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(54) Title: FORMULATION AND SYSTEM FOR INTRA-ORAL DELIVERY OF PHARMACEUTICAL AGENTS

(57) Abstract: A stable formulation is disclosed that enables the effective intra-oral delivery to a patient of a pharmaceutical agent. The formulation comprises the pharmaceutical agent mixed with an orally-acceptable oral-absorption enhancer in an orally-acceptable carrier-solvent, wherein the oral-absorption enhancer is adapted to modify the surface membrane such that absorption through the surface membrane is initiated or increased. The oral-absorption enhancer may comprise hydroxypropyl-beta-cyclodextrin and surfactants including benzalkonium chloride, benzethonium chloride, polysorbate 80, sodium lauryl sulfate, Brij surfactants, Tween and Pluronic surfactants. Also disclosed is a system for delivering the formulation including a mechanism for dispensing predetermined doses of the inventive formulation intra-orally as with an aerosol or spray pump or propellant device.

FORMULATION AND SYSTEM FOR INTRA-ORAL DELIVERY OF PHARMACEUTICAL AGENTS

RELATED APPLICATIONS

This application is related to, and claims the benefit of priority under, U.S. provisional patent application Serial No. 60/119,923, filed February 12, 1999.

FIELD OF THE INVENTION

This invention relates to a formulation effective for the intra-oral delivery of pharmaceutical agents and to a system comprising the formulation in a metered-dose applicator device for dispensing the pharmaceutical agents intra-orally.

BACKGROUND OF THE INVENTION

The poor aqueous solubility and the hydrophobic nature of many therapeutic agents prevent them from being suitable for conventional oral delivery, due to their poor absorption and bioavailability. In other cases, the current means of delivery are primarily limited to parental means, often compromising the desired level of patient compliance. Many small and large molecule proteins and peptides are effective therapeutically, yet are not ordinarily easily absorbed through, or are otherwise not effective when administered through, the GI tract, including insulin, calcitonin, human growth factors, and others.

Difficulties inhere in administering certain pharmaceutical agents orally (such as proteins), as saliva and/or gastrointestinal compounds tend to degrade or digest the pharmaceutical agents, rendering them ineffective. For example, patients suffering from diabetes are required to administer insulin to themselves by injection on a

regular basis. Injection delivery of insulin and other drugs is inconvenient and can be painful, discomforting, and embarrassing.

Injectionable drug delivery also may be used to achieve a quick and efficient administration. Chronic pain management is an area where speedy drug delivery is desired. For example, there is a significant increase in the prevalence and number of cancer deaths worldwide. Pain occurs in more than 80% of cancer patients before death. Because of its high frequency, combined with the lack of availability of opioids in many countries and the under-treatment of pain, the World Health Organization declared pain a world medical emergency in 1986. Since then, emphasis has been on the appropriate treatment of cancer pain. As a result, the use of opioid analgesics has increased worldwide. Fentanyl is an opioid analgesic commonly used in chronic pain management. Currently, research is being conducted which searches for alternative means of quickly and effectively administering this drug.

Efforts to achieve quicker and more convenient methods of drug delivery have involved the development of nasal and pulmonary delivery mechanisms. These delivery mechanisms have been available for a select number of pharmaceutical agents. For example, aerosol delivery systems with various inhalation-actuated aerosol-dispensing devices have been employed for treatment of asthma, and recently they have been investigating for delivery of insulin. Such devices are breath-activated and designed for delivery to the pulmonary system. *See, e.g.*, U.S. Pat. No. 5,544,646 to Lloyd *et al.*, "*Systems for the Intrapulmonary Delivery of Aerosolized Aqueous Formulations*"; U.S. Pat. No. 5,320,094 to Laube, "*Method of*

Administering Insulin"; and U.S. Pat. No. 4,648,393 to Landis *et al.*, "*Breath Activated Medication Spray*", all of which are incorporated herein.

There remains a need for improved formulations and methods for delivering pharmaceutical agents to patients. In particular, there is a need for a quick and easy method of administration that may be used effectively for a wide range of pharmaceutical agents and that avoids long-term toxicological effects as experienced with lung delivery.

SUMMARY OF THE INVENTION

The invention comprises a formulation effective for the delivery of pharmaceutical agents through the mucosa of the intra-oral cavity comprising at least one pharmaceutical agent, one or more oral-absorption enhancers, and optionally, one or more solvent carriers, propellants (*e.g.*, where a propellant device is used for delivery), stabilizers, anti-microbial agents, and auxiliary components. The invention further relates to a system for delivering the formulation including a mechanism for dispensing predetermined doses of the inventive formulation intra-orally as with an aerosol or spray pump or propellant device.

BRIEF DESCRIPTION OF THE FIGURES

For a better understanding of the invention, exemplary embodiments are described below, considered together with the accompanying figures, in which:

FIG. 1 is a graph showing the effect of inventive formulations containing insulin administered to rats intra-orally wherein plot A reflects application of the invention and plots B,C, and D reflect controls; and

FIG. 2 is a graph showing the effects of inventive formulations containing highly purified porcine insulin administered intra-orally to two human subjects; and

FIGS. 3 and 4 are graphs showing the effects of inventive formulations containing human recombinant insulin administered intra-orally to two human subjects.

DETAILED DESCRIPTION OF THE INVENTION

Applicants have discovered a formulation that enables the delivery of pharmaceutical agents through the mucosa of the intra-oral cavity. This target site provides a large surface area and cell membranes with high permeability and significant vascularization for rapid and efficient drug absorption. The formulation of this invention comprises at least one pharmaceutical agent, one or more oral-absorption enhancers, and optionally, one or more solvent carriers, propellants (*e.g.*, where a propellant device is used for delivery), stabilizers, anti-microbial agents, and auxiliary components such as flavor enhancers typically included in orally-administered formulations. The invention further relates to a system for delivering the formulation. The system comprises a mechanism for dispensing predetermined doses of the inventive formulation intra-orally as with a pump or propellant device, which are described further below. The mechanism is referred to as a metered-dose applicator (MDA™), wherein MDA™ is a trademark of MQS, Inc., the assignee of the present application (located in Jamesburg, NJ).

The invention provides an efficient and convenient drug delivery method for many pharmaceutical agents that results in rapid onset of therapeutic action, avoids the hepatic first pass effect, and reduces the amount of drug needed for an effective

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