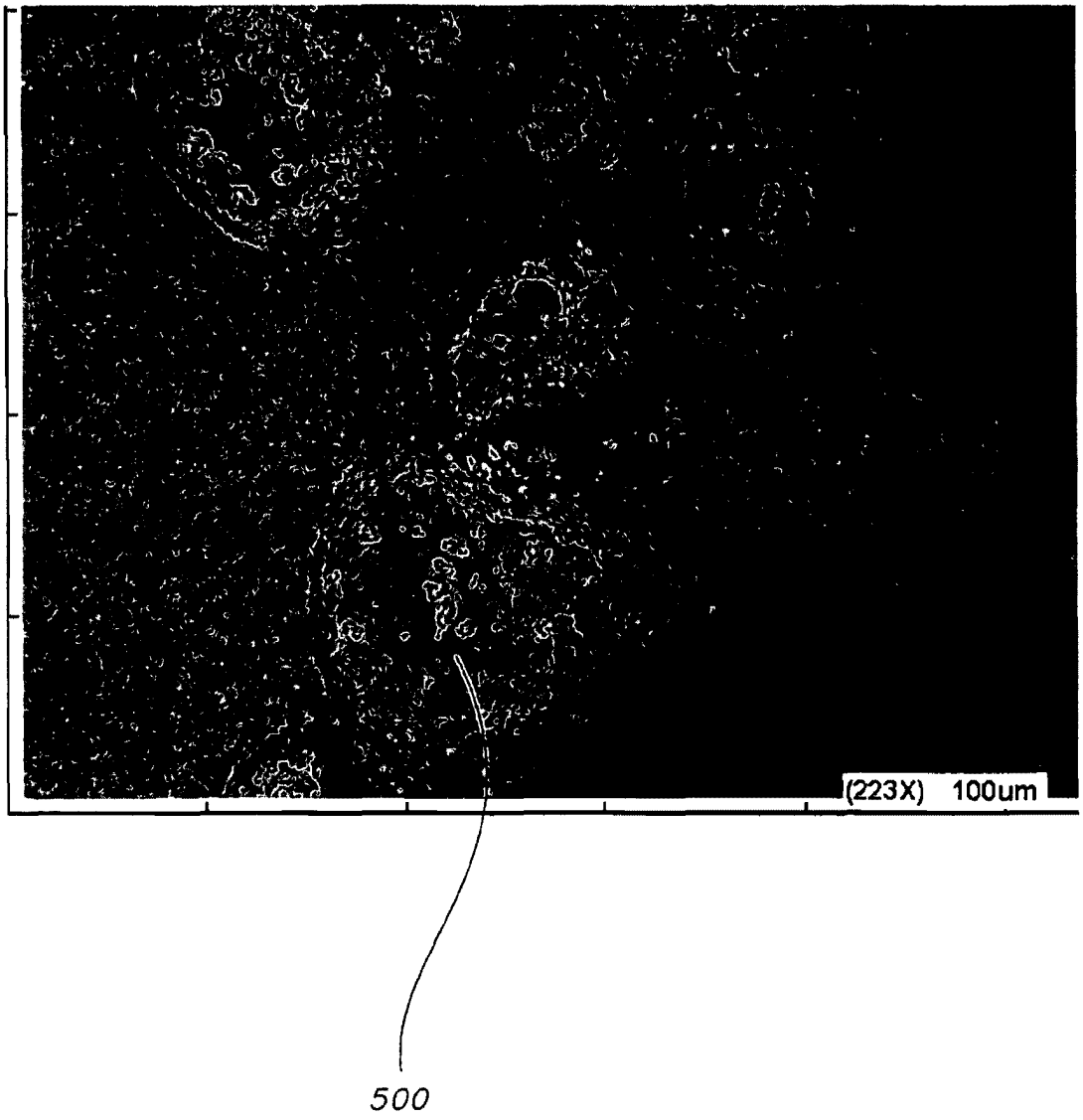


FIG. 21

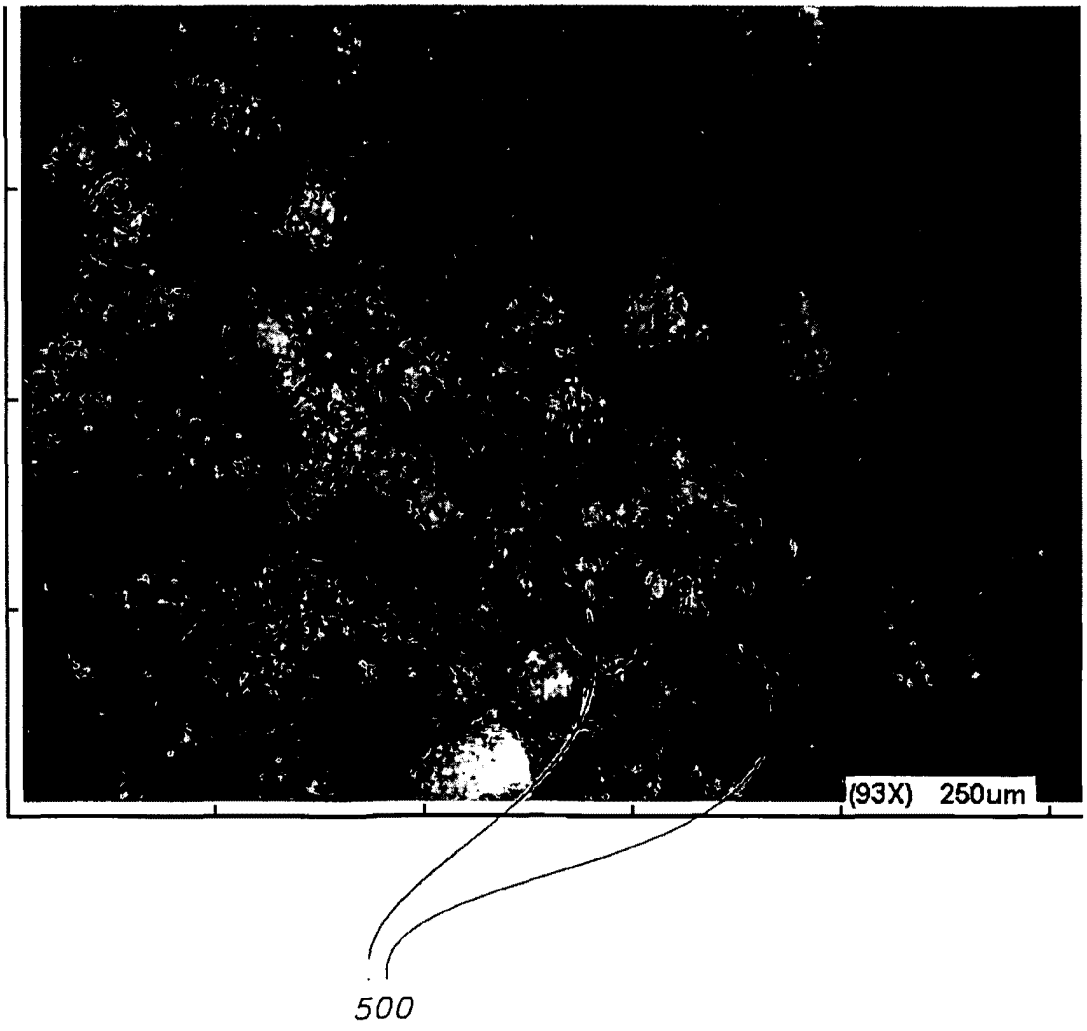


FIG. 22

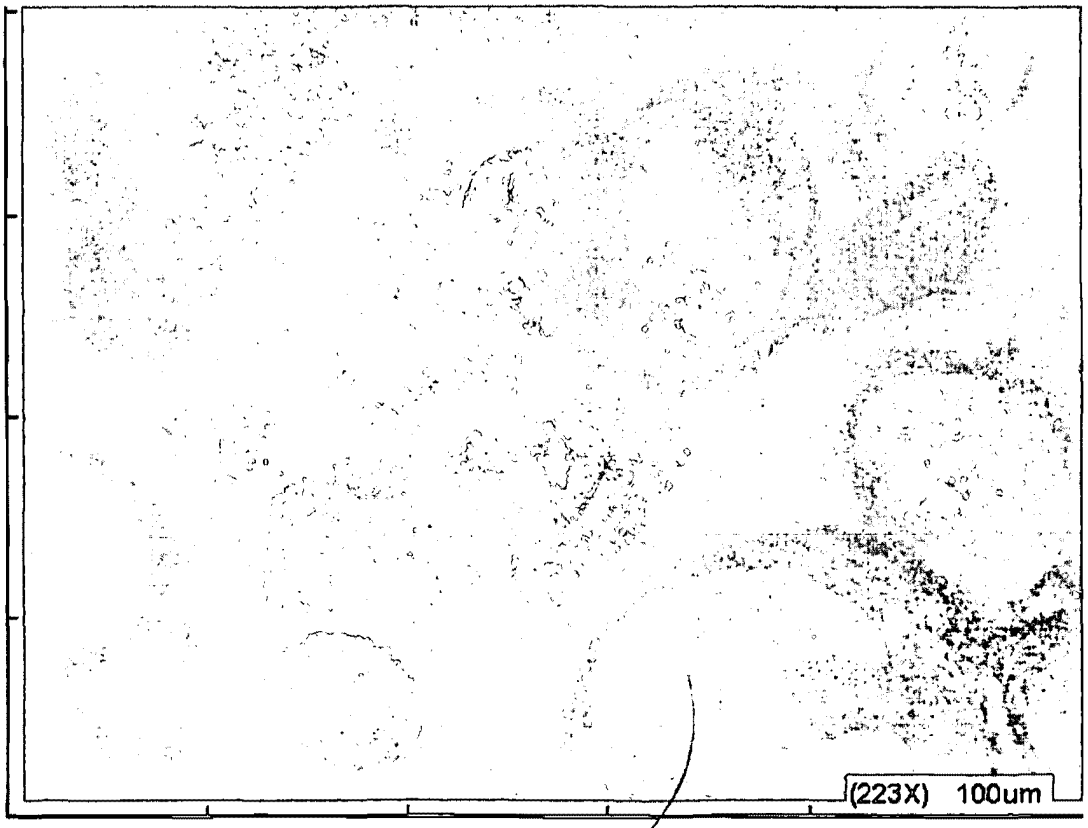


