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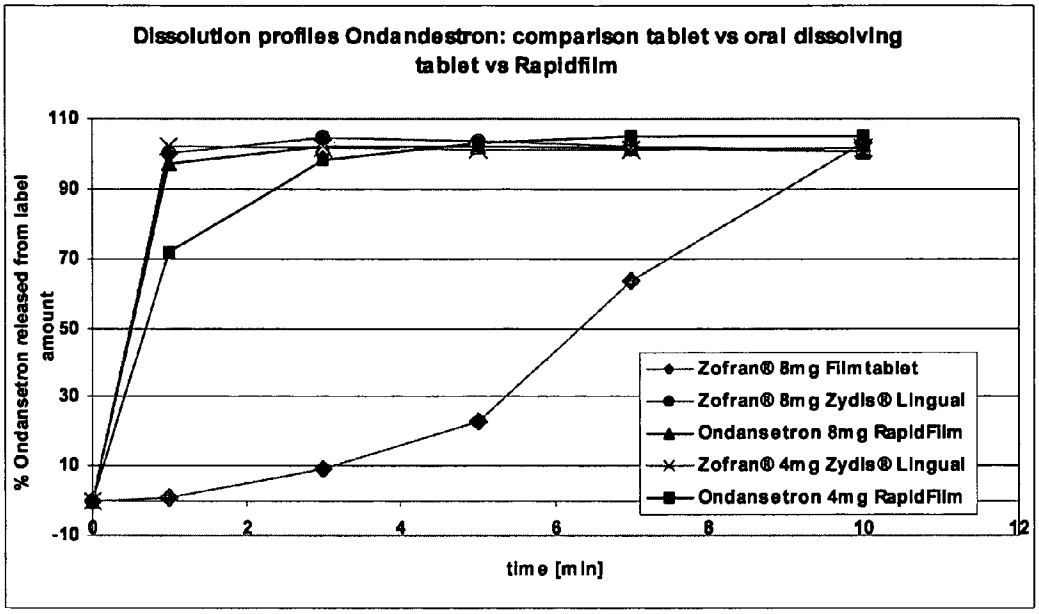
(54) Title: NON-MUCOADHESIVE FILM DOSAGE FORMS



(57) Abstract: Orally disintegrating film dosage forms for delivering active pharmaceutical agents, methods of formulating the dosage forms to retard absorption through the oral mucosa, and methods of using the dosage forms for the treatment of various medical conditions are provided.

WO 2008/040534 A2

NON-MUCOADHESIVE FILM DOSAGE FORMS

RELATIONSHIP TO PRIOR APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/848,965, filed October 2, 2006 (now abandoned).

FIELD OF THE INVENTION

The present invention relates to orally disintegrating film dosage forms for delivering active pharmaceutical agents, methods of formulating the dosage forms to promote gastrointestinal absorption comparable to immediate release solid oral dosage forms, and to methods of using the dosage forms for the treatment of various medical conditions.

BACKGROUND OF THE INVENTION

Orally administered film strip dosage forms have been recently developed for the pharmaceutical industry, and are currently used for the sale of several popular over-the-counter drug products, including Listerine® breath strips, Triaminic® thin strips (active agent = diphenhydramine HCl), and Sudafed PE™ quick dissolve strips (active ingredient = phenylephrine HCl). The absolute bioavailability of diphenhydramine when ingested orally is approximately 61%, and the time to maximum serum concentration is about 3-4 hours. Phenylephrine is subject to extensive presystemic metabolism in the gut wall, such that the absolute bioavailability of phenylephrine when ingested orally is approximately 40% relative to intravenous dosing, and peak plasma concentrations are achieved in about 1-2 hours.

In addition, several manufacturers have proposed formulations that could be used to deliver prescription drugs. The vast majority of these formulations are "mucoadhesive" formulations designed for adhesion of the dosage form to mucosal tissue in the mouth, and transmission of the drug from the dosage form through the mucosal tissue into the systemic circulation. As described in U.S. Patent No. 6,750,921 to Kim et al., film-forming agents have been used to manufacture drug delivery formulations for percutaneous or transdermal application, but these necessarily involve an adhesive composition to retain the agent in situ long enough to cause sustained release of the active ingredient. Bioerodible films are described in Tapolsky et al., U.S. Patent No. 5,800,832. The films have an adhesive layer and a non-adhesive backing layer and are intended to adhere to the mucosal surface. Biegajski et

al., U.S. Patent No. 5,700,478, describes a water-soluble pressure-sensitive mucoadhesive suitable for use in a mucosal-lined body cavity.

The purported advantage of these mucoadhesive films resides in their ability to bypass the gastrointestinal tract, and barriers in the gastrointestinal tract to drug absorption such as first pass metabolism and decomposition of the active ingredient in the stomach. An additional advantage for these dosage forms, when compared to tablets, capsules and other dosage forms that must be swallowed, is that some patient populations have difficulty swallowing, such as children and the elderly.

Until now the prior art has been focused principally on improving the delivery profile of a given pharmaceutical agent with this dosage form, by increasing its rate of dissolution or absorption, or bypassing metabolic processes that reduce the bioavailability of the drug. The prior art has not appreciated that an innovator's drug product, be it a tablet, capsule, or other oral dosage form, has already proven itself effective through rigorous clinical testing, and that the innovator's product may already provide the optimum bioavailability of pharmaceutical agent. What is needed is a film product that mimics the pharmacokinetics of an innovator's product, and that follows the same metabolic and bioabsorption pathways as the innovator's product, to ensure that the dosage form achieves the proven clinical efficacy of the innovator product.

