

A&A Ref: 149832

PUBLICATION PARTICULARS AND ABSTRACT
(Section 32(3)(a) - Regulations 22(1)(g) and 31)

21	01	PATENT APPLICATION NO	22	LODGING DATE	43	ACCEPTANCE DATE
----	----	-----------------------	----	--------------	----	-----------------

• • 20 04 / 20 67

15 March 2004

28 - 04 - 2005

51	INTERNATIONAL CLASSIFICATION	NOT FOR PUBLICATION
----	------------------------------	---------------------

A61K

CLASSIFIED BY: ISA

71	FULL NAME(S) OF APPLICANT(S)
----	------------------------------

Access Pharmaceuticals, Inc.

72	FULL NAME(S) OF INVENTOR(S)
----	-----------------------------

MORO, Daniel G.
NOWOTNIK, David P.

CALLAHAN, Howard

EARLIEST PRIORITY CLAIMED	COUNTRY	NUMBER	DATE
	33 US	31 09/931,319	32 16 August 2001

NOTE: The country must be indicated by its International Abbreviation - see schedule 4 of the Regulations

54	TITLE OF INVENTION
----	--------------------

Mucoadhesive erodible drug delivery device for controlled administration of pharmaceuticals and other active compounds

57	ABSTRACT (NOT MORE THAN 150 WORDS)
----	------------------------------------

NUMBER OF SHEETS 53

The sheet(s) containing the abstract is/are attached.

If no classification is furnished, Form P.9 should accompany this form.

~~The figure of the drawing to which the abstract refers is attached.~~

(57) Abstract: The present invention relates to a layered pharmaceutical delivery device for the administration of pharmaceuticals or other active compounds to mucosal surfaces. The device may also be used by itself without the incorporation of a therapeutic. The device of the present invention consists of a water-soluble adhesive layer, a non-adhesive, bioerodible backing layer and one or more pharmaceuticals if desired in either or both layers. Upon application, the device adheres to the mucosal surface, providing protection to the treatment site and localized drug delivery. The "Residence Time", the length of time the device remains on the mucosal surface before complete erosion, can be easily regulated by modifications of the backing layer.

MUCOADHESIVE ERODIBLE DRUG DELIVERY DEVICE FOR CONTROLLED ADMINISTRATION OF PHARMACEUTICALS AND OTHER ACTIVE COMPOUNDS

FIELD OF THE INVENTION

[01] The present invention relates to a bioerodible pharmaceutical carrier device that adheres to mucosal surfaces for the localized and systemic, controlled delivery of pharmaceuticals or other active compounds and/or the protection of the underlying treatment site.

BACKGROUND OF THE INVENTION

[02] The localized treatment of body tissues, diseases and wounds requires that a particular pharmaceutical be administered and maintained at the treatment site for a therapeutically effective period of time. The topical treatment of wet, mucosal surfaces has been problematic, since natural bodily fluids can rapidly wash away a topically applied active compound before the appropriate therapeutic action to the underlying surface can occur. In the mouth, saliva, the natural replacement of the mucosal tissue, and the actions of eating, speaking and drinking are just some of the problems that have limited the usefulness of a variety of pharmaceutical carrier devices.

[03] Gels, pastes, tablets and films have been developed as bioadhesive carriers and are well known in the art. These types of products, however, do not exhibit all of the major characteristics required for an efficient and patient acceptable pharmaceutical delivery device for mucosal treatment. The important characteristics include, water erodability, ease of handling and application to the treatment site, comfort with minimal foreign body sensation, rapid adhesion, prolonged residence time for the protection of the treatment site and/or the delivery of a pharmaceutical or other active compound, and ease

of removal from the underlying mucosal surface by natural erosion or dissolution of the delivery device at the treatment site.

[04] Bioadhesive gels used especially in the oral mucosal cavity are known in the art. For example, U.S. Patent No. 5,192,802 describes a bioadhesive teething gel composed of a mixture of sodium carboxymethyl cellulose and xanthan gum. This gel composition may have potential use in the treatment of canker sores, fever blisters and hemorrhoids. However, these types of gel systems have limited residence times, since bodily fluids such as saliva will quickly wash gels away from the treatment site. Other bioadhesive gels described in U.S. Pat. Nos. 5,314,915; 5,298,258 and 5,642,749 use an aqueous or oily medium and different types of bioadhesive and gelling materials, but still suffer from the inherent limitation of all gel products. Another type of bioadhesive products known in the art is denture adhesive pastes. These products, however, were developed primarily for their adhesive properties only, and not to protect tissue or deliver pharmaceuticals to the underlying mucosal surface. However, active compounds such as local anesthetics may be formulated with the paste for the relief of sore gums. Denture adhesive pastes are described in U.S. Pat. Nos. 4,894,232 and 4,5518,721. In the '721 patent, the combination of sodium carboxymethyl cellulose and polyethylene oxide in polyethylene glycol is used to provide a bioadhesive composition. Mucoadhesive pastes have also been used as protective films and drug delivery systems. Orabase®-B, a commercialized paste product that has both film forming and adhesive properties, is used for the relief of mouth sores. This product does provide numbing of the treatment site, but the residence time is minimum due to the quick dissolution by saliva. This product contains guar gum, sodium carboxymethyl cellulose, tragacanth gum and pectin.

[05] Bioadhesive tablets are described in U.S. Patent No. 4,915,948. A xanthan gum or pectin in combination with an adhesion enhancing material such as a polyol is the water-soluble bioadhesive used in this device. Although the residence time is greatly enhanced, these tablets are not user friendly, especially when used in the oral cavity, due to their unpleasant feeling, solidity, bulkiness and slow dissolution time. Also, solid devices cannot readily adhere to curved surfaces, especially crevices within the oral cavity. Bioadhesive tablets described in U.S. Patent Nos. 4,226,848; 4,292,299, and 4,250,163 are single or bilayer devices having an average thickness of 0.2 to 2.5 mm. These devices are less bulky, but have limited residence times. They are composed of a non-adhesive material such as cellulose ether, a bioadhesive ingredient such as polyacrylic acid, sodium carboxymethyl cellulose, or polyvinylpyrrolidone, and a binder for tableting purposes. The cellulose derivatives used in these devices may or may not be water-soluble. The bilayer devices described in the '299 patent contain methyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose. Bandages and bioadhesive laminated films are also known in the art. The films as described in U.S. Patent Nos. 3,996,934 and 4,286,592 are thinner, more flexible and therefore elicit a decreased foreign body sensation. The laminated films are usually composed of an adhesive layer, a reservoir layer and a backing layer and are designed to deliver drugs through the skin or mucosa. These films are typically not water soluble, thus they are not dissolved or washed away by bodily fluids and must be removed after the prescribed treatment time.

[06] Film delivery systems for use on mucosal surfaces are also known in the art. These types of systems, which are water-insoluble and usually in the form of a laminated, extruded or composite film, are described in U.S. Patent Nos. 4,517,173; 4,

572, 832; 4,713, 243; 4,900,554 and 5,137, 729. The '173 patent relates to a membrane-adhering film composed of at least three layers, including a layer containing a pharmaceutical, a layer with limited water solubility, and an intermediate layer. The pharmaceutical layer contains a drug and a cellulose derivative selected from hydroxypropyl cellulose, methyl cellulose, and hydroxypropylmethyl cellulose. The layer having limited water solubility consists of a combination of one or more cellulose derivatives and a hydrophobic fatty acid, and the intermediate layer is made of cellulose derivatives. The '832 patent describes a soft film for buccal delivery. The film is composed of a water soluble protein, a polyol, and a polyhydric alcohol such as cellulose and polysaccharides and coloring and flavoring agents. The '243 patent relates to a single or multi-layered bioadhesive thin film made from 40-95% water soluble hydroxypropyl cellulose, 5-0% water-insoluble ethylene oxide, 0-10% water-insoluble ethyl cellulose, propyl cellulose, polyethylene or polypropylene and a medicament. These films are three-layered laminates and are composed of a bioadhesive layer, a reservoir layer, and a non water-soluble outer protective layer. The '729 patent teaches a soft, adhesive film for use on oral mucosa. The film is comprised of a mixture of vinyl acetate non water-soluble homopolymer, an acrylic acid polymer, a cellulose derivative and a systemic drug.

