IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Provisional Application for United States Patent

TITLE: TRANSDERMAL DRUG DELIVERY SYSTEM (TDDS) TO DELIVER A THERAPEUTICALLY RELEVANT FORMULATION OF NALOXONE TO STOP OR REVERSE THE EFFECTS OF AN OPIOID OVERDOSE AND TO MAINTAIN STEADY-STATE LEVELS OF THE DRUG TO PREVENT OPIOID OVERDOSE OVER A PROLONGED DURATION EXTENDING SEVERAL DAYS.

INVENTOR:

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SPECIFICATION

FIELD OF THE INVENTION:

[0001] The present invention is in the field of drug delivery systems. More specifically in the field of transdermal delivery of a non-specific, competitive opioid antagonist. The invention facilitates the application of the opioid antagonist reversing the effects of an opioid overdose and maintaining a steady-state level of short half-life drugs to prevent an opioid overdose recurrence over a prolonged duration extending several days. This invention is a simple and easy to use device that can be readily available when and where it is needed most and usable by non-medical professionals.

BACKGROUND:

[0002] Opioid dependence and the abuse of and addiction to opioids and prescription pain relievers is a serious global problem that affects the health, social, and economic welfare of all societies.

[0003] Prescriptions of opioids have increased from around 76 million in 1991 to nearly 259 million in 2012 according to the Centers for Disease Control (CDC).

[0004] Naloxone (NLX) is a non-specific, competitive pure opioid antagonist and works by reversing the depression of the central nervous system (CNS) and respiratory system caused

by opioids. It was patented in 1961 and approved for opioid overdose by the Food and Drug Administration in 1971.

[0005] Until November, 2015 and the FDA approval of a naloxone nasal spray, naloxone was only approved in injectable forms. Naloxone shows a very short duration of therapeutic effect requiring frequent invasive administration of intravenous (IV)., intramuscular (IM) or intranasal (IN) delivery of the drug.

[0006] Transdermal drug delivery systems (TDDS) being non-invasive offer an improved approach to administration of drugs by maintaining a therapeutic concentration of drug in plasma over a prolonged duration extending to several days. This invention offers a simple, easy to use device that can be applied and used by anyone.

[0007] To simplify the administration of a life-saving opioid antagonist, a transdermal delivery system for naloxone is needed to enable emergency first responders, law enforcement and high-risk patients to be able to quickly administer delivery of an opioid antagonist. High-risk patients include those proscribed high doses of opioids for pain, any dose of opioid accompanied by a benzodiazepine or users of nonmedical use of opioids. TDDS offers an advantageous mode of drug delivery and drug administration by eliminating the first pass hepatic metabolism and providing sustained drug release for a prolonged period of time. Chemical formulations offer tremendous potential to enhance the transport of NLX drug molecules combined with enhanced transdermal delivery of opioid antagonists. This invention will achieve similar effectiveness as IV, IM or IN of naloxone administration in reversing both respiratory depression and depressive effects on the central nervous system caused by opioid overdose. A TDDS system can achieve therapeutically relevant levels of NLX to 1) prevent death and 2) address the rapid dissipation of the drug in IV dosing if opioid receptors are to be stopped from repeat CNS and respiratory depression.

BRIEF SUMMARY OF THE INVENTION:

[0008} Transdermal patches have long been used for the administration of small-molecule lipophilic drugs that can be readily absorbed through the skin. This non-invasive delivery route is advantageous for the administration of many drugs incompatible with oral delivery, as it allows for direct absorption of the drug into the systemic circulation, by-passing

both the digestive and hepatic portal systems which can dramatically reduce the bioavailability of many drugs. Transdermal delivery also overcomes many of the challenges associated with subcutaneous injection by greatly reducing patient discomfort, needle anxiety, risk of accidental needle stick injury to the administrator and issues surrounding needle disposal.

[0009] Despite these many advantages, transdermal delivery of drugs is confined to classes of molecules compatible with absorption through the skin. Delivery of small molecule salts and therapeutic proteins are not typically viable with traditional transdermal delivery, as the skin provides an effective protective barrier to these molecules even in the presence of absorption-enhancing excipients.

[0010] Previous attempts to deliver a controlled therapeutic dose of NLX through the skin have been unsuccessful in achieving desirable penetration rates in the high-end of the therapeutic range. Naloxone does not have optimal physicochemical properties for transdermal delivery. NLX is a non-specific, competitive opioid antagonist used to reverse opioid induced CNS and respiratory depression. NLX shows a very short duration of therapeutic effect thus requires frequent administration by IV, intramuscular, or internasal application.

[0011] The most recent approach to delivery of therapeutically relevant levels of NLX is with the application of enhanced transdermal drug delivey systems to the skin. Studies have shown that the transdermal flux of NLX can be enhanced and optimized by TDDS technology in combination with charged (protonated) drugs that have increased solubility in an acqueous patch reservoir and increased permeability through acqueous pathways facilitated by the TDDS technology.

[0012] This invention incorporates an easy to administer, acceptable shelf-life product for non-medical personnel to address two elements of opioid overdose, 1) CNS respiratory depression and 2) a steady-state level of the drug to prevent an opioid overdose recurrence over a prolonged duration extending several days. This invention is designed to be widely available to high-risk populations to reverse opioid CNS respiratory depression and to deliver a steady-state level to address the rapid dissipation of NLX resulting in an opioid overdose recurrence.