FIG. 23

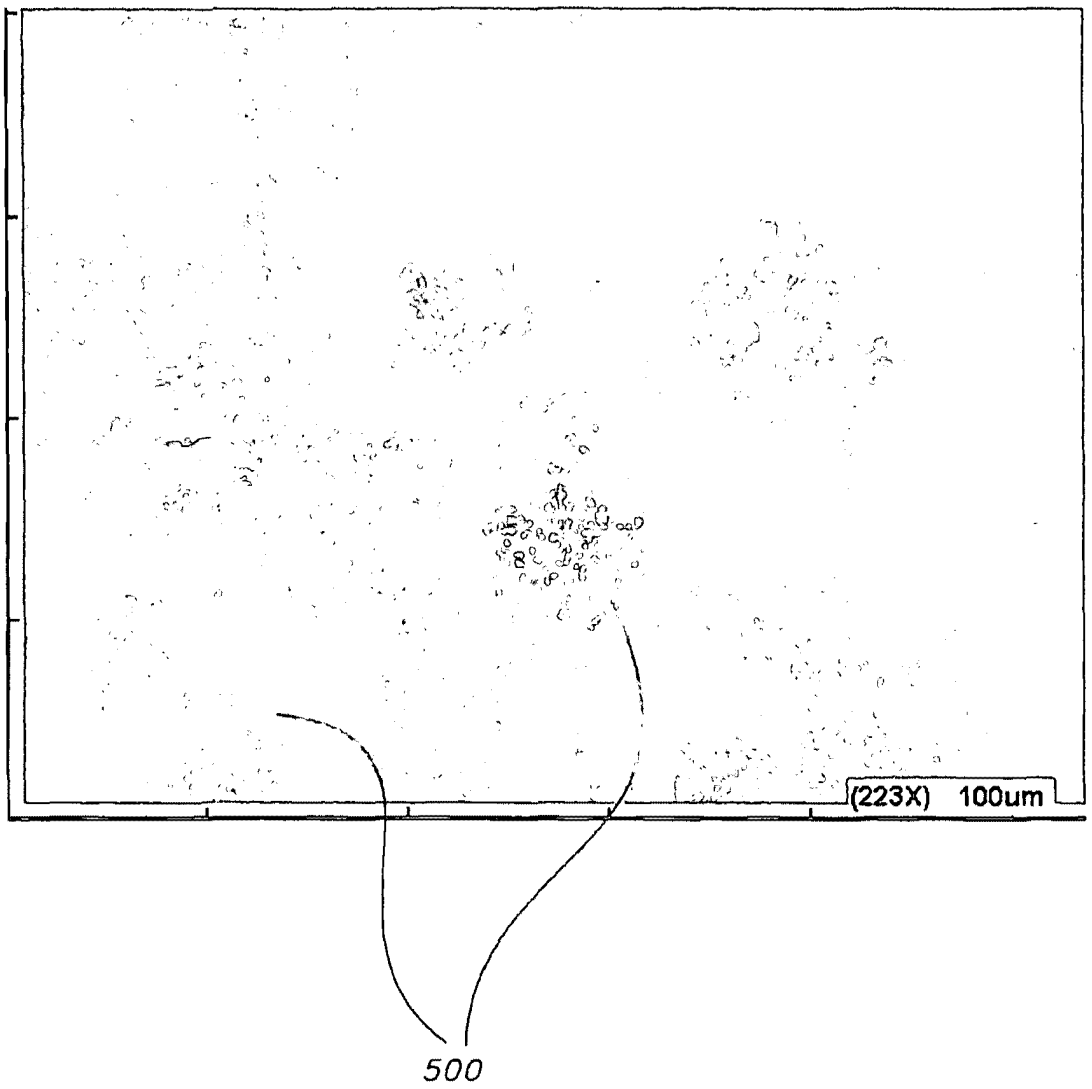


FIG. 24

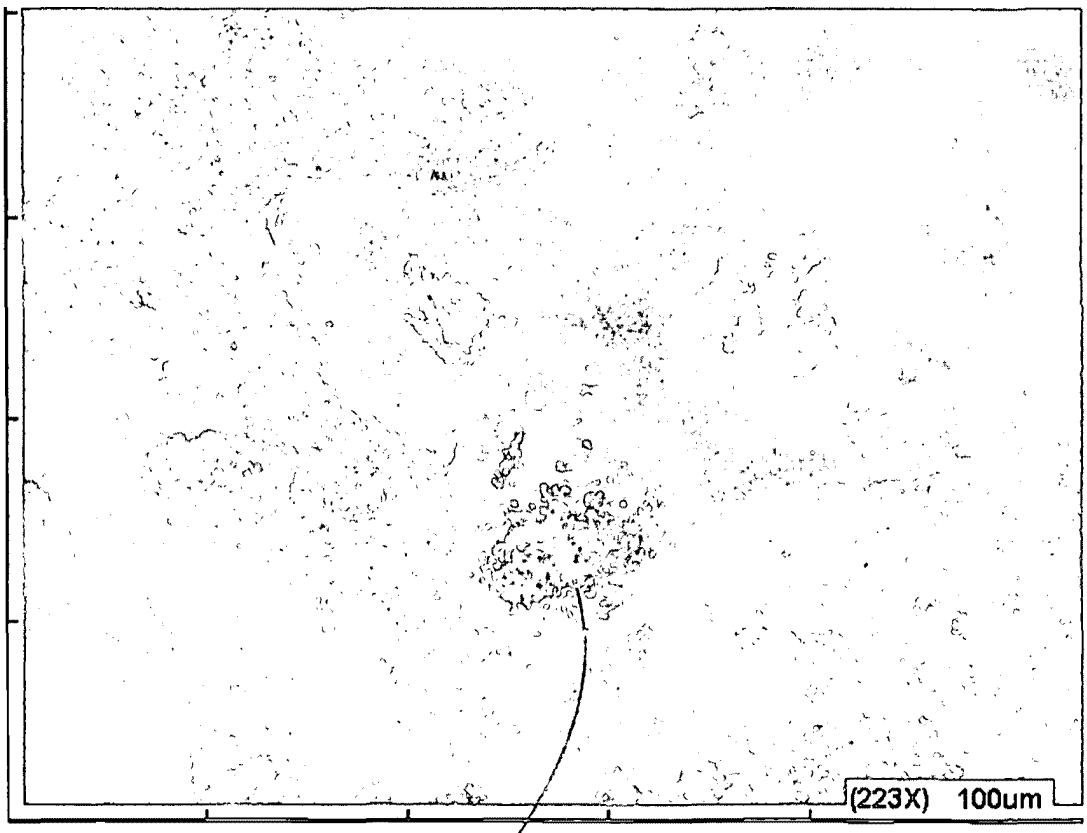


FIG. 25