[07] In the '554 patent, the device is designed for use in the oral cavity and is composed of an adhesive layer including a mixture of an acrylic acid polymer, a water-insoluble cellulose derivative, a water-insoluble or sparingly soluble backing layer, and a pharmaceutical. The adhesive layer contains the active ingredient and upon application to the treatment site, the drug is delivered to the underlying mucosal surface. This patent

also teaches that all three of the aforementioned components are required to attain an appropriate adhesive device suitable for mucosal treatment and drug delivery.

[08] Finally, water soluble films for the delivery of pharmaceutical compounds are also known in the art. U.S. Patent Nos. 5,800,832 and 6,159,498 describe a bioerodible, water soluble pharmaceutical device to treat mucosal surfaces. These bilayer devices are composed of an adhesive layer and a non-adhesive backing layer, and the pharmaceutical may be contained in either or both layers.

[09] The composition of the adhesive layer comprises polyacrylic acid, sodium carboxymethyl cellulose, and polyvinyl pyrrolidone, alone or in combination thereof. In addition to these mucoadhesive polymers, film forming polymers such as hydroxyethyl cellulose and hydroxypropyl cellulose are present. This layer can also contain a pharmaceutical compound. The backing layer of these devices comprises only film-forming polymers, such as hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose. These polymers are known to exhibit low bioadhesion and are approved for use in a variety of pharmaceutical applications. The residence time is claimed to be regulated by only variations of the backing layer. To increase the residence time, the components of the backing layer can be crosslinked with glyoxal solution, rendering the polymers less water soluble, and therefore, slower to dissolve, while being exposed to bodily fluids like saliva. A second approach is to change the composition of the backing layer by using a mixture of different and higher molecular weight polymers from the same family of hydroxyethyl and hydroxypropyl celluloses. These alterations to the backing layer are easy to accomplish. However, they do not provide a consistent, controllable and reproducible residence time for the final device. In

addition, in order to produce this device under the teachings of these inventions, it is required to cast the mucoadhesive layer and/or backing layer preferably onto a hard and non-porous surface. Then, each layer is dried yielding a laminated film. The casting surface therefore becomes an integral part of the device or must be carefully removed from the laminated film prior to cutting to the desired shape and subsequent packaging. The removal of such a non-flexible film would be difficult to accomplish without stretching or breaking the material. The associated manufacturing processes to produce such a device are complicated and therefore may not commercially viable or cost effective.

SUMMARY OF THE INVENTION

[10] One object of this invention is to provide a novel, versatile, water-erodible, pharmaceutical carrier device for use on mucosal surfaces. Another object of this invention is to provide a pharmaceutical carrier device for use on mucosal surfaces capable of providing a wide range of Residence Times for a multitude of active compounds through formulation alterations of the erodible backing layer. Another object of this invention is to provide a water-erodible device that can be used without an active ingredient to provide protection of mucosal surfaces. A further object of this invention is to provide a cost-effective, commercially viable and scaleable pharmaceutical carrier device for use on mucosal surfaces using simple manufacturing processes.

[11] The device is applied to mucosal surfaces and provides protection of the application site while delivering pharmaceuticals to treat specific diseases or disorders. The device causes minimum discomfort, is easy to use and provides an effective Residence Time that can be tailored to deliver therapeutics over different time intervals. In one embodiment, the device comprises a mucoadhesive multi-layered film that is

water-soluble and bioerodible. In another embodiment, the pharmaceutical delivery device comprises a multi-layered film having an adhesive layer and a coated, precast backing layer containing a pharmaceutical or other active compound in either or both layers. The film may be cut or fabricated into any desired shape, such as a disc, square, oval, parallelepiped, etc., that provides convenience for use in application and/or treatment. The adhesive layer of the device is water soluble and the backing layer is bioerodible. The adhesive layer comprises a film-forming polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, or hydroxyethylmethyl cellulose, alone or in combination, and a bioadhesive polymer such as polyacrylic acid, polyvinyl pyrrolidone, sodium carboxymethyl cellulose, tragacanth gum, sodium alginate, or any other known naturally occurring or synthetic mucoadhesive polymer alone, or in combination. The non-adhesive backing layer is a premade film alone or in combination with other layers. The precast film is comprised of hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or other water soluble film-forming polymer, alone or in combination thereof. The precast film may also include plasticizers or other excipients required to enhance the film forming properties of the polymer and to impart flexibility to the final, multi-layered device. The non-adhesive backing layer is further modified to render it water erodible instead of water soluble. For definition purpose, water erodible means a material or substance that does not dissolve in water or bodily fluids in total, however will disintegrate and completely break apart upon exposure to water or bodily fluids. This is accomplished by coating the backing layer film with a more hydrophobic

polymer selected from a group of Eudragit® and/or ethyl cellulose and methyl cellulose polymers that are approved by the FDA for use in pharmaceutical applications. Other hydrophobic polymers known to those skilled in the art may also be used. The hydrophobic coating layer can be applied first to the premade film by conventional coating techniques and then the reverse, uncoated side can be used as the support on which the mucoadhesive polymer solution is cast to a desired thickness. The type and amount of hydrophobic polymer used will provide a wide and controlled range of Residence Times for the layered film device. In addition, using the modified, precast, erodible backing layer can eliminate the need to use a rigid support material such as a polyethylene film like "Mylar" or other non-porous material as the casting surface on which both the adhesive layer and backing layer are produced. This rigid casting surface is no longer an integral component of the layered device, which from a safety and production point of view, is extremely desirable.

[12] In another embodiment, the devices of the current invention can also be produced using a non-rigid, non-porous surface other than a polyethylene film as the casting and support material. Coated paper is preferred but other materials known to those skilled in the art are also acceptable. In this process, the hydrophobic layer can be first applied to the support paper, then the precast film is laminated to the hydrophobic layer under pressure using a roller and a polymeric solution that will bind both materials together after solvent drying, and finally the mucoadhesive solution is coated onto the composite layers and dried to remove the coating solvent. The incorporation of the plasticized precast film between these layers imparts significant overall flexibility to the final device. It is also preferred to use a polymeric solution to bind the mucoadhesive

layer to the precast laminated film upon drying. The resulting multi-layered device is then peeled from the carrier paper and cut into the desired shape.

[13] In the preferred embodiment, the mucoadhesive coating solution or suspension, with or without an active ingredient, is first coated onto a carrier release paper and subsequently dried using a standard oven. A precast, water soluble plasticized film coated with the appropriate hydrophobic composition that provides the desired Residence Time is laminated to the dried adhesive film using a polymeric laminating solution, roller and pressure, and the multilayered device is then dried in a standard oven. The multilayered film may be then separated from the paper, cut into a desired shape and packaged, or the multilayered film and the release paper can be cut into a desired shape and packaged. With the latter example, the release paper will be an integral part of the final device and must be removed prior to application of the mucoadhesive side of the patch onto a mucosal surface. Since a rigid casting support material like "Mylar" is not being used, the potential for injury to the patient is also eliminated. It is apparent to those skilled in the art that variations in the coating sequences and coating processes in addition to manufacturing conditions such as temperature, humidity, carrier release paper and drying time can have a major effect on the quality, reproducibility and cost-effectiveness of the final device. It is understood that other known processes for producing multilayered patches, in addition to the aforementioned casting processes, can be used to produce devices outlined in this invention disclosure.

DETAILED DESCRIPTION OF THE INVENTION

[14] In the present invention, a unique bioerodible pharmaceutical layered device that adheres to mucosal surfaces is provided. The present invention is most applicable to the treatment of body tissues, diseases, or wounds that may have moist

surfaces and that are susceptible to bodily fluids, such as the mouth, vagina, anus, or other types of mucosal surfaces. Pharmaceuticals or other active compounds can be incorporated in the device, if desired, and upon application and adherence to the specific mucosal site, protection of the underlying tissue results. Concomitantly, pharmaceuticals are delivered to the treatment site, the surrounding tissues and other bodily fluids for a prolonged period of time. The device provides an appropriate, controlled residence time for effective drug delivery at the treatment site. The residence time is easily tailored to provide a range from minutes to hours, dependent upon the type of drug used and the therapeutic indication. In one embodiment, the pharmaceutical delivery device comprises a layered film patch having a water soluble adhesive layer and a water erodible backing layer, having a pharmaceutical in either or both layers.