OBJECTS OF THE INVENTION

Accordingly, it is an object of the present invention to provide non-mucoadhesive orally disintegrating film dosage forms that mimic the pharmacokinetic profile of orally administered drug products such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

Another object of the invention is to provide non-mucoadhesive orally disintegrating film dosage forms that follow the same metabolic and bioabsorption pathways through the gastrointestinal tract as existing orally administered drugs, such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

Still another object of the present invention is to provide methods of formulating and testing non-mucoadhesive orally disintegrating film dosage forms so that they follow the same metabolic and bioabsorption pathways, and obtain the same pharmacokinetic profiles, as existing orally administered drugs such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

Another object of the present invention is to provide methods of treatment using the film dosage forms of the present invention, and methods that promote bioequivalence to orally administered drug products such as tablets, capsules, liquid suspensions, and orally dissolving/dispersing tablet (ODT).

Yet another object of the present invention is to provide techniques and methodologies for retarding the absorption of drugs from orally disintegrating films through the oral mucosa.

SUMMARY OF THE INVENTION

The present invention provides film dosage forms that are formulated or administered for gastrointestinal absorption of the active pharmaceutical agent, and that are bioequivalent to and interchangeable with existing orally administered drug products. These film dosage forms are non-mucoadhesive; they quickly disintegrate in the mouth when exposed to saliva; and they are absorbed predominantly through the gastrointestinal tract. Most importantly, these dosage forms are specially formulated to meet exacting bioavailability requirements, or to be bioequivalent to existing orally administered dosage forms.

Therefore, in a first principal embodiment, the invention provides a non-mucoadhesive orally disintegrating film, able to disintegrate upon contact with saliva in the buccal cavity within about sixty seconds, comprising a defined amount of an active pharmaceutical agent, a hydrophilic binder and a water-soluble diluent, wherein: (a) said film is formulated for delivery of said active agent through the gastrointestinal tract when applied to the tongue; (b) said film comprises from about 0.05% to about 50% (w/w) of said active pharmaceutical agent, based on the total weight of the formulation; and (c) said film is bioequivalent to an immediate release tablet or or orally dissolving/dispersing tablet (ODT) that comprises said active pharmaceutical agent in said defined amount.

In one embodiment, the immediate release tablet or orally dissolving/dispersing tablet (ODT) is characterized by slow or delayed bioavailability (i.e. a "slowly bioavailable drug"). The inventors have developed orally disintegrating film dosage forms which, it is believed, will unexpectedly be bioequivalent to these conventional "slowly bioavailable drugs," without any substantial modification of the release characteristics from the film dosage form, as long as the film can disintegrate when placed on the tongue within about sixty seconds. Thus, for example, the immediate release dosage form can be characterized by:

- a T_{max} (i.e. time to maximum plasma concentration) of greater than about 1.5 hours, 2.0 hours, 2.5 hours, 3.0 hours, 3.5 hours, 4.0 hours, 4.5 hours or even 5.0 hours;
- a disintegration time of greater than about 10 or 20 minutes, but less than about 90 or 60 minutes;
- a 90% dissolution time of greater than about 10 or 20 minutes, but less than about 90 or 60 minutes; and/or
- a film coating that delays the release and absorption of active ingredient from the dosage form.

Of course, the invention could also be practiced with drugs having other pharmacokinetic profiles, and in other embodiments the T_{max} of the drug is less than 3.0, 2.5, 2.0, 1.5 or 1.0 hours.

In another embodiment, the film strip of the present invention, or the immediate release dosage form, can be defined by its pharmacokinetics, and in one embodiment, the film strip or immediate release dosage form has an absolute bioavailability of greater than 65%, 75%, 85% or even 95% when administered orally. In another embodiment, the film strip or immediate release dosage form has an absolute bioavailability that is greater than about 45%, 50%, or 55%, and peak plasma concentrations (C_{max}) in less than 3.0, 2.5 or 2.0 hours. Finally, because the film dosage form is specially formulated or administered for gastrointestinal absorption, the film dosage form has a comparable absolute bioavailability or T_{max} as an immediate release tablet or capsule or orally dissolving/dispersing tablet (ODT) that comprises the same amount of active pharmaceutical agent.

The films themselves, and the methods of using the films, are characterized by a number of features that ensure their bioequivalence to a comparable immediate release tablet or capsule or orally dissolving/dispersing tablet (ODT), including:

- the films may be engineered or used so that the active pharmaceutical agent is swallowed and absorbed predominantly or entirely through the gastrointestinal tract, instead of being absorbed through the oral mucosa;
- if necessary, the films or active pharmaceutical agents may be formulated so that absorption of active pharmaceutical agent through the oral mucosa is retarded;
- the films are typically designed for rapid disintegration when taken orally, and are most often swallowed in less than thirty or sixty seconds after administration;
- the films are usually applied directly onto the tongue to promote mixing with the saliva and subsequent swallowing of the active ingredient, and thereby discourage mucosal absorption; and
- water could be aditionally swallowed within about thirty or sixty seconds after administration of the film, to further promote swallowing of the active agent and gastrointestinal absorption.

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