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(54) **PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES**

(75) Inventors: **Gilles H. Tapolsky**, The Woodlands, TX (US); **David W. Osborne**, The Woodlands, TX (US)

(73) Assignee: **Arius Two, Inc.**, Raleigh, NC (US)

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A61F 13/00 (2006.01)
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(58) **Field of Classification Search** 424/435, 424/486

See application file for complete search history.

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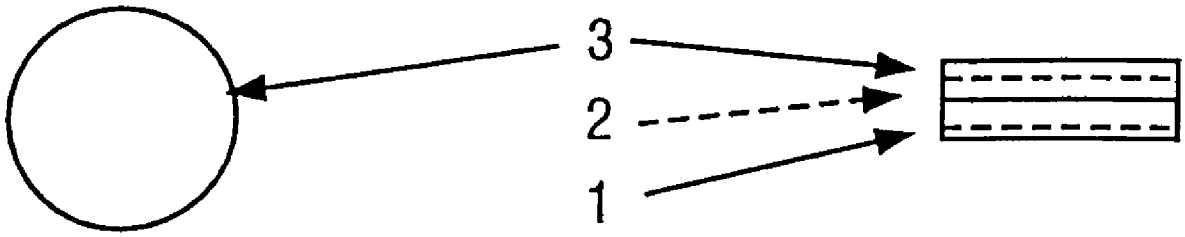
Assistant Examiner—Abigail Fisher
(74) *Attorney, Agent, or Firm*—McCarter & English LLP

(57) **ABSTRACT**

The present invention relates to a pharmaceutical delivery device for application of a pharmaceutical to mucosal surfaces. The device comprises an adhesive layer and a non-adhesive backing layer, and the pharmaceutical may be provided in either or both layers. Upon application, the device adheres to the mucosal surface, providing localized drug delivery and protection to the treatment site. The kinetics of erodability are easily adjusted by varying the number of layers and/or the components.

7 Claims, 1 Drawing Sheet



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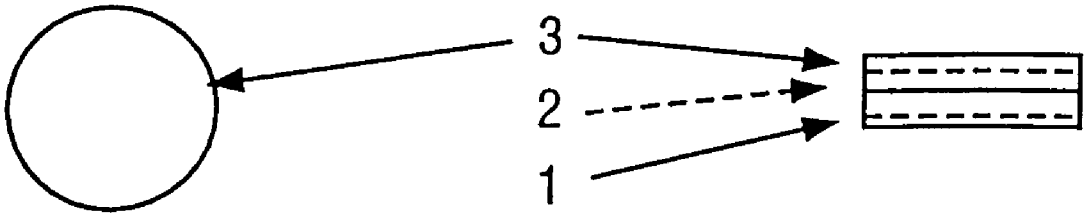