DETAILED DESCRIPTION OF THE INVENTION:

[0013] According to our invention we have discovered that therapeutic levels of a non-specific, competitive pure opioid antagonist can be delivered transdermally by topical application

of the drug in the base form to the skin utilizing enhanced trandermal delivery system technology combined with chemical enhancers to facilitate transdermal drug delivery.

[0014] Transdermal drug delivery offers a number of advantages including improved patient compliance, sustained release, avoidance of gastric irritation, as well as elimination of pre-systemic first-pass effect. However, only few medications can be delivered through the transdermal route in therapeutic amounts without the presence of chemical enhancers and enhanced transdermal drug delivery to cross the skin in therapeutically relevant amounts. Our invention is designed to achieve time to maximum plasma concentration levels, or T-Max, compared to I.M., IV and intranasal to be similar. By combining ease of use in a TDDS with the benefit of achieving steady-state levels to prevent opioid overdose recurrence over a prolonged duration extending several days.

[0015] Although NLX is currently administered by injection in the form of water soluble hydrochloride or by nasal spray, our transdermal skin penetration TDDS technology can deliver the base form of NLX with chemical enhancers to achieve therapeutically relevant dosages to reverse CNS respiratory depression from opioid overdose. TDD systems include reservoir devices, matrix devices, multiple polymer devices and multilayer matix systems to control the rate of release from the drug reservoir to the skin surface ensuring a steady-state level of the opioid antagonist to prevent recurrence of opioid CNS respiratory depression due to the mean serum half-life of NLX and thus eliminating the need for repeat IV. dosing of NLX injections.

[0016] Chemical penetration enhancers are often used in topical and transdermal formulations to enhance the absorption, uptake and delivery of active pharmaceutical ingredients (drug or drug substance) into the skin. Design of specific chemical enhancer formulations requires the comprehensive understanding of the effect of these agents on the skin permeability. It is indeed feasible to match the specific chemical enhancer formulation with the physicochemical properties of the drug to specifically enhance the permeation and uptake of the drug into the skin. Such formulations include, but are not limited to, a combination of one or more chemical enhancers; one or more solvents or vehicles that improve portioning of the drug and chemical enhancers into the skin; and a gelling agent or matrix for their incorporation as a topical or transdermal formulation. Several exemplars of chemicals under each category have been previously disclosed in the literature. However, the specific combination in which each ingredient is employed so that they match the physicochemical properties of the drug and

improve its skin penetration are neither trivial nor singularly dependent on the specific properties of the individual chemicals. It is important to note that the effect of each ingredient on skin is dependent of the concentration employed in the formulation and there are synergistic effects to be anticipated from their combination in a single formulation. These effects can be additive, positively synergistic, or negatively synergistic. This then implies that the kinetics of skin penetration and cumulative effects of the drug delivered into and across the skin from these formulations depends on the specific formulation employed. It follows, therefore, that the physiological and biological and therapeutic endpoints of the drug is determined to a large extent by the formulation in addition to the drug properties. These endpoints include, but are not limited to, the pharmacokinetics/pharmacodynamics (PK/PD), cumulative absorption as determined by the area under the curve (AUC), bioequivalence, therapeutic index (TI), to highlight a few. Furthermore, the specific formulation of the drug affects not only its potency but also the tolerance/safety on the skin on application. This can include, but is not limited to, adverse effects such as irritation, skin toxicity, erythema amongst others. The physicochemical and structural properties of naloxone indicate that it is a small molecule with reasonable hydrophobicity attributed by its aromatic nature. Chemical enhancers that improve transport of such molecules generally, but not exclusively, tend to be long chain hydrocarbons with a polar head group such as surfactants, fatty acids and fatty esters. Unsaturation (single or double) in the hydrocarbon chain can additionally aid permeation of resiquimod. Oleic acid, linoleic acid, linolinic acid, palmitic acid, myristic acid, etc. are exemplars of fatty acids. We have developed formulations to deliver a broad range of drugs across the skin. These formulations will be optimized further and/or redesigned for delivery of naloxone.

[0017] TDDS technology is currently being utilized to enhance delivery of small and large molecules. With the emergence of microfabrication manufacturing technology over the past several decades, enhanced TDDSs have been developed by academic laboratories and pharmaceutical companies. Enhanced TDDSs facilitate delivery of the drug across the skin. TDDSs are ideal for patient adherence as they do not stimulate nerves that are associated with pain. TDDSs improve patient compliance as patients with needle phobia will be more likely to apply the patch because of its painlessness. Additionally, patients can administer the drug by themselves.

[0018] Various materials suited for the fabrication of the various layers of the patch are under consideration as well as different types of enhanced TDDS technology. Another object of this provisional patent is to provide drug reservoir/permeation chemical enhancer compositions for transdermal drug delivery. In order to increase the range of drugs available for transdermal delivery the use of chemical and physical enhancement techniques have been developed in an attempt to compromise skin barrier function in a reversible manner without concomitant skin irritation.

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