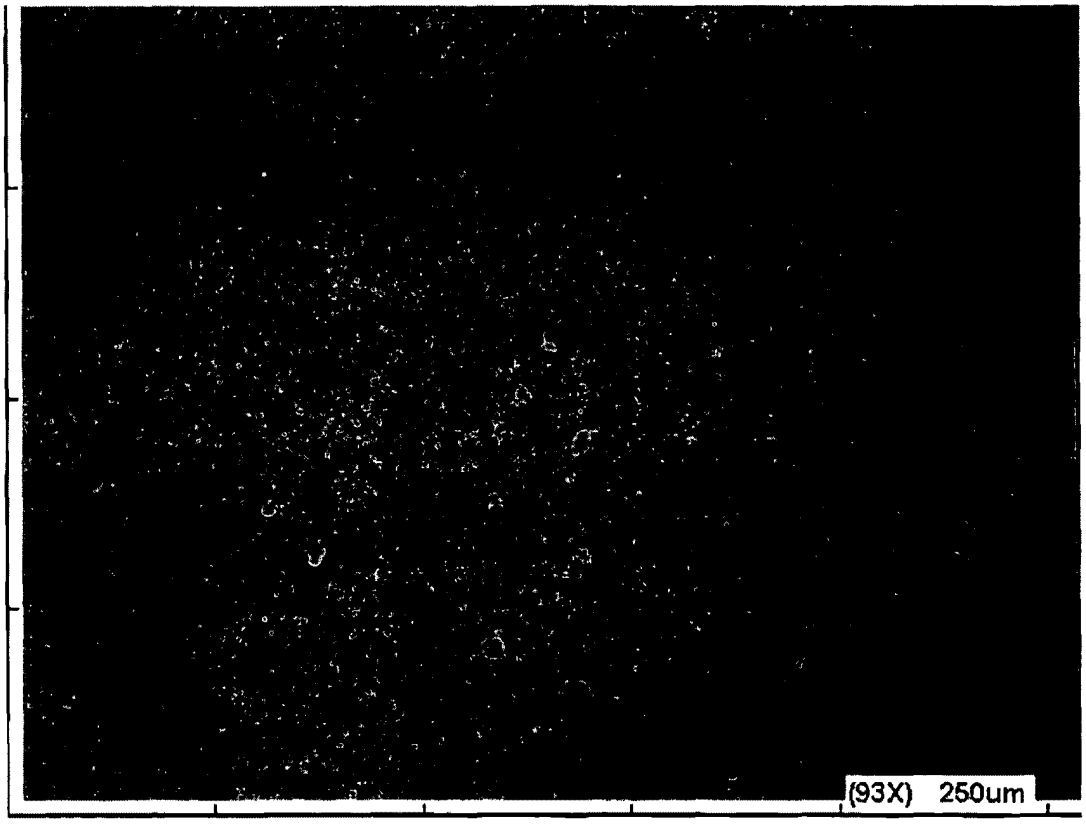


FIG. 26

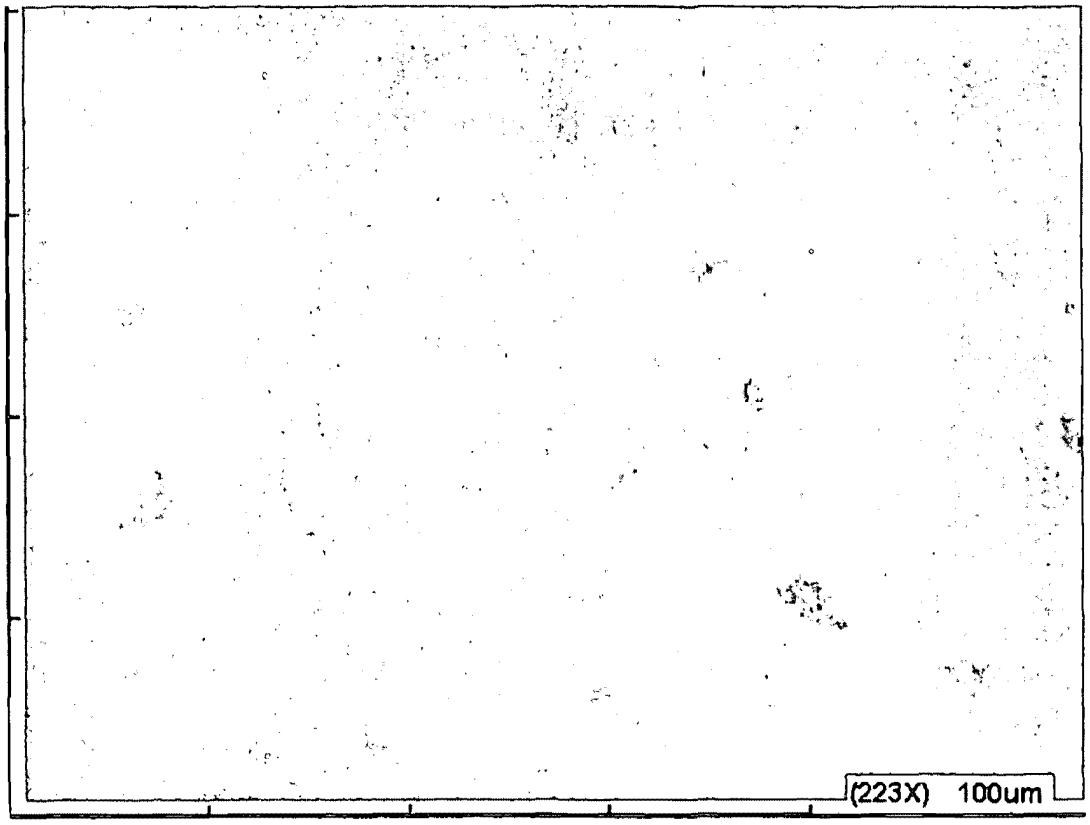


FIG. 27

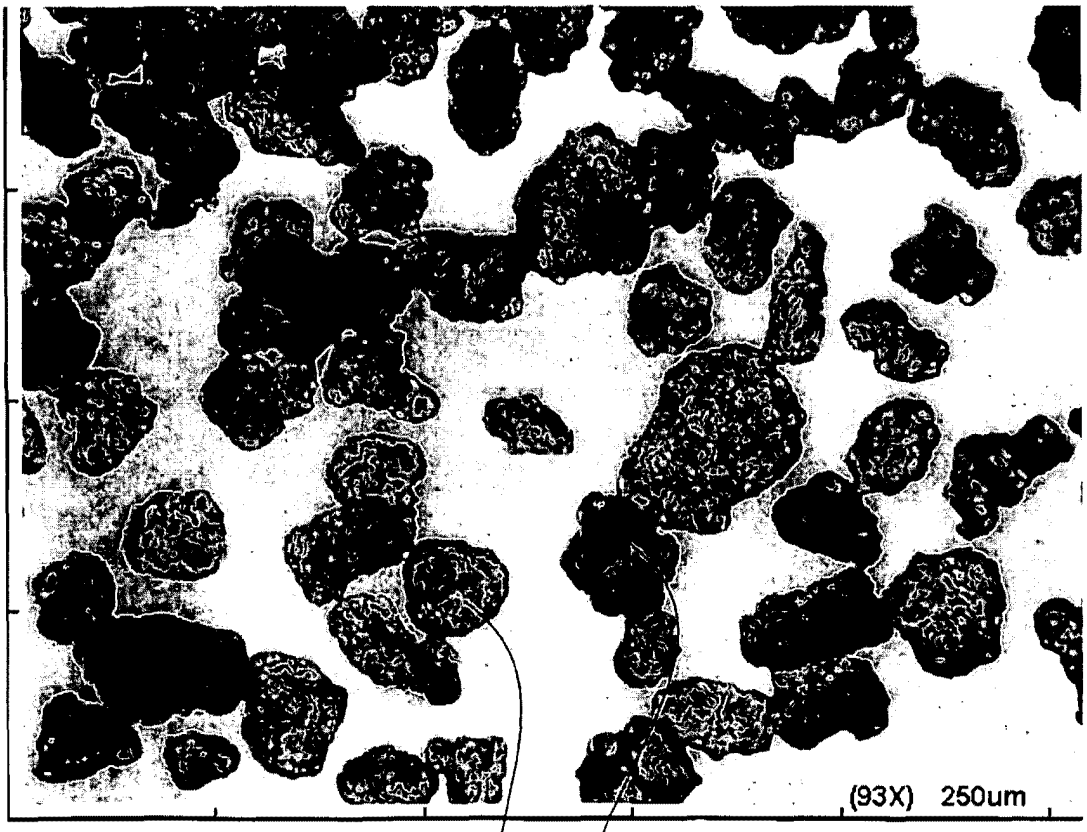