FIG.1

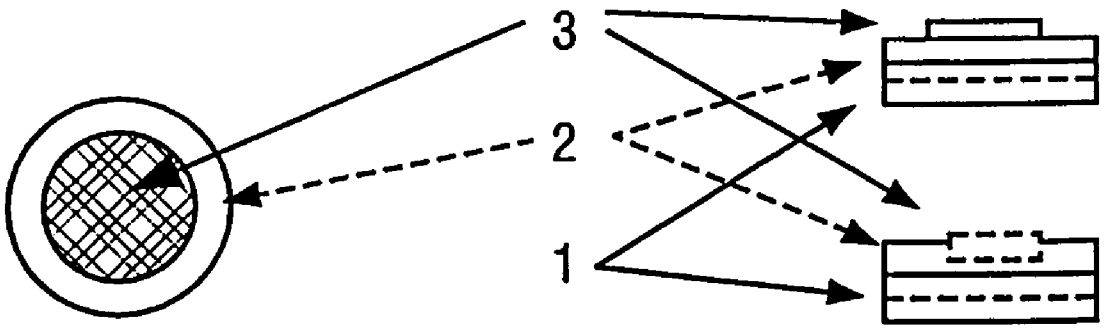

FIG.2

PHARMACEUTICAL CARRIER DEVICE SUITABLE FOR DELIVERY OF PHARMACEUTICAL COMPOUNDS TO MUCOSAL SURFACES

The instant application is a continuation of U.S. patent application Ser. No. 09/684,682, filed Oct. 4, 2000, which is a divisional of U.S. patent application Ser. No. 09/069,703, filed Apr. 29, 1998 which is a continuation-in-part application of PCT/US97/18605, filed Oct. 16, 1997, which is a PCT application claiming priority from Ser. No. 08/734,519, filed Oct. 18, 1996, which applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates generally to a water-erodable pharmaceutical carrier which adheres to mucosal surfaces for the localized delivery of pharmaceutical compounds and protection of the treatment site.

BACKGROUND OF THE INVENTION

The localized treatment of body tissues, diseases, and wounds requires that the particular pharmaceutical component be maintained at the site of treatment for an effective period of time. Given the tendency of natural bodily fluids to rapidly wash away topically applied pharmaceutical components, the topical treatment of wet mucosal tissues has been problematic. In the mouth, saliva, natural replacement of the mucosal tissue, as well as, eating, drinking, and speaking movements are some of the problems that have limited the effectiveness and residence time of pharmaceutical carriers.

Bioadhesive carriers are known in the art and include gels, pastes, tablets, and films. These products, however, may lack one or several of the preferred characteristics for an efficient and commercially acceptable pharmaceutical delivery device. Some characteristics which are preferred by users of bioadhesive carriers include water-erodability; ease of handling and application to the treatment site; ease of comfort; minimal foreign body sensation; and unidirectional, specific release into the mucosal tissue. Other preferred characteristics for an effective and user-friendly product for the treatment of mucosal surfaces include the use of pharmaceutically approved components or materials; instantaneous adhesion to mucosal surface upon application; increased residence time for the protection of the affected tissue or the delivery of the pharmaceutical component; and ease of removal of the delivery device from the affected tissue or natural erosion of the delivery device at the delivery site.

Bioadhesive gels which are used for application to mucosal tissues and especially the oral cavity are known in the art. For example, U.S. Pat. No. 5,192,802 describes a bioadhesive teething gel made from a blend of sodium carboxymethyl cellulose and xanthan gum. The gel may also have potential use in the treatment of canker sores, fever blisters, and hemorrhoids. However, this type of pharmaceutical carrier has a very limited residence time, given that body fluids such as saliva quickly wash it away from the treatment site. Bioadhesive gels are also described in U.S. Pat. Nos. 5,314,915; 5,298,258; and 5,642,749. The gels described in those patents use an aqueous or oily medium and different types of bioadhesive and gelling agents.

Denture adhesive pastes are another type of bioadhesive product known in the art. However, these preparations are

the topical delivery of is pharmaceuticals, although drugs such as local anesthetics may be used in the paste for the relief of sore gums. U.S. Pat. Nos. 4,894,232 and 4,518,721 describe denture adhesive pastes. The '721 patent describes a combination of sodium carboxymethyl cellulose and polyethylene oxide in polyethylene glycol.

Pastes have also been used as film protectants and as drug delivery systems. One such example having film forming and adhesive properties is the product commercialized under the name Orabase®-B, which is a thick gel or paste for the relief of mouth sores. Ingredients include guar gum, sodium carboxymethyl cellulose, tragacanth gum, and pectin. Even though it does provide numbing to the area of application, the film forming behavior and bioadhesion do not last. Thus, this product has a limited residence time.

Bioadhesive tablets are described in U.S. Pat. No. 4,915,948. The water-soluble bioadhesive material used in this device is a xanthan gum or a pectin combined with an adhesion enhancing material such as a polyol. Although residence time is improved with the use of bioadhesive tablets, they are not user friendly, especially when used in the oral cavity, given the unpleasant feelings associated with their solidity, bulkiness, and slow erosion time.