[15] The present invention offers advantages with respect to increased residence time over bioadhesive gels and pastes known in the art. Paste and gel products such as Orajel, Orabase, and Kanka have short residence times in the order of minutes. This is a result of limited or poor adhesion. Upon application of a gel product to the mucosal surface, the mucoadhesive components do not instantaneously penetrate the lipophilic surface of the mucosa. Instead, these hydrophilic components quickly mix with saliva or other bodily fluids and therefore are removed from the application site resulting in a minimal residence time. A similar mechanism of action can be expected to occur with paste products, however to a slightly lesser extent. This is due to the higher viscosity and greater hydrophobicity of the paste causing a slower erosion process to occur. The multilayered film of the present invention provides for immediate adhesion to the mucosal surface due to the combination of mucoadhesive polymers within water-soluble

film-forming polymers, and its thin, flexible solid form. A solid device will dissolve or erode more slowly than a gel or paste device due to dissolution kinetics.

[16] Bioadhesive tablets known in the art also have serious limitations, primarily due to their bulkiness and rigidity causing an unpleasant sensation and discomfort after application to the oral cavity. These tablets provide effective residence times, but because they are an order of magnitude larger than the device in the present invention, the preferred application site is on the upper gingival or sublingual area. This site is suitable for systemic delivery of an active compound, but may not be satisfactory for localized, unidirectional delivery. The device of the present invention offers both local and systemic delivery with an effective and controlled residence time and minimal discomfort and ease of application as a result of its thinner, more flexible configuration.

[17] Finally, film systems known in the art that are used to deliver pharmaceuticals also have other limitations. These films, unlike the pharmaceutical device of the present invention, are occlusive and water insoluble and are fabricated to be removed after treatment of a mucosal surface. Removal of a non-erodible device may cause some damage to the mucosa, or may damage healing mucosa when the device is used to cover a lesion. The pharmaceutical device of the present invention is designed to be water erodible, and therefore does not require removal. Once applied to a mucosal surface, water absorption softens the device, and over time, the device slowly erodes away delivering a specific pharmaceutical to the treatment site.

[18] In one embodiment, the present invention is composed of a multi-layered film having an adhesive layer, a precast, non-adhesive, water soluble backing layer, and a hydrophobic coating layer. The hydrophobic coating layer renders the backing layer

water-erodible and provides a wide range of predictable and controlled residence times. The adhesive layer is water soluble and the backing layer is water erodible. All components used to manufacture the device are FDA approved materials. The pharmaceutical or other active agent may be included in either layer, but is preferably incorporated in the adhesive layer. This layer is in direct contact with the treatment site and the active compound will be released at a rate related to the dissolution of the adhesive layer. The backing layer will control the rate at which the adhesive layer hydrates, therefore will affect the rate of dissolution of the adhesive layer.

[19] In one preferred manufacturing embodiment, the multilayered film is produced by first coating a carrier release paper with the mucoadhesive coating solution at a known thickness and then dried using a conventional oven to produce the adhesive layer. The adhesive layer must remain adhered to the carrier release paper during this processing step, since further coatings will be applied on top of it to produce the final multilayered product. However, after the final multilayered film is produced, the composition must release without damage from the carrier paper prior to cutting into a preferred shape. It is obvious to one skilled in the art that these unique adhesion properties are a function of the type of mucoadhesive polymers used, the manufacturing conditions, the environmental conditions and the type of carrier substrate used. A precast water soluble film that has been previously coated with a hydrophobic polymer is then laminated to the dry adhesive. The lamination is maximized by pressing the films together using a roller with slight pressure after wetting the precast film with a polymeric solution that can bind both layers together after drying. The polymeric, binding solution must be compatible with both the precast film and the components of the adhesive film.

In the preferred embodiment, an alcoholic solution, or an alcoholic/water solution of polyvinylpyrrolidone at a concentration between 1-30%, and more preferably 5-20%, will provide a good lamination. It is understood by one skilled in the art that a wide variety of polymers with different molecular weights can be used to bind layers together. The choice of the most appropriate polymer to use alone or in combination will be related to the type of mucoadhesive polymers in the adhesive layer, the composition of the precast film and the active compound present if any in either layer. The polymers used to bind must also be safe and approved by the FDA. It is also understood that multilayered films produced using different coating sequences and processing alterations from those outlined above would fall within the scope of this invention.

[20] The adhesive layer may comprise at least one film-forming water-soluble polymer, typically selected from a family of cellulose polymers (the "film-forming polymer") and at least one or more polymers known in the art for its bioadhesive property (the "bioadhesive polymer"). The film-forming polymer may comprise hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethylmethyl cellulose, alone or in combination thereof. The molecular weight of the film-forming polymer is in the range of 10^2 to 10^6 , and more preferably between 10^3 to 10^5 . The film-forming polymer may be crosslinked and/or the adhesive layer plasticized to alter the dissolution characteristics. The bioadhesive polymer contained in the adhesive layer may comprise polyacrylic acid(PAA), which may or may not be partially crosslinked, sodium carboxymethyl cellulose(NaCMC), polyvinylpyrrolidone(PVP), tragacanth gum, sodium alginate or any other known naturally occurring or synthetic mucoadhesive polymer alone, or in combination thereof. These bioadhesive polymers are preferred because they

exhibit good instantaneous mucoadhesive properties in the dry, film state. In the case of sodium carboxymethyl cellulose, typical average molecular weights range between 50,000 and 700,000 Daltons, and preferably between 60,000 to 500,000 Daltons, with a degree of substitution of 0.7. The substitution range varies between 0.5 and 1.5, and preferably between 0.6 and 0.9. The polyvinyl pyrrolidone can be characterized according to its average molecular weight and comprises between 5,000 and 150,000 Daltons, preferably between 10,000 and 100,000 Daltons. In some instances, the combination of some grades of polyvinyl pyrrolidone with polyacrylic acid may result in precipitation, causing a non-homogeneous adhesive layer to result and a potentially less than optimum mucoadhesive property. Such combinations of polyacrylic acid and polyvinyl pyrrolidone should be avoided.

[21] The chemical nature of the bioadhesive polymers used in the present invention, including chain, side groups and crosslinking agents, generates interactions between the mucosal constituents and the polymer or polymers, such as physical entanglement, Van der Waals forces, and hydrogen bonding. Since the mucosal surface differs from one individual to another and changes naturally over time, the use of a combination of at least two bioadhesive polymers and/or the use of a combination of different grades of the same polymer will provide maximum adhesion of the device for a wide range of different mucosal surfaces. However, the use of a single mucoadhesive polymer is effective as well. The ratio of bioadhesive polymer to film-forming polymer in the adhesive layer can be varied and depends upon the type and amount of pharmaceutical or other active ingredient used and other factors. However, the content of combined components in the adhesive layer is between 5 and 95% by weight, preferably

between 10 and 80% by weight. In terms of weight percent of the different bioadhesive polymers PAA, NaCMC, PVP, Tragacanth, and Sodium Alginate, some examples are detailed later. Preferred combinations include PAA and NaCMC, NaCMC and PVP, PAA and PVP, Tragacanth, Sodium Alginate, NaCMC and PVP, and also include the use of different molecular weight grades of the same polymer.