FIG. 28

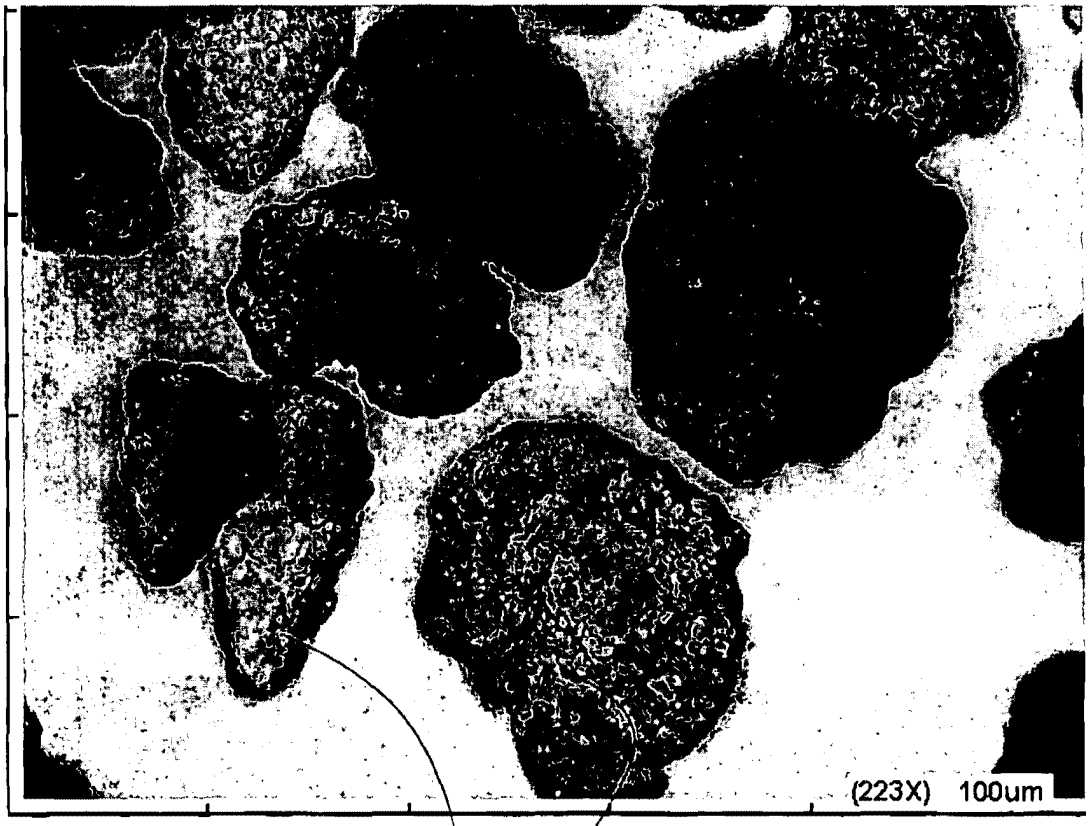


FIG. 29

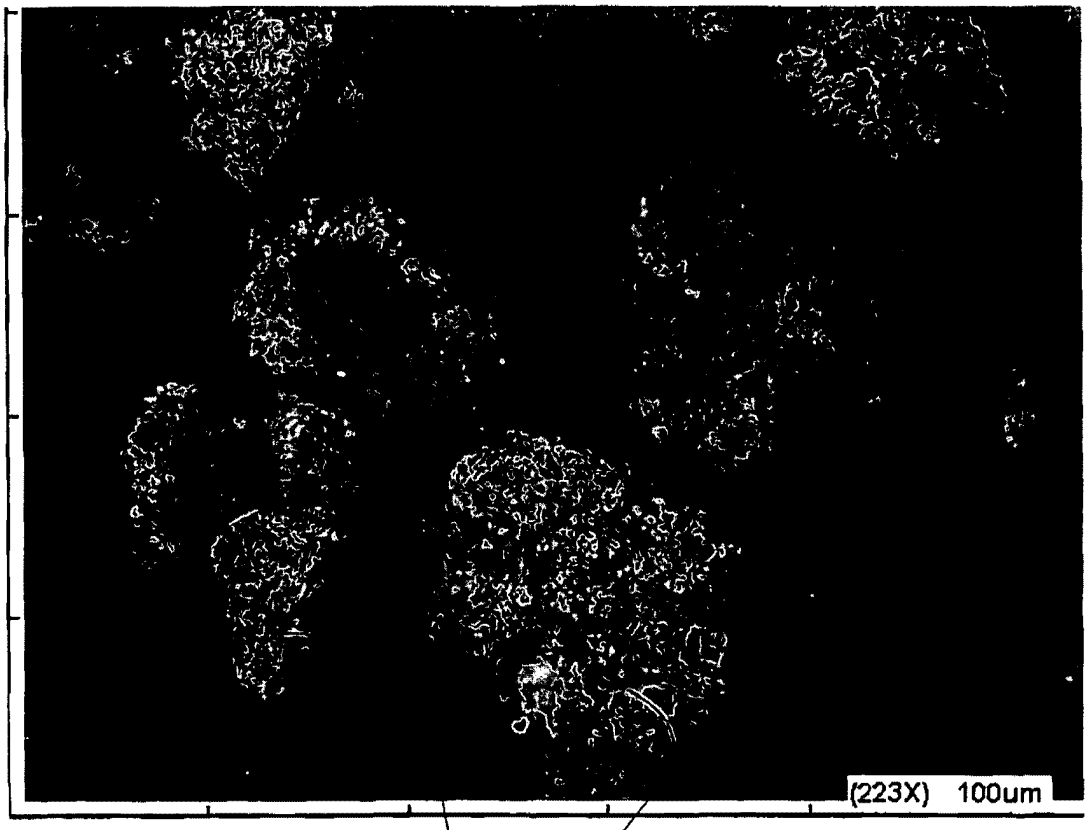


FIG. 30