Bioadhesive tablets are also described in U.S. Pat. Nos. 4,226,848; 4,292,299; and 4,250,163, and are single layer or bilayer devices having an average thickness of 0.2 to 2.5 mm. The bioadhesive tablets described in these patents utilize a non-adhesive component such as cellulose ether, a bioadhesive component such as polyacrylic acid, sodium carboxymethyl cellulose, or polyvinylpyrrolidone, and a binder for tableting purposes. The cellulose derivatives may or may not be water-erodable.

The use of bandages or bioadhesive laminated films, which are thinner and flexible and therefore have a decreased foreign body sensation, is described in U.S. Pat. Nos. 3,996,934 and 4,286,592. These products are used to deliver drugs through the skin or mucous. The laminated films usually include an adhesive layer, a reservoir layer, and a backing layer. Bioadhesive devices designed to release drug through the skin at a given rate and over a period of time are usually not water soluble, and thus are not dissolved or washed away by bodily fluids.

In addition to film systems for the delivery of drug through the skin, film delivery systems for use on mucosal surfaces are also known. These types of systems, which are water-insoluble and usually in the form of laminated, extruded or composite films, are described in U.S. Pat. Nos. 4,517,173; 4,572,832; 4,713,243; 4,900,554; and 5,137,729. The '173 patent describes and claims a membrane-adhering film consisting of at least three layers, including a pharmaceutical layer, a poor water soluble layer, and an intermediate layer. The pharmaceutical layer includes the drug and a cellulose derivative selected from hydroxypropyl cellulose, methyl cellulose, and hydroxypropyl methyl cellulose. The poor water soluble layer is made by the combination of one or more cellulose derivatives with a poor water soluble fatty acid, and the intermediate layer is made of cellulose derivatives. The '832 patent relates to a soft film for buccal delivery, made by the combined use of a water soluble protein, a polyol, and a polyhydric alcohol such as cellulose and polysaccharides, and also teaches the use of coloring or flavoring agents. The '243 patent describes a single or multi-layered bioadhesive thin film made from 40-95% water soluble hydroxypropyl cellulose, 5-60% water-insoluble ethylene oxide, 0-10% water-insoluble ethyl cellulose, propyl cellulose, polyethyl-

layer, and a non water-soluble outer protective layer. The '729 patent teaches a soft adhesive film applicable to the oral mucosa containing a systemic drug and comprising a mixture of a vinyl acetate non water-soluble homopolymer, an acrylic acid polymer, and a cellulose derivative. Finally, the '554 patent describes a device for use in the oral cavity having an adhesive layer including a mixture of an acrylic acid polymer, a water-insoluble cellulose derivative, and a pharmaceutical preparation, and a water-insoluble or sparingly soluble backing layer. The adhesive layer contains the pharmaceutical, and upon application to the mucosal surface, delivers the drug. The '554 patent also states that "it is impossible to achieve an adhesive device for application to body tissue without all three components, that is, acrylic acid polymer, water insoluble cellulose derivative and a water insoluble or sparingly soluble backing layer."

JP 56-100714 describes a preparation which comprises a coating layer and an active ingredient layer. The coating layer adheres to the mucosal membrane and is comprised of a cellulose ether or an acrylic acid polymer or salt. The active ingredient layer comprises an ointment base comprised of water-insoluble substances such as fats and oils, waxes, hydrocarbons, higher fatty acids, higher alcohols, polyhydric alcohols or glycerol esters. A surfactant and active ingredient are also present in the active ingredient layer. Thus, the active ingredient is mixed with an essentially non-water erodable substance. The previous examples of thin films to be applied in the oral cavity by adhesion onto the mucosal tissues all utilize polymers which are water-insoluble by nature or which are made water-insoluble by crosslinking, and claim a long residence time. Therefore, unfortunately, the above examples of thin films do not provide a water erodable device with good adhesive properties. Therefore, upon release of the desired amount of drug, the thin films of water insoluble polymers must be peeled off the site of application. Such peeling often removes tissue from the mucosal tissue and is painful to the patient. What is needed in the art is a water-erodable pharmaceutical delivery device which provides good adhesion and localized delivery of a pharmaceutical with minimal discomfort to the patient.