[22] The non-adhesive backing layer is a premade film comprised of a water-soluble, film-forming pharmaceutically acceptable polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, ethylene oxide-propylene oxide co-polymers, or other water soluble film-forming polymers, alone or in combination thereof. The non-adhesive backing layer is further modified to render it water erodible instead of water soluble. This is accomplished by incorporating or coating the backing layer film with a more hydrophobic polymer selected from a group of FDA approved Eudragit polymers, ethyl cellulose and methyl cellulose polymers that are approved for use in other pharmaceutical dosage forms. Other hydrophobic polymers may be used, alone or in combination with other hydrophobic or hydrophilic polymers, provided that the layer derived from these polymers or combination of polymers erodes in a moist environment. The precast backing layer film can be precoated in advance with the hydrophobic coating solution or can be applied to the layered device as the final coating step. In one embodiment, the application of an erodible layer to the precast film allows the backing layer to act as the support layer if desired on which the adhesive solution can be cast without dissolving the backing layer during the manufacture of the layered device. The elimination of polyethylene or other rigid, non-erodible non-porous

surface results, and therefore the device no longer represents a potential threat of user injury.

[23] In another embodiment, the backing layer is first applied to a carrier release paper or other non-porous surface, then dried and the precast film is laminated to the hydrophobic layer by wetting it with a polymeric binding solution and pressing the materials together using a roller with pressure. The composite is then dried to eliminate any of the coating solvents, and the mucoadhesive coating solution with or without an active compound is applied using a doctor blade onto the surface and dried. The resulting multilayered film is then carefully peeled from the carrier release paper and cut into the desired shape.

[24] In the preferred manufacturing embodiment, a dry adhesive layer of known thickness with or without an active ingredient is produced on a carrier release paper by techniques known in the art. A precast film that has been previously coated with a backing layer of the appropriate hydrophobic composition is then laminated to the adhesive layer by wetting it with a polymeric binding solution and pressing the materials together using a roller under pressure. The composite film is then dried, carefully removed from the carrier paper and cut into the desired shape. The primary purpose of the coated precast film is to regulate the Residence Time of the device but it also imparts significant flexibility and therefore provides a more user friendly and comfortable product. It is obvious that a device produced under the conditions disclosed above will be more cost effective and scaleable, since the number of coating passes and manufacturing steps are reduced. The associated direct labor costs and material handling for films produced within the scope of this invention will be therefore lower than other

multilayered films disclosed in the prior art. Another major advantage with these multilayered film devices is that the adhesive layer containing an active can be controlled more reproducibly and uniformly. When the adhesive is applied first to the carrier release paper, the resultant coating thickness variability is only a function of the variability of the thickness of the surface on which it is cast. If the adhesive is coated last, its coating variability is a function of the thickness variability of all previous coats. In addition, the content uniformity of any active if used in the mucoadhesive coating will also be more variable throughout the entire multilayered film due to the cumulative variability of previous coatings.

[25] The type of solution used to coat the precast backing layer typically is composed of a mixture of a hydrophobic Eudragit polymer or copolymer, or ethyl or methyl cellulose, and a water soluble polymer such as polyvinyl pyrrolidone, hydroxypropyl methyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, polyvinyl alcohol or any other water soluble polymer that can be completely comixed with Eudragit or ethyl cellulose, dissolved in Ethanol, ethanol/water or other suitable volatile organic solvent. The ratio of hydrophobic Eudragit or ethyl cellulose to water soluble polymer ranges from 0.5 to 18:1, and more preferably 1:0 to 10:1. The coating solution may also contain a plasticizing agent, such as propylene glycol, polyethylene glycol, or glycerine in a small amount, 0 to 2% by weight, in order to improve the "flexibility" of this layer in the mouth and to adjust the erosion rate of the device. In addition, humectants such as hyaluronic acid, glycolic acid, and other alpha hydroxyl acids can also be added to improve the "softness" and "feel" of the device. Finally, colors and opacifiers may be added to help distinguish the resulting non-adhesive backing layer

from the mucoadhesive layer. Some opacifiers include titanium dioxide, zinc oxide, zirconium silicate, etc.

[26] The amount of mixed coating applied to the precast backing layer, using a suitable doctor blade or lab coater apparatus, ranges between zero and 1.5 mm, most preferably between 0.05 and 0.4 mm. The amount of solids present in the coating solution, the resulting solution viscosity and coating thickness applied determine the amount of coating film to be deposited on the precast backing layer. Typically, increasing the hydrophobic polymer to water soluble polymer ratio will provide a device with a longer residence time, while keeping coating thickness, viscosity, coating solids, polymer composition, and other variables constant. In addition, increasing the coating thickness of the Eugragit and/or ethyl cellulose/ water-soluble polymer mixture while keeping all other variables constant will also provide an increased residence time. This will be clearly shown in examples shown later in this disclosure.

[27] The residence time of the device of the present invention is dependent upon the composition of the modified backing layer and the rate of dissolution of the water-soluble polymers used. The residence time is easily controlled, from minutes to hours, by the amount of coating solution applied to the backing layer and the specific composition of the coating solution. The devices of the present invention are therefore more versatile than those films, tablets and gels known in the art and can be used with a wider range of pharmaceuticals or other active compounds requiring different therapeutic delivery times. The devices of the present invention also typically provide, when desired, a longer residence time than those devices known in the art. This is a result of the selection of the appropriate backing layer formulation, providing a slower rate of erosion

of the backing layer and therefore allowing the mucoadhesive layer to remain in contact with the treatment site for a longer period of time before complete erosion. The device of the present invention will maximize the unidirectional delivery of an active compound to the treatment site while minimizing the systemic delivery of the drug that results from surface erosion due to saliva or other bodily fluids. The device of the present invention is more therapeutically effective for most indications than those devices known in the art, since a sustained level of drug is delivered at a more controlled rate over a longer treatment time.

[28] The pharmaceutical component or other active compound of the present invention may comprise a single pharmaceutical or a combination of pharmaceuticals. These active ingredients may be incorporated in the adhesive layer, backing layer or in both. If desired, flavoring agents known in the art may be added to mask the taste of the active compound. Penetration enhancers may also be included in the adhesive layer to help reduce the resistance of the mucosa to drug transport. Typical enhancers known in the art include ethylenediamine tetracetic acid, chitosans, dimethyl sulfoxide, etc. Ingredients to enhance drug solubility and/or stability of the drug may also be added to the layer or layers containing the active ingredient. Examples of stabilizing and solubilizing agents are cyclodextrins.

[29] Pharmaceuticals that may be used, either alone or in combination, include antiallergic compounds, antianginal agents, anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides and disinfectants, vasoconstrictors, hemostatics, chemotherapeutics, antibiotics, keratolytics, cauterizing

agents, hormones, growth hormones and growth hormone inhibitors, analgesic narcotics, and antiviral drugs.

[30] Examples of antiallergic compounds include amlexanox, astemizole, azelastine, emirolast, alocpatadine, cromolyn, fenpiprane, repirinast, tranilast, and traxanox.

[31] Examples of antianginal agents include nifedipine, atenolol, bepridil, carazolol, and epanolol.

[32] Examples of anti-inflammatory analgesic agents include acetaminophen, methyl salicylate, monoglycol salicylate, aspirin, mefenamic acid, flufenamic acid, indomethacin, diclofenac, alclofenac, diclofenac sodium, ibuprofen, ketoprofen, naproxen, pranoprofen, fenoprofen, sulindac, fenclofenac, clidanac, flurbiprofen, fentiazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, tiaramide hydrochloride, etc.

[33] Examples of steroidal anti-inflammatory agents include hydrocortisone, prednisolone, dexamethasone, triamcinolone acetonide, fluocinolone acetonide, hydrocortisone acetate, prednisolone acetate, methylprednisolone, dexamethasone acetate, betamethasone, betamethasone valerate, flumetasone, fluorometholone, beclomethasone dipropionate, etc.

[34] Examples of antihistamines include diphenhydramine hydrochloride, diphenhydramine salicylate, diphenhydramine, chlorpheniramine hydrochloride, chlorpheniramine maleate isothipendyl hydrochloride, tripeleminamine hydrochloride, promethazine hydrochloride, methdilazine hydrochloride, etc.

[35] Examples of local anesthetics include dibucaine hydrochloride, dibucaine, lidocaine hydrochloride, lidocaine, benzocaine, p-buthylaminobenzoic acid 2-(diethylamino) ethyl ester hydrochloride, procaine hydrochloride, tetracaine, tetracaine hydrochloride, chlorprocaine hydrochloride, oxyprocaine hydrochloride, mepivacaine, cocaine hydrochloride, piperocaine hydrochloride, dyclonine, dyclonine hydrochloride, etc.