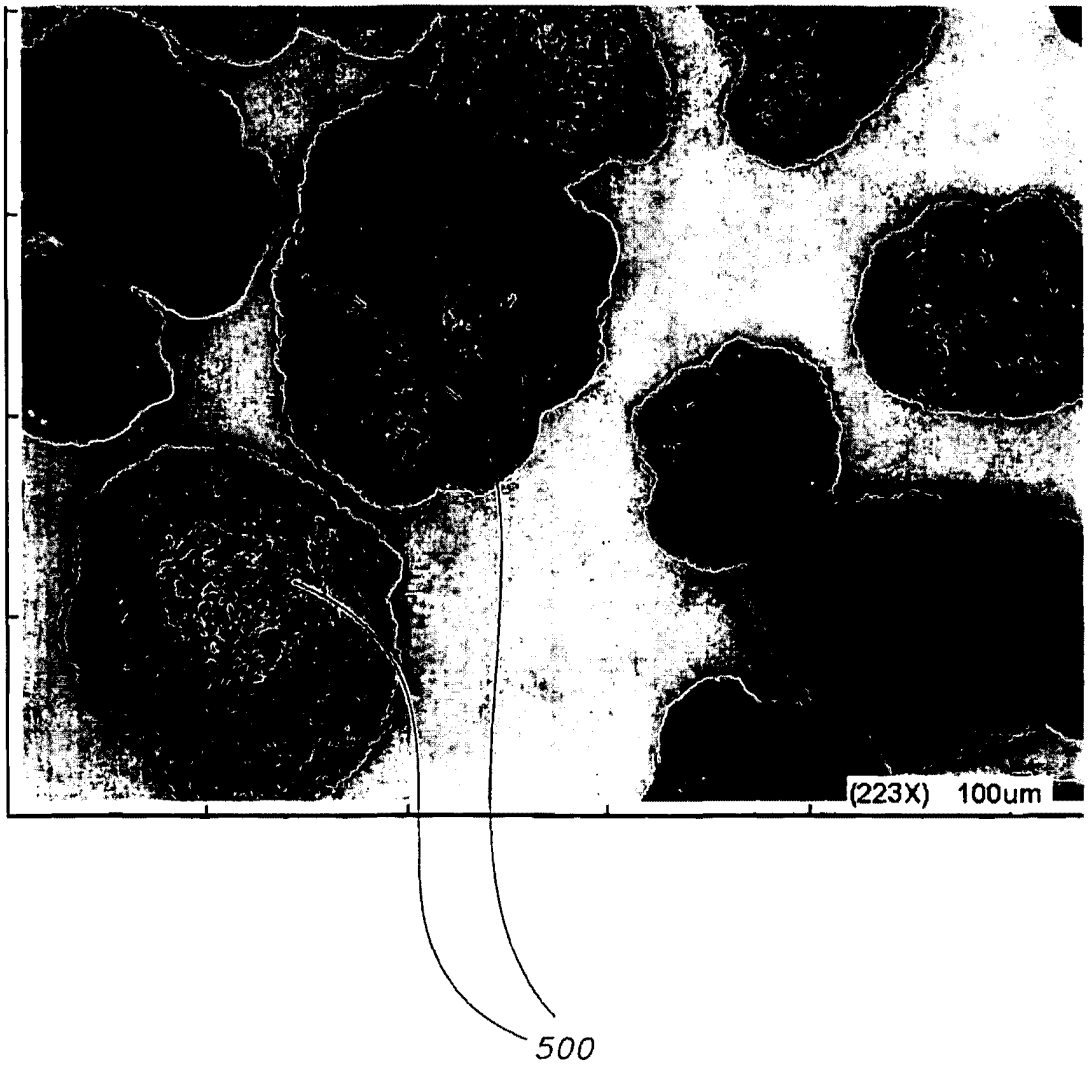
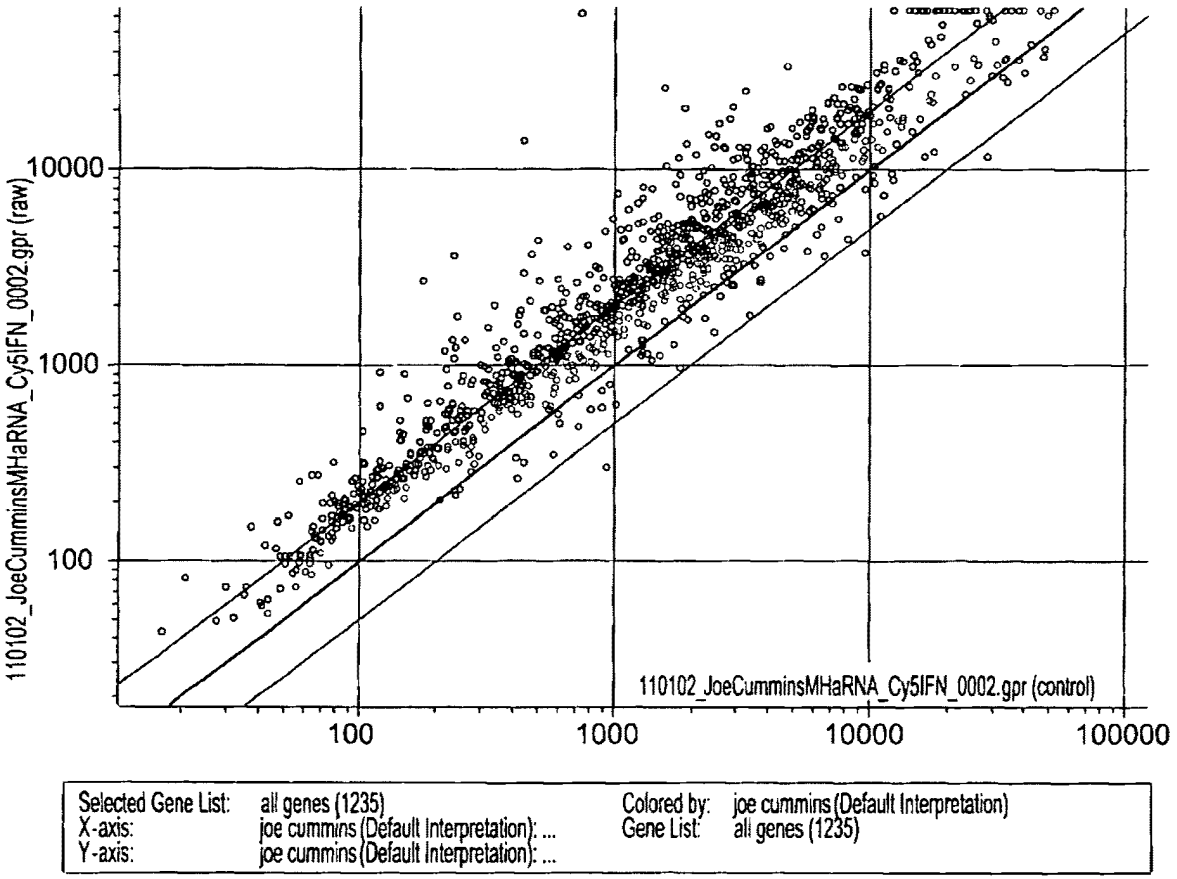
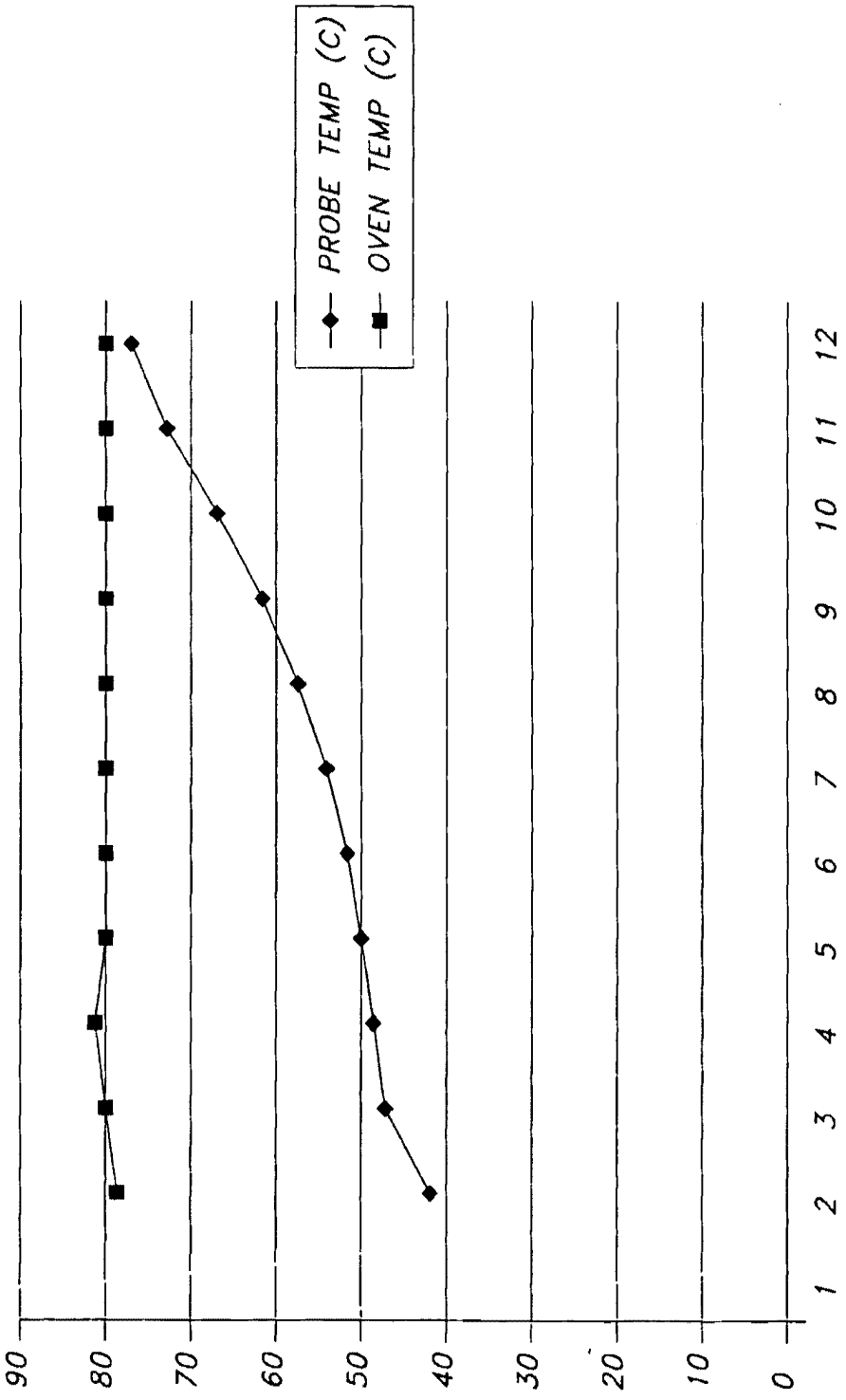