SUMMARY OF THE INVENTION

The present invention relates to a novel water-erodable pharmaceutical carrier device for application to mucosal surfaces to provide protection of and localized delivery of pharmaceutical to the site of application, surrounding tissues, and other bodily fluids such as blood or lymph, having an effective residence time, with minimal discomfort and ease of use. In one embodiment, the pharmaceutical delivery device includes a layered film disk which is water-erodable. The device comprises a layered film disk having an adhesive layer and a backing layer, both water-erodable, having the pharmaceutical in one or more of the layers.

In another embodiment, the pharmaceutical delivery device further comprises a third layer between the first adhesive layer and the second backing layer. The third layer is a water-erodable adhesive layer which has a surface area sufficient to encompass said first adhesive layer and contact the mucosal surface. In this manner, localized delivery of a pharmaceutical may be accomplished in a unidirectional manner toward the mucosal layer.

The adhesive layer(s) comprise(s) a film-forming polymer such as hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxyethyl methyl cellulose, sodium carboxymethyl cellulose, collagen and derivatives, gelatin, albumin, polyaminoacids and derivatives, polyphosphazenes, polysaccharides and derivatives, chitin, or chitosan, alone or in combination and a bioadhesive polymer such as polyacrylic acid, polyvinyl pyrrolidone, or sodium carboxymethyl cellulose, alone or in combination.

The non-adhesive backing layer(s) comprise(s) hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxyethylmethyl cellulose, hydroxypropylmethyl cellulose, polyvinyl alcohol, polyethylene glycol, polyethylene oxide, or ethylene oxide-propylene oxide co-polymers, alone or in combination.

In another embodiment of the invention, one or more of the layers of the device further comprise a component which acts to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device. A component which acts to adjust the kinetics of the erodability is a water-based emulsion of a polylactide, polyglycolide, lactide-glycolide copolymers, poly-ϵ-caprolactone and derivatives, polyorthoesters and derivatives, polyanhydrides and derivatives, ethyl cellulose, vinyl acetate, cellulose acetate, and polyisobutylene, alone or in combination. Another component which acts to adjust the kinetics of the erodability is alkyl-glycol, propylene glycol, polyethyleneglycol, oleate, sebacate, stearate or esters of glycerol, or phthalate, alone or in combination.

In another embodiment of the invention, the number of layers of the device further may be varied to adjust the kinetics of the erodability and provide a convenient manner of altering the release of the pharmaceutical and the lifespan of the device.

In a preferred embodiment, the backing layer comprises two or more layers with different erodibility kinetics.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. **1** is a three layered film disk wherein layers **2** and **3** are bioadhesive layers and layer **1** is a backing layer.

FIG. **2** is a three layered film disk wherein two of the layers are bioadhesive layers and the other layer is a backing layer. The bioadhesive layer, layer **3**, which will adhere to the mucosal tissue is of smaller surface area and encompassed by the second bioadhesive layer, layer **2**, to provide unidirectional delivery. Layer **1** is a backing layer.

DETAILED DESCRIPTION OF THE INVENTION

As used herein, the term "water-erodable" means that the component, device, layer, etc. erodes in water-based media such as saliva, over time. Such erosion in water may be due to factors such as dissolution, dispersion, friction, gravity, etc.

As used herein, the term "kinetics of erodability" or "erosion kinetics" refers to the timing of the release of pharmaceutical from the carrier device (release profile), as well as, the timing of the erosion of the device itself over time (lifespan or residence time of the device). As described herein, kinetics of erodability are based on factors such as type and amount of components in the device, thickness and number of layers in the device, and additives or excipients in the device. In a case in which all the components of the device are very water soluble, the kinetics of erodability will closely parallel the solubility kinetics.

In the present invention, a novel water-erodable pharmaceutical device which adheres to mucosal surfaces is provided. The present invention finds particular use in the localized treatment of body tissues, diseases, or wounds which

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