[36] Examples of bactericides and disinfectants include thimerosal, phenol, thymol, benzalkonium chloride, benzethonium chloride, chlorhexidine, povidone iodine, cetylpyridinium chloride, eugenol, trimethylammonium bromide, benzoic acid, sodium benzoate, etc.

[37] Examples of vasoconstrictors include naphazoline nitrate, tetrahydrozoline hydrochloride, oxymetazoline hydrochloride, phenylephrine hydrochloride, tramazoline hydrochloride, etc.

[38] Examples of hemostatics include thrombin, phytonadione, protamine sulfate, aminocaproic acid, tranexamic acid, carbazochrome, carbaxochrome sodium sulfanate, rutin, hesperidin, etc.

[39] Examples of chemotherapeutic drugs include sulfamine, sulfathiazole, sulfadiazine, homosulfamine, sulfoxazole, sulfisomidine, sulfamethizole, nitrofurazone, taxanes, platinum compounds, topoisomerase I inhibitors, and anthrocyline.

[40] Examples of antibiotics include penicillin, meticillin, oxacillin, cefalotin, cefalordin, erythromycin, lincomycin, tetracycline, chlortetracycline, oxytetracycline, metacycline, chloramphenicol, kanamycin, streptomycin, gentamicin, bacitracin, cycloserine, and clindamycin.

[41] Examples of keratolytics include salicylic acid, podophyllum resin, podolifox, and cantharidin.

[42] Examples of cauterizing agents include the chloroacetic acids and silver nitrate.

[43] Examples of hormones include estrone, estradiol, testosterone, equilin, and human growth hormone.

[44] Examples of growth hormone inhibitors are octreotide and somatostatin.

[45] Examples of analgesic narcotics include fentanyl, buprenorphine, codeine sulfate, levorphanol, and morphine hydrochloride.

[46] Examples of antiviral drugs include protease inhibitors, thymidine kinase inhibitors, sugar or glycoprotein synthesis inhibitors, structural protein synthesis inhibitors, attachment and adsorption inhibitors, and nucleoside analogues such as acyclovir, penciclovir, valacyclovir, and ganciclovir.

[47] The amount of active agent or pharmaceutical(s) in the device of the present invention depends upon the therapeutic requirements, although, preferably, the pharmaceutical component comprises 0.001 to 30% by weight of the device, and more preferably between 0.005 and 20% by weight.

[48] Flavoring agents, preservatives, plasticizers, opacifiers, stabilizing and solubilizing compounds, penetration enhancers and coloring agents may also be included in the adhesive layer, backing layer, or both layers of the device. Preferably, these components represent no more than 5% by weight of the final device.

[49] The thickness of the device may vary, depending upon the thickness of each individual layer. Preferably, the thickness of the layered disc of the present

invention ranges from 0.05 mm to 1 mm, and more preferably from 0.1 to 0.5 mm. The thickness of each individual layer may vary from 10 to 90% of the overall thickness of the layered device, and preferably varies from 30 to 60%. Therefore, the preferred thickness of each layer may vary from 0.002 mm to 0.9 mm, and more preferably from 0.003 to 0.6mm.

[50] The pharmaceutical delivery device of the present invention may be prepared by various methods known in the art. In one embodiment, the components are dissolved in the appropriate solvent or combination of solvents to prepare a solution. Solvents for use in the present invention may comprise water, methanol, ethanol, isopropyl alcohol, acetone, methyl ethyl ketone, heptane, or dichloroethane, alone or in combination. The residual solvent content in the dried, multilayered film may act as a plasticizer, an erosion-rate-modifying agent or may provide some pharmaceutical benefit. Desired residual solvent may reside in either or both layers.

[51] Each solution is then coated onto the precast backing layer that acts as the substrate or support layer. Eventually, one of the components might be in suspension. While it is desirable for all components in each coating solution to be in solution, coating solutions in which one or more components are partially or fully suspended in the coating solution may also be used. Each solution is cast and processed into a thin film by techniques known in the art, such as by film dipping, film coating, film casting, spin coating, or spray drying. The thin film is then dried. This drying process may be accomplished using any suitable type of oven. However, the solvent residuals are dependent upon the drying procedure and parameters used. Alternatively, the individual layers of the multi-layered device can be produced independently and then laminated

together or may be filmed one on top of the other. In one embodiment of the present invention, a precast film used as the backing and support layer is coated first with an alcoholic polymeric solution containing the appropriate mixture of hydrophobic and water soluble polymers. After subsequent drying, the coated precast backing layer is then top-coated or coated on the reverse side with the appropriate mucoadhesive solution that may or may not contain a pharmaceutical or other active agent. After appropriate drying, the multilayered film obtained may be cut into any size or shape, for application to the mucosal tissue. Some possible shapes include disks, ellipses, squares, rectangles, and parallelepipeds.

[52] In the preferred embodiment, the components are dissolved in the appropriate solvent or combination of solvents to prepare a solution. The polymeric coating solution containing the appropriate mixture of hydrophobic and water soluble polymers is applied to the precast water soluble backing layer. The solution is cast and processed into a thin film by techniques known in the art, such as by film dipping, film coating, film casting, spin coating, or spray drying. The thin film is then dried and the coated precast film is stored for future use. The mucoadhesive solution with or without an active compound is applied to a carrier release substrate at a desired thickness. The solution is cast and processed into a film by techniques known in the art, such as by film dipping, film coating, film casting, spin coating, or spray drying and the film is subsequently dried. The coated precast backing layer is then laminated to the dried adhesive film that is attached to the carrier release substrate. This is accomplished by first wetting the coated precast backing layer with a polymeric binding solution, then pressing both films together using a roller under pressure. The composite material is then dried

using a standard oven. The residual solvent content in the dried, multilayered film may act as a plasticizer, an erosion-rate-modifying agent or may provide some pharmaceutical benefit. Desired residual solvent may reside in either or both layers. Other laminating procedures known in the art can also be used. The polymeric binding solution is carefully designed to penetrate the matrix of the layers that it is bonding together, without dissolving or geometrically disrupting them, and upon drying, deposit a polymer that adheres to both layers and creates a bond. The multilayered, composite film is then carefully peeled away from the carrier release substrate, cut into a desired shape and put into an appropriate package.

[53] Methods for treating mucosal surfaces, specifically oral mucosa, surrounding tissues, and bodily fluids for localized and systemic drug delivery are provided. In one embodiment, the method comprises applying a multi-layered, adherent film to the treatment site in order to provide drug delivery and protection to the underlying area. The adherent film may comprise any of the layered devices provided herein. In the preferred embodiment, the method comprises application of a multi-layered pharmaceutical carrier device having a first mucoadhesive layer, a second backing layer that imparts flexibility to the device and may also act as a support layer and a third layer that regulates the residence time of the device. The pharmaceutical or other active compound may be present in the adhesive layer, backing layer, or both layers.

EXAMPLE 1.

[54] A 300 gram batch of mucoadhesive coating solution was prepared using 268.2 grams of deionized and 0.22 μ filtered water, 5.40 grams of hydroxyethyl cellulose, Natrosol 250 L NF (BF Goodrich), 3.19 grams Amlexanox, 2-amino-7-isopropyl-5-oxo-5H-{1} benzopyranol {2,3-b}-pyridine-3-carboxylic acid (Takeda Chemical Industries),

7.81 grams Noveon AA1, Polycarbophil (BF Goodrich), 13.50 grams sodium carboxymethyl cellulose, 7LF PH (BF Goodrich), 0.96 grams sodium benzoate, NF(Spectrum Chemicals), and 0.95 grams propylene glycol, USP(Spectrum Chemicals). A Lightnin® mixer with an A-100 propeller was used to effectively homogenize this viscous mucoadhesive coating suspension at a speed of 1000 rpm. The resulting percentage of film forming polymer was 1.8% and the mucoadhesive polymers was 7.1%. This adhesive coating suspension was used in some of the examples shown below.