FIG. 31



Normalized to GAPDH, most of the ISGs are induced.

FIG. 32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OVEN TEMP (C)
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80
70
60
50
40
30
20
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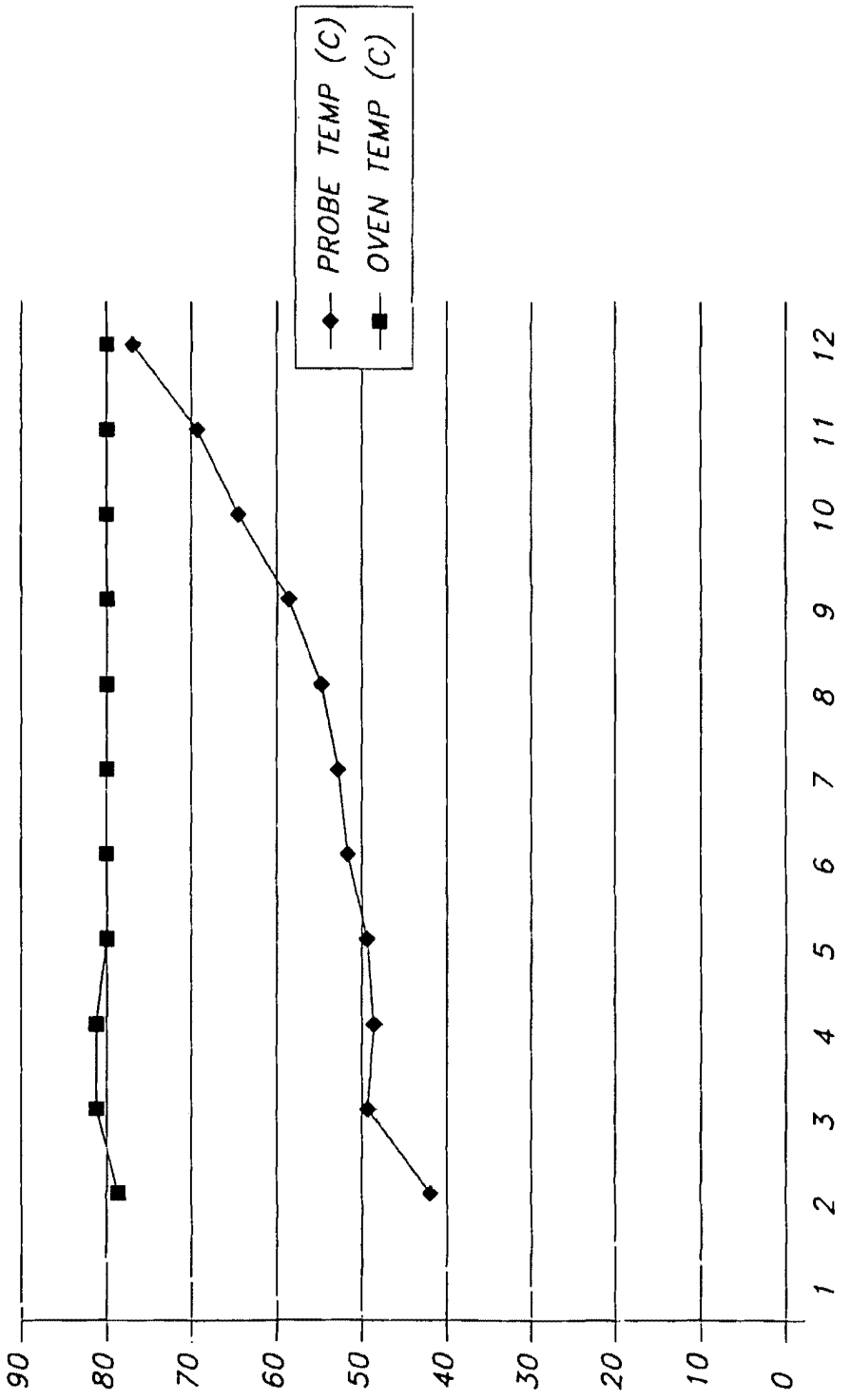
0
1
2
3
4
5
6
7
8
9
10
11
12

FIG. 33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OVEN TEMP (C)
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1
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7
8
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10
11
12