EXAMPLE 2.

[55] A 500 gram batch of mucoadhesive coating solution was prepared using 451.5 grams of deionized and 0.22 μ filtered water, 8.0 grams of hydroxyethyl cellulose, Natrosol 250 L NF (BF Goodrich), 9.0 grams Amlexanox, 2-amino-7-isopropyl-5-oxo-5H-{1} benzopyranol {2,3-b}-pyridine-3-carboxylic acid (Takeda Chemical Industries), 11.0 grams Noveon AA1, Polycarbophil (BF Goodrich), 17.0 grams sodium carboxymethyl cellulose, 7LF PH (BF Goodrich), 1.0 grams of hydroxypropyl cellulose, Klucel EF Pharm (BF Goodrich), 1.5 grams sodium benzoate, NF(Spectrum Chemicals), and 1.0 grams propylene glycol, USP (Spectrum Chemicals). A Lightnin® mixer with an A-100 propeller was used to effectively homogenize this viscous mucoadhesive coating suspension at a speed of 1000 rpm. The resulting percentage of film forming polymer was 1.8% and the mucoadhesive polymers was 5.6%. This adhesive coating suspension was used in some of the examples to follow.

EXAMPLE 3.

[56] A 1784.4 gram batch of mucoadhesive coating solution was prepared using 1520 grams of deionized and 0.22 μ filtered water, 36.0 grams of hydroxyethyl cellulose, Natrosol 250 L NF (BF Goodrich), 73.6 grams benzocaine, ethyl p-

aminobenzoate, USP (Spectrum Chemicals), 20.0 grams PVP, USP, one million molecular weight (BASF), 36.0 grams sodium alginate, NF (Spectrum Chemicals), 24.0 grams tragacanth, NF (Spectrum Chemicals), 62.0 grams sodium carboxymethyl cellulose, 7LF PH (BF Goodrich), 6.4 grams sodium benzoate, NF(Spectrum Chemicals), and 6.4 grams propylene glycol, USP(Spectrum Chemicals). A Lightnin® mixer with an A-100 propeller was used to effectively homogenize this viscous mucoadhesive coating suspension at a speed of 1000 rpm. This adhesive coating suspension was used in some of the examples to follow.

EXAMPLE 4.

[57] Several coating solutions were prepared and used to produce multilayered films of different residence times. Stock solutions of both polyvinylpyrrolidone (pvp), 16% w/w of PVP, USP, one million molecular weight (BASF), dissolved in ethanol, USP, 190 proof(Spectrum Chemicals), and ethyl cellulose, 20% w/w of ethyl cellulose dissolved in ethanol, USP, 190 proof were prepared. Aliquots of both stock solutions were combined and mixed to create a range of coating solutions as follows:

4a. twenty grams of pvp solution plus 16 grams of ethyl cellulose solution produced a mixed coating solution ratio of 1:1 (ethyl cellulose: pvp)

4b. twenty grams of pvp solution plus 20 grams of ethyl cellulose solution produced a mixed coating solution ratio of 1.25:1 (ethyl cellulose:pvp)

4c. twenty grams of pvp solution plus 28 grams of ethyl cellulose solution produced a mixed coating solution ratio of 1.75:1 (ethyl cellulose;pvp)

4d. twenty grams of pvp solution plus 32 grams of ethyl cellulose solution produced a mixed coating solution ratio of 2:1 (ethyl cellulose:pvp)

4e. twenty grams of pvp solution plus 40 grams of ethyl cellulose solution produced a mixed coating solution ratio of 2.5:1 (ethyl cellulose:pvp)

4f. twenty grams of pvp solution plus twenty grams of water (laminating solution)

4g. 3.84 grams of pvp powder plus 18.58 grams of ethanol plus 9.63 grams of water (laminating solution)

EXAMPLE 5.

[58] Similar to example 4, additional hydrophobic coating solutions were prepared using stock solutions of both polyvinylpyrrolidone, 16% w/w of PVP, USP, one million molecular weight(BASF), dissolved in ethanol, USP, 190 proof(Spectrum Chemicals), and Eudragit® RS-100 NF(Rohm GmbH), 48% w/w of polymer dissolved in ethanol, USP, 190 proof. Aliquots of both stock solutions were combined and mixed to create a range of coating solutions as follows:

5a. twenty grams of pvp solution plus 6.67grams of Eudragit® solution produced a mixed coating solution ratio of 1:1 (Eudragit®: pvp)

5b. twenty grams of pvp solution plus 13.34 grams of Eudragit® solution produced a mixed coating solution ratio of 2:1 (Eudragit®: pvp)

5c. twenty grams of pvp solution plus 23.33 grams of Eudragit® solution produced a mixed coating solution ratio of 3.5:1 (Eudragit®: pvp)

5d. twenty grams of pvp solution plus 26.67 grams of Eudragit® solution produced a mixed coating solution ratio of 4:1 (Eudragit®: pvp)

5e. twenty grams of pvp solution plus 40.0 grams of Eudragit® solution produced a mixed coating solution ratio of 6:1 (Eudragit®: pvp)

5f. twenty grams of pvp solution plus 60.0 grams of Eudragit® solution produced a mixed coating solution ratio of 9:1 (Eudragit®: pvp)

EXAMPLE 6.

[59] Similar to example 4, additional hydrophobic coating solutions were prepared and used to produce multilayered films of different residence times. Stock solutions of both ethyl cellulose (25% w/w of Ethocel 7 from Dow Chemical Corp. dissolved in ethanol, USP, 190 proof) and hydroxypropyl methyl cellulose (10% w/w of Methocel E5 from Dow Chemical Corp. dissolved in ethanol, USP, 190 proof) were

prepared. Aliquots of both stock solutions were combined, along with small amounts of red food coloring from Adams Extracts, Inc. (for visual differentiation), and mixed to create a range of coating solutions as follows:

6a. twenty grams of ethyl cellulose solution plus 50.00 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 1:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6b. twenty grams of ethyl cellulose solution plus 40.00 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 1.25:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6c. twenty grams of ethyl cellulose solution plus 33.33 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 1.5:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6d. twenty grams of ethyl cellulose solution plus 25.00 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 2:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6e. twenty grams of ethyl cellulose solution plus 20.00 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 2.5:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6f. twenty grams of ethyl cellulose solution plus 16.67 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 3:1 (ethyl cellulose:hydroxypropyl methyl cellulose)

6g. twenty grams of ethyl cellulose solution plus 12.50 grams of hydroxypropyl methyl cellulose solution produced a mixed coating solution ratio of 4:1 (ethyl cellulose:hydroxypropyl methyl cellulose) 6h. only the 25% ethyl cellulose solution.

EXAMPLE 7.

[60] Multi-layered films were prepared using the hydrophobic coatings solutions outlined in example 4 with the mucoadhesive coating suspension detailed in example 1. First, a piece of hydroxypropyl methyl cellulose precast film(Watson Polymer Films), 0.004inches thick was cut approximately 18 inches x 11.5 inches and placed in the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.15 mm. and each solution from example 4 was

applied to individual precast pieces of the backing film. The films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of deposited hydrophobic/water soluble polymer resulted. Each coated film was removed and put back into the frame with the uncoated side of the backing layer facing up. The 16% pvp solution from example 4 was applied to the uncoated side of each backing layer with the doctor blade adjusted to 0.50 mm. These films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of pvp resulted. The adhesive coating suspension from example 1 was then used to coat each of the coated backing layer samples, using a 1.2 mm. setting on the doctor blade. The films were dried as before, and a second coating and drying step using the adhesive layer was conducted. These multilayered films were kept in a water impermeable plastic bag prior to being used for in-vivo testing. Samples were designated as 7.4a, 7.4b, 7.4c, 7.4d, and 7.4e. For example, sample 7.4c refers to a multilayered film composed of a backing layer of hydroxypropyl methyl cellulose coated with a film composed of a mixture of ethyl cellulose and polyvinyl pyrrolidone at a ratio of 1.75:1 outlined in example 4 and a mucoadhesive layer from example 1., using a coating setting for the hydrophobic coating solution at 0.15 mm.

EXAMPLE 8.

[61] The experimental process outlined in example 7 was repeated exactly, with the exception that the coating setting for the hydrophobic/water soluble coating process was 0.25mm instead of 0.15mm. The effect of increasing the amount of coating thickness and the resulting residence time will be shown and tabulated in later examples. Samples were designated similarly as in example 7. For example, sample 8.4b is the same

compositionally as sample 7.4b, except the 8.4b sample contains a thicker ethyl cellulose/pvp coating.

EXAMPLE 9.

[62] Multi-layered films were prepared using the Eudragit®/pvp coatings solutions outlined in example 5 with the mucoadhesive coating suspension detailed in example 2. First, a piece of hydroxypropyl methyl cellulose precast film(Watson Polymer Films), 0.004inches thick was cut approximately 18 inches x 11.5 inches and placed in the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.25 mm. and each solution from example 5 was applied to individual precast pieces of the backing film. The films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of deposited hydrophobic/water soluble polymer resulted. Each coated film was removed and put back into the frame with the uncoated side of the backing layer facing up. The 16% pvp solution from example 4 was applied to the uncoated side of each backing layer with the doctor blade adjusted to 0.50 mm. These films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of pvp resulted. The mucoadhesive coating suspension from example 2 was then used to coat each of the coated backing layer samples, using a 1.2 mm. setting on the doctor blade. The films were dried as before, and a second coating and drying step using the adhesive layer was conducted. These multilayered films were kept in a water impermeable plastic bag prior to being used for in-vivo testing. Samples were designated as 9.5a, 9.5b, 9.5c, 9.5d, 9.5e and 9.5f. For example, sample 9.5c refers to a multilayered film composed of a backing layer of hydroxypropyl methyl cellulose coated with a film composed of a mixture of Eudragit® and polyvinyl pyrrolidone at a ratio of 3.5:1 outlined in example 5 and a

mucoadhesive layer from example 2. using a doctor blade setting for the hydrophobic coating solution at 0.25 mm.

EXAMPLE 10.

[63] The experimental process outlined in example 9 was repeated exactly, with the exception that the doctor blade setting for the hydrophobic/water soluble coating process was 0.5mm instead of 0.25mm. The effect of increasing the amount of coating thickness and the resulting residence time will be shown and tabulated in later examples. Samples were designated similarly as in example 9. For example, 10.5b is the same compositionally as sample 9.5b, except the 10.5b sample contains a thicker Eudragit®/pvp coating.

EXAMPLE 11.

[64] Using the stock solutions detailed in example 4, 5.0 grams of pvp solution plus 7.0 grams of ethyl cellulose solution were mixed. To this solution, 0.7 grams of green food color(Kroger Company), 2% dye(yellow 5 and blue 1) in propylene glycol/water was added and thoroughly mixed. A piece of hydroxypropyl methyl cellulose precast film(Watson Polymer Films), 0.004inches thick was cut approximately 18 inches x 11.5 inches and placed in the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.15 mm. and the solution was coated and dried on the precast backing layer. A smooth, green colored, uniform coating resulted. The film was removed and reversed in the holder, and coated and dried similarly as detailed in example 7 using the 16% pvp solution of example 4 and the mucoadhesive coating suspension shown in example 1. The resulting layered film exhibited a good contrast in color, a green outer layer that provides an appropriate residence time and the white, opaque mucoadhesive layer that is meant to be applied to

the oral mucosa. Thus, the inclusion of an innocuous FDA approved dye provides a visual aid to the end user for the proper orientation of the mucoadhesive layer onto the treatment site. A sample was designated as 11.

EXAMPLE 12.

[65] Multi-layered films were prepared using the hydrophobic coating solutions outlined in example 6 with the mucoadhesive coating suspension detailed in example 2. First, a piece of hydroxypropyl methyl cellulose precast film(Watson Polymer Films), 0.004inches thick was cut approximately 18 inches x 11.5 inches and placed in the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.25 mm. and solutions from example 6 were applied to individual precast pieces of the backing film. The films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of deposited hydrophobic/water soluble polymer resulted. Each coated film was removed and put back into the frame with the uncoated side of the backing layer facing up. The 16% pvp solution from example 4 was applied to the uncoated side of each backing layer with the doctor blade adjusted to 0.50 mm. These films were then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of pvp resulted. The adhesive coating suspension (Example 1 or 2) was then used to coat each of the coated backing layer samples, using a 1.2 mm. setting on the doctor blade. The films were dried as before, and a second coating and drying step using the same adhesive layer was conducted. These multilayered films were kept in a water impermeable plastic bag prior to being used for in-vivo testing. Samples were designated as 12.6a, 12.6b, 12.6c, 12.6d, and 12.6e. For example, sample 12.6c refers to a multilayered film composed of a backing layer of hydroxypropyl methyl cellulose coated with a film composed of a mixture of ethyl cellulose and hydroxypropyl

methyl cellulose at a ratio of 1.5:1 outlined in example 6 and a mucoadhesive layer from example 2., using a coating setting for the hydrophobic coating solution at 0.25 mm.

EXAMPLE 13.

[66] The experimental process outlined in example 12 was repeated exactly, with the exception that the adhesive used was from example 3. The sample was designated similarly as in example 12. So, sample 13.6d is the same compositionally as sample 12.6d, except the 13.6d sample contains the benzocaine adhesive instead of the amlexanox adhesive.

EXAMPLE 14.

[67] Multi-layered films were prepared using the hydrophobic coating solution 6d outlined in example 6 with the mucoadhesive coating suspension detailed in example 1 with a slightly higher amount of amlexanox, but the processing order for producing a multi-layered film was changed. First, a piece of polypropylene-coated paper was stretched out on the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.25 mm. and the 6d solution from example 6 was applied to the paper. The film was then dried in the oven portion of the lab coater, and a smooth, integral layer of deposited hydrophobic/water erodible soluble polymer resulted. The 0.004" hydroxypropyl methyl cellulose precast film (Watson Polymer Films) was then laminated to the hydrophobic film, using the laminating solution 4f from example 4. The 16% pvp solution from example 4 was then applied to the uncoated side of the backing layer with the doctor blade adjusted to 0.60 mm. The film was then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of pvp resulted. Finally, the doctor blade setting was adjusted to 1.75 mm. and the adhesive solution from example 14 was applied to the precast film and dried in the lab coater. This

multilayered film was kept in a water impermeable plastic bag prior to being used for in-vivo testing.

[68] This process was successfully scaled up at a contractor's site. The single sheet process has been replaced with a roll of paper. This allows for longer strips of film to be produced with the potential of a continuous coating process to produce cost-effective and scaleable quantities of product. Samples from this scaled-up process were designated as 14.6d.

EXAMPLE 15.

[69] The experimental process outlined in example 14 was repeated exactly, with the exception that the adhesive was from example 3. The sample was designated similarly as in example 12. So, sample 15.6d is the same compositionally as sample 14.6d, except the 15.6d sample contains the benzocaine adhesive instead of the amlexanox adhesive.

EXAMPLE 16.

[70] Multi-layered films were prepared using a hydrophobic coating solution outlined in example 6 with the mucoadhesive coating suspension detailed in example 14. First, a piece of hydroxypropyl methyl cellulose precast film(Watson Polymer Films), 0.004inches thick was cut approximately 18 inches x 11.5 inches and placed in the paper and foil holder of a Werner Mathis AG Lab Coater, type LTF. The doctor blade setting was adjusted to 0.25 mm. and solution 6d from example 6 was applied to an individual precast piece of the backing film. The film was then automatically dried in the oven portion of the lab coater, and a smooth, integral layer of deposited hydrophobic/water soluble polymer resulted. This coated film was removed and stored for later use. A piece of polypropylene-coated paper was put into the frame. The adhesive coating suspension

from example 14 was then used to coat the paper using a 1.75 mm. setting on the doctor blade. The film was dried as before. Then the two strips of layered film were laminated together using laminating solution 4g from example 4 with the adhesive facing the hydroxypropyl methyl cellulose precast film(Watson Polymer Films). These were dried and kept in a water impermeable plastic bag prior to being used for in-vivo testing.