FIG. 34

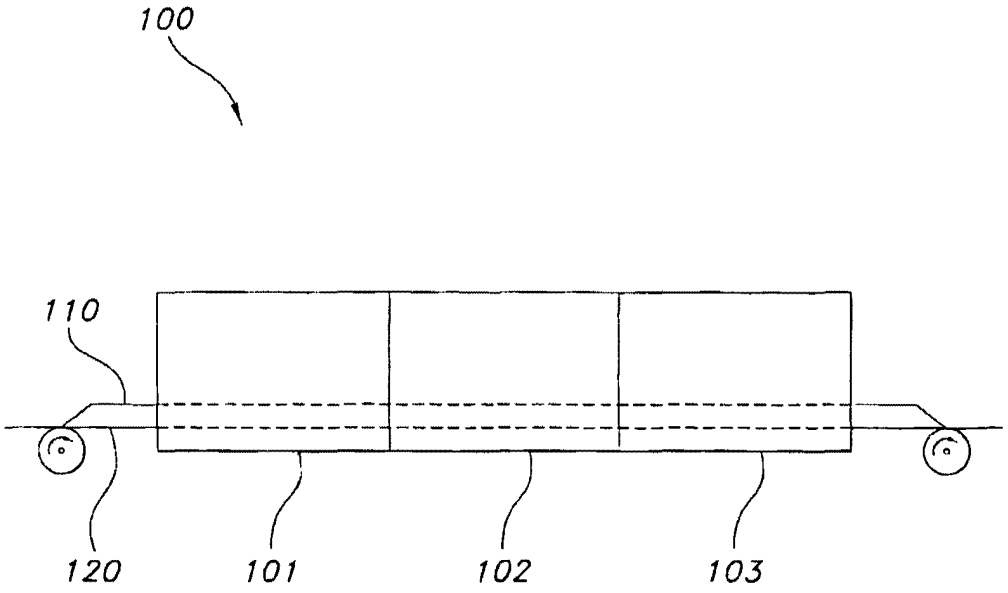

FIG. 35

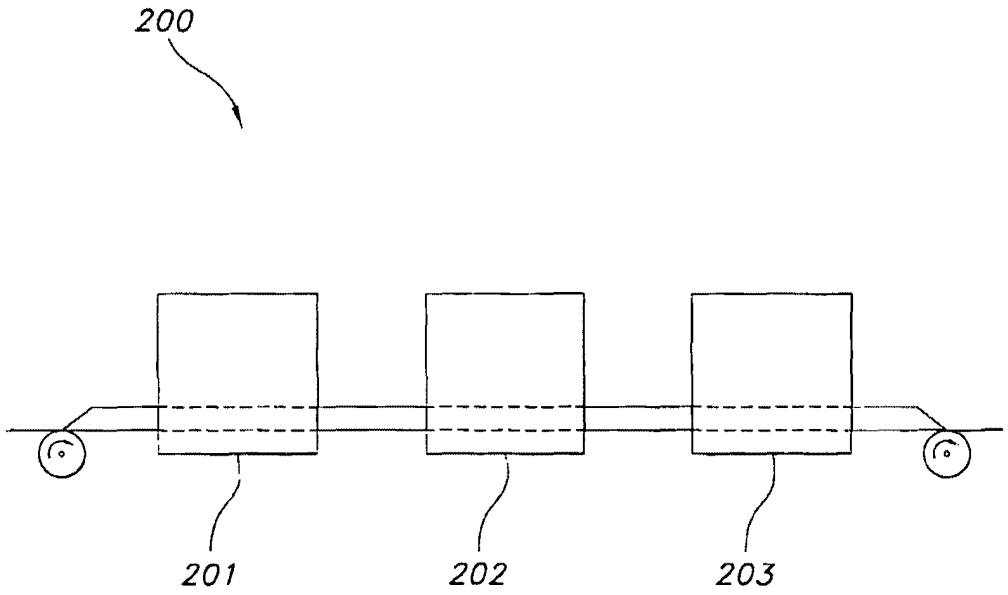

FIG. 36

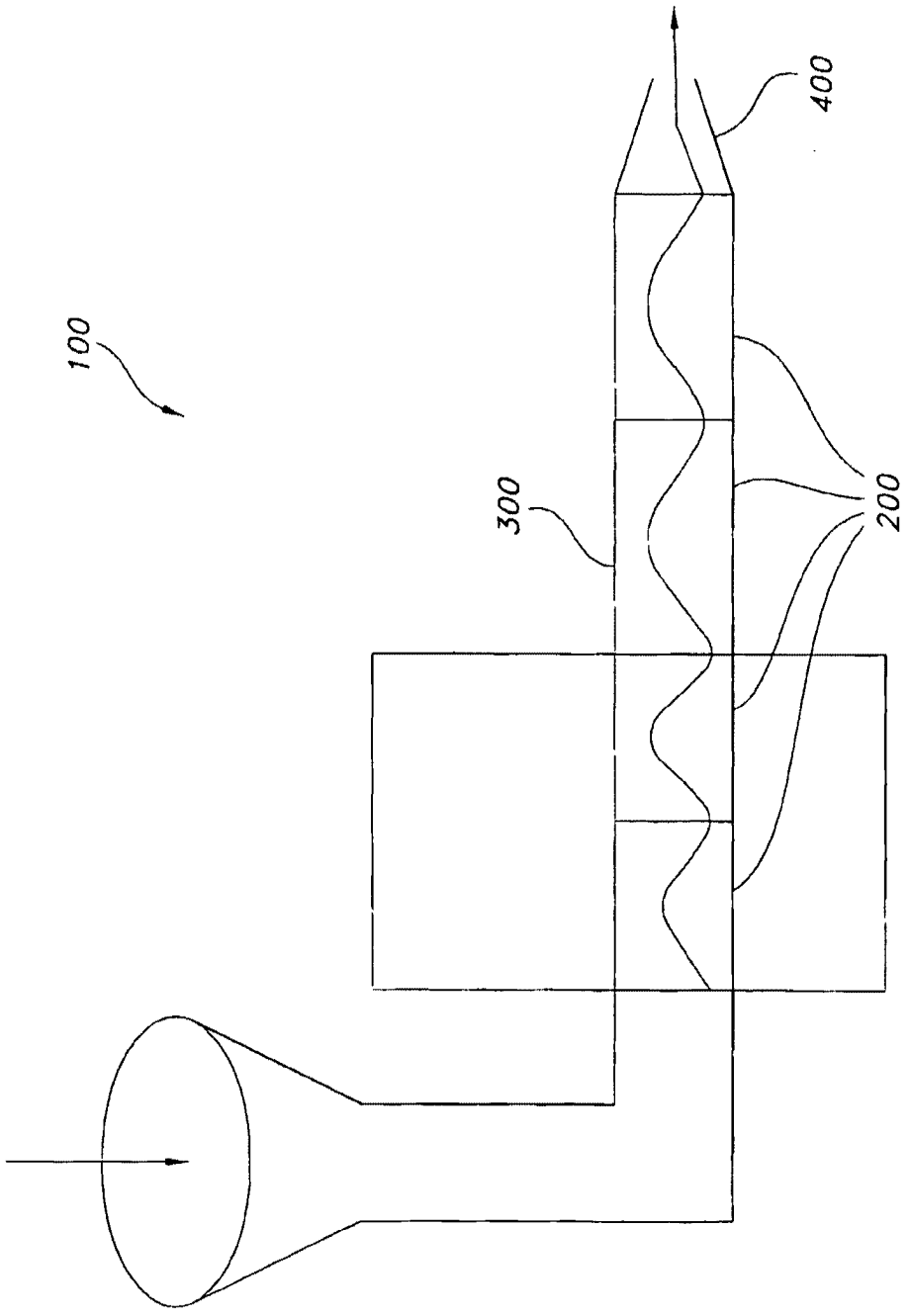

FIG. 37

FIG. 38

Ex.	Polymer Component Reference	% Solids of solution	Viscosity (cp) at 5 rpm	% moisture	Film thickness (mils)	Film strength	Tear Resistance	Tendency to go to roof of mouth	180° bend test	Film molding	Dis-solution (sec)	Rating of dissolution in mouth	Time in oven (min)
EI	PEO/PVP (60/40)	45.0	14800	2.21	3.8	Adequate	Excellent	Low	Passed	No	3	Fast to Moderate	9
EJ	PEO/PVP (40/60)	50.0	6600	2.86	4	Weak	Low to moderate	High	Passed	No	3	Fast	8
EK	PEO/Starch (80/20)	40.0	3440	2.27	4.5	Adequate to good	Excellent	High	Passed	No	3	Fast to Moderate	8
EL	PEO/CMC (80/20)	37.5	121,200	1.96	4.1	Good	Excellent	High	Passed	No	5	Slow	9
EM	PEO/CMC (60/40)	30.0	82,000	4.21	3.45	Weak	Good	High	Passed	No	3	Slow to Moderate	9
EN	PEO/CMC (40/60)	30.0	185,000	3.07	3.5	Adequate	Very low	High	Failed	No	4	Slow	9
EO	PEO/HPC (80/20)	37.5	21,200	1.65	4	Good	Excellent	High	Passed	No	4	Fast	8
EP	PEO/HPC (60/40)	37.5	17,000	2.84	3.8	Adequate	Excellent	High	Passed	No	4	Fast	9
EQ	PEO/HPC (40/60)	42.5	43,400	2.83	4.5	Poor to adequate	Poor to good	High	Passed	No	7	Fast to Moderate	7
ER	PEO/HPC (20/80)	42.5	46,400	2.33	4.4	Adequate to good	Poor	Low	Passed	No	14-15	Slow	9
ES	PEO/HPMC (80/20)	37.5	29,000	2.14	4.4	Adequate	Good	High	Passed	Yes	4	Fast to Moderate	8
ET	PEO/HPMC (60/40)	37.5	47,000	2.37	3.9	Poor to adequate	Slight	High	Passed	Yes	3	Fast to Moderate	9
EU	PEO/HPMC (40/60)	35.0	54,800	3.55	4.5	Adequate to good	Low	Low	Passed	Yes	8	Slow	8
EV	PEO/HPMC (20/80)	35.0	96,600	4.43	4.5	Good	Low	Low	Passed	No	22	Slow	10
EW	PEO/PVA (80/20)	37.5	41,600	2.92	9	Weak	Moderate	High	Passed	No	3	Moderate	10

PATENT

Attorney's Docket No. 1199-26

COMBINED DECLARATION AND POWER OF ATTORNEY

(ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL, DIVISIONAL, CONTINUATION OR CIP)

As a below named inventor, I hereby declare that:

TYPE OF DECLARATION

This declaration is of the following type: *(check one)*

- ☐ Original
- ☐ Supplemental
- ☐ Design
- ☐ National Stage PCT
- ☐ Divisional
- ☐ Continuation
- ☒ Continuation-in-Part (CIP)

INVENTORSHIP IDENTIFICATION

NOTE: If the inventors are each not the inventors of all the claims an explanation of the facts, including the ownership of all the claims at the time the last claimed invention was made, should be submitted.

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the **original**, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

POLYETHYLENE OXIDE-BASED FILMS AND DRUG DELIVERY SYSTEMS MADE THEREFROM

the specification of which: *(complete (a), (b) or (c))*

(a) ☐ is attached hereto.

(b) ☒ was filed on May 28, 2003 as
☒ Serial No. 10/856,176 or
☐ Express Mail No. _____, as Serial No. not yet known
and was amended on _____. *(If applicable)*

(c) ☐ was described and claimed in PCT International Application No. PCT/_____
filed on _____ and as amended under PCT Article 19 on _____. *(If any)*

ACKNOWLEDGMENT OF REVIEW OF PAPERS AND DUTY OF CANDOR

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above, and that the filing of said specification, if heretofore filed, was authorized by me.

I acknowledge the duty to disclose information which is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

CLAIM OF PRIORITY OF EARLIER FOREIGN APPLICATION(S) UNDER 35 U.S.C. §119(a)-(d)

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

(List prior foreign/PCT application(s) filed within 12 months (6 months for design) prior to this U.S. application.)

NOTE: Where item (c) is entered above and the International Application which designated the U.S. claimed priority check item (e), enter the details below and make the priority claim.

COUNTRY (orPCT)	APPLICATION NO.	DATE OF FILING *(Day/Month/Year)*	PRIORITY CLAIMED UNDER 35 USC §119
			☐ YES ☐ NO
			☐ YES ☐ NO

CLAIM FOR BENEFIT OF PRIOR U.S. PROVISIONAL APPLICATION(S) UNDER 35 U.S.C. §119(e)

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

(List prior U.S. provisional applications.)

PROVISIONAL APPLICATION NO.	FILING DATE *(Day/Month/Year)*
60/473,902	28/05/03

CLAIM FOR BENEFIT OF EARLIER U.S./PCT APPLICATION(S) UNDER 35 U.S.C. 120

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in such prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application(s) and the national or PCT international filing date of this application:

(List prior U.S. applications or PCT international applications designating the U.S. for benefit under 35 U.S.C. §120.)

U.S. APPLICATIONS		STATUS *(Check One)*		
U.S. SERIAL NO.	U.S. FILING DATE *(Day/Month/Year)*	Patented	Pending	Abandoned
10 / 074,272	February 14, 2002	☐	☐	☐
60 / 328,868	October 21, 2001	☐	☐	☐
60/386,937	June 7, 2002	☐	☐	☐
60/414,276	September 27, 2002	☐	☐	☐
60/371,940	April 11, 2002	☐	☐	☐
60/443,741	January 30, 2003	☐	☐	☐
10/768,809	January 30, 2004	☐	☐	☐

PCT APPLICATIONS DESIGNATING THE U.S.			STATUS *(Check One)*		
PCT APPLN. NO.	PCT FILING DATE *(Day/Month/Year)*	U.S. SERIAL NOS ASSIGNED (If any)	Patented	Pending	Abandoned
PCT/US02/32575	October 11, 2002		☐	☐	☐
PCT/US02/32594	October 11, 2002		☐	☐	☐
PCT/US02/32542	October 11, 2002		☐	☐	☐

35 USC 119 PRIORITY CLAIM, IF ANY, FOR ABOVE LISTED U.S./PCT APPLICATIONS

PRIORITY APPLICATION NO.	PRIORITY COUNTRY	FILING DATE *(Day/Month/Year)*	ISSUE DATE *(Day/Month/Year)*

POWER OF ATTORNEY

As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) at Customer Number 23869 to prosecute this application and transact all business in the Patent and Trademark Office in connection therewith.

PLEASE SEND CORRESPONDENCE TO:	PLEASE DIRECT TELEPHONE CALLS TO:
Daniel A. Scola, Esq. HOFFMANN & BARON, LLP 6900 Jericho Turnpike Syosset, NY 11791	Jamie M. Lamann (973) 331-1700

DECLARATION

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

SIGNATURE(S)

Full Name of First Joint Inventor:	Robert K. Yang
Country of Citizenship:	US
Residence Address:	138-10 Franklin Avenue, Apt. #2C, Flushing, New York 11355
Post Office Address:	Same as above
Date: 10/26/2004	Inventor's signature Robert K. Yang
Full Name of Second Inventor:	Richard C. Fuisz
Country of Citizenship:	US
Residence Address:	1287 Ballantrae Farm Drive, McLean, Virginia 22101
Post Office Address:	Same as above
Date: _____	Inventor's signature _____
Full Name of Third Joint Inventor:	Gary L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, Tennessee 37660
Post Office Address:	Same as above
Date: _____	Inventor's signature _____

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Date: _____	Inventor's signature _____
Full Name of Second Inventor:	Richard C. Fuisz
Country of Citizenship:	US
Residence Address:	~~1287 Ballantrae Farm Drive, McLean, Virginia 22101~~ 1127 Caryleg Lane McLean, VA 22101
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
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Country of Citizenship:	US
Residence Address:	1287 Ballantrae Farm Drive, McLean, Virginia 22101
Post Office Address:	**Same as above**
Date: _____	Inventor's signature _____
Full Name of Third Joint Inventor:	Gary L. Myers
Country of Citizenship:	US
Residence Address:	908 Colfax Avenue, Kingsport, Tennessee 37660
Post Office Address:	**Same as above**
Date: 10-28-04	Inventor's signature 

Full Name of Fourth Inventor:	Joseph M. Fuisz
Country of Citizenship:	US
Residence Address:	~~6708 Cricket Place~~, McLean, Virginia ~~22101~~ 1200 23rd St, NW, Apt 905, Washington DC 20037
Post Office Address:	**Same as above**
Date: _____	Inventor's signature

NOTE: All above spaces identifying inventors must be completed or deleted before any inventor executes this application

PTO/SB/06 (12-04)
Approved for use through 7/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Filing Date: **04/22/08**

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PATENT APPLICATION FEE DETERMINATION RECORD

Substitute for Form PTO-875

Application or Docket Number: 12/107,389

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	75		N/A	
SEARCH FEE (37 CFR 1.16(k), (i), or (m))	N/A	N/A	N/A	255		N/A	
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A	105		N/A	
TOTAL CLAIMS (37 CFR 1.16(i))	18 minus 20 =	0	X$ 25	0	OR	X$50	
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2 minus 3 =	* 0	X$100	0		X$210	
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						
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))			185			370	
			TOTAL	435		TOTAL	0

* If the difference in column 1 is less than zero, enter "0" in column 2.

APPLICATION AS AMENDED – PART II

		(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 ($)	OTHER THAN SMALL ENTITY ADDITIONAL FEE ($)
AMENDMENT A	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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T FEE	

		(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA	RATE ($)	ADDITIONAL FEE ($)	OR	RATE ($)	ADDITIONAL FEE ($)
AMENDMENT B	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))					N/A		OR	N/A	
						TOTAL ADD'T FEE		OR	TOTAL ADD'T 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.

This collection of information is required by 37 CFR 1.16. 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, 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.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.