[71] This process has been scaled up at a contractor's site. The single sheet process has been replaced with a roll of paper. This allows for much longer strips of film to be produced with the potential of a continuous coating process to produce cost-effective and scaleable quantities of product. Samples from this scaled-up process were designated as 16.6d.

EXAMPLE 17.

[72] The experimental process outlined in example 16 was repeated exactly, with the exception that the adhesive was from example 3. This process has also been scaled up at a contractor's site. Samples from this scaled-up process were designated similarly as in example 12. So, sample 17.6d is the same compositionally as sample 16.6d, except the 17.6d sample contains the benzocaine adhesive instead of the amlexanox adhesive.

EXAMPLE 18.

[73] To ascertain the in-vivo performance of the multilayered drug delivery devices, films from the preceeding examples were cut into 0.5 inch disks using a die punch. The mucoadhesive layer was carefully oriented onto the oral, mucosal cheek surface using an index finger and applying continuous pressure to maximize initial adhesion for two to four seconds. Parameters such as initial tack, comfort, and residence time were recorded. These results are tabulated as follows:

DETAILED DESCRIPTION OF THE INVENTION

Sample #	Initial Tack	Comfort	Residence Time
7.4a	Ok	good	51 min.
7.4b	Ok	good	75 min.
7.4c	Ok	good	79 min.
7.4d	Ok	good	99 min.
7.4e	Ok	good	125 min.
8.4a	Ok	good	68 min.
8.4b	Ok	good	94 min.
8.4c	Ok	good	131 min.
8.4d	-	-	-
8.4e	-	-	-
9.5a	Ok	good	40 min.
9.5b	-	-	-
9.5c	-	-	-
9.5d	Ok	Ok	115 min.
9.5e	Ok	Ok	120 min.
9.5f	Ok	Ok	>120 min.
10.5a	Ok	good	50 min.
10.5b	Ok	good	65 min.
10.5c	Ok	good	100 min.
10.5d	Ok	Ok	165 min.
10.5e	Ok	Ok	180 min.
10.5f	Ok	Ok	>240 min.

11	Ok	good	158 min.
12.6a	Ok	good	54 min.
12.6b	Ok	good	57 min.
12.6c	Ok	good	59 min.
12.6d	Ok	good	58 min.
12.6e	Ok	good	91 min.
12.6f	Ok	good	95 min.
12.6g	Ok	good	78 min.
12.6h	Ok	good	144 min.
13.6d	Ok	good	64 min.
14.6d	Ok	good	60 min.
15.6d	Ok	good	50 min.
16.6d	Ok	good	57 min.
17.6d	Ok	good	74 min.

[74] It is clear from the above table that longer residence times for these multilayered pharmaceutical drug delivery devices are provided using coating solutions that contain higher amounts of hydrophobic polymer relative to the water-soluble polymer present. In addition, by increasing the amount of coating thickness, a concomitant increase in residence time results.

[75] It is also appears that using ethyl cellulose instead of Eugdragit® as the hydrophobic polymer component in the coating solution provides a longer residence time at the same relative concentration to the water soluble polyvinylpyrrolidone component. In all likelihood, this is a result of the greater hydrophobicity of ethyl cellulose. One other conclusion is that the presence of a food dye and propylene glycol in the hydrophobic

coating solution also provided an increase in residence time, about double what was expected. Our hypothesis is that the dye and/or propylene glycol plasticize the hydrophobic coating matrix, causing a slower erosion process to occur and therefore increasing the residence time. This finding also allows the user to potentially modify the residence time by changes in propylene glycol and dye concentration in the final hydrophobic coating layer of the multilayered film device.

[76] Those skilled in the art will recognize that, while specific embodiments and examples have been described, various modifications and changes may be made without departing from the scope and spirit of this invention.

CLAIMS:

1. A water-erodible coating layer for controlling the residence time of a water-soluble thin-film device that is adhered to a moist surface of a body tissue,
5 comprising at least one hydrophobic polymer and at least one water-soluble polymer wherein the ratio of the hydrophobic polymer(s) to the water soluble polymer(s) is from 1:1 to 9:1 by weight.
2. The water-erodible coating layer of claim 1, wherein the water-
10 soluble polymer(s) is/are selected from the group consisting of polyvinyl pyrrolidone, polyvinyl alcohol, hydroxyethyl cellulose, hydroxypropyl cellulose and hydroxypropylmethyl cellulose.
3. The water-erodible coating layer of either claim 1 or claim 2,
15 wherein the hydrophobic polymer is selected from the group consisting of methyl cellulose; ethyl cellulose; anionic, cationic and neutral methacrylate polymers and copolymers (Eudragit® polymers); and a combination thereof.
4. The water-erodible coating layer of claim 1, further comprising a
20 plasticizer.
5. The water-erodible coating layer of claim 4, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol and glycerin.
25
6. The water-erodible coating layer of claim 1, further comprising humectant.
7. The water-erodible coating layer of claim 6, wherein the humectant is
30 selected from the group consisting of hyaluronic acid and glycolic acid.

8. The water-erodible coating layer of claim 1, further comprising a coloring agent.

9. The water-erodible coating layer of claim 1, further comprising an opacifying agent.

5

10. A water-soluble thin-film device capable of adhering to a moist surface of a body tissue, comprising the water-erodible coating layer of claim 1.

10 11. The water-soluble thin-film device of claim 10, further comprises a water-soluble adhesive layer.

12. The water-soluble thin-film device of claim 11, wherein the water-soluble adhesive layer comprises at least one water-soluble film-forming polymer and at least one bioadhesive polymer.

15

13. The water-soluble thin-film device of claim 12, wherein the water-soluble film-forming polymer(s) is/are selected from the group consisting of polyvinyl alcohol, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyethylene oxide and polyethylene glycol.

20

14. The water-soluble thin-film device of claim 12 or 13, wherein the bioadhesive polymer(s) is/are selected from the group consisting of polyvinylpyrrolidone, polyacrylic acid and sodium carboxymethyl cellulose.

25 15. The water-soluble thin-film device of any one of claims 10, 11, 12, 13 or 14 further comprising a water-soluble non-adhesive backing layer disposed between the water-erodible coating layer and the water-soluble adhesive layer.

30 16. The water-soluble thin-film device of claim 15 wherein the water-soluble non-adhesive backing layer is hydroxypropylmethyl cellulose.

17. The water-soluble thin-film device of claim 13 wherein the water-soluble film-forming polymer has a molecular weight between 25,000 and 1,500,000 Daltons.

5 18. The water-soluble thin-film device of claim 17 wherein the water-soluble film-forming polymer has a molecular weight between 30,000 and 500,000 Daltons.

19. The water-soluble thin-film device of claim 10, further comprising a plasticizer in either or both of water-erodible coating layer and/or the water
10 insoluble adhesive layer.

20. The water-soluble thin-film device of claim 19, wherein the plasticizer is selected from the group consisting of propylene glycol, polyethylene glycol and glycerin.

15

21. The water-soluble thin-film device of claim 11, further comprising an active compound in the water-soluble adhesive layer.

22. The water-soluble thin-film device of either claim 15 or claim 21,
20 further comprising an active compound in the water-soluble non-adhesive backing layer.

23. The water-soluble thin-film device of any one of claims 21 or 22, wherein the active compound is selected from the group consisting of an anti-allergic, an anti-inflammatory analgesic, an anti-anginal, a steroidal anti-inflammatory, an antihistamine, a local anesthetic, a bactericide, a disinfectant, a vasoconstrictor, a hemostatic, a chemotherapeutic, an antibiotic, a keratolytic, a cauterizing agent, a hormone, a growth hormone inhibitor, an analgesic narcotic and an anti-viral.

30

24. A coating layer according to any one of claims 1 to 9, substantially as herein described and illustrated.

25. A device according to any one of claims 10 to 23, substantially as herein described and illustrated.

5 26. A new coating layer, or a new device, substantially as herein described.