Targeted Transdermal Drug Delivery Systems to Manage Regular Drug Administration and Reduce Patient Noncompliance

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Purpose

Patient noncompliance introduces human error to medicine, and limits the extent of effective clinical care. A portable, automated patch can simplify this process by regulating and dispensing the necessary amount of medication that a patient requires systemically, directly through the skin. This device will be low-profile, noninvasive, water-resistant, easy to use, affordable, and durable, in order to reduce the hassle and any possibility of patient noncompliance. The types and doses of medication must be carefully programmed by a medical professional to ensure proper treatment. Transdermally administered medication has proven to be successful in the past in the treatment of chronic pain. To test the viability of such a versatile transdermal delivery system, we will attempt to replace traditional medication for chronic obstructive pulmonary disease (COPD) patients using prednisolone. The inconvenience of frequent dosing, multiple pills, and inhalers are major contributors to noncompliance.

Background Information

Chronic obstructive pulmonary disease, or COPD, is the third-leading cause of death in the United States [1]. The patch aims to relieve acute and/or chronic asthma symptoms and treat COPD before it reaches serious and potentially life-threatening levels. There are over 3,300 deaths every year due to asthma [2] and 130,000 due to COPD [1]. Furthermore, these conditions also limit the activities patients can participate in - the patch will reduce or eliminate these limitations.

Forty-eight percent of adults who were taught procedures to avoid asthma triggers do not comply with suggestions [3]. In a study of adolescent non-compliance with asthma remedies, 45 of 49 patients admitted to "instances of non-compliance, either in the past or ongoing" [4]. Shortcomings of current treatment options lead to administrative difficulty and patient misuse. A "drug patch" applied to the skin would assist in medication compliance and provide a continuous delivery of medication.

Figure 1: Asthmatics are the largest population of patients who do not comply with physician mandated medication for their condition. Higher noncompliance rate leads to longer post-attack rehabilitation times, and higher incidences of chronic disease conditions.

Figure 2: A proposed model of a patch for transdermal drug introduction. The drug will be preserved and protected by multiple layers; additional layers will be required for patient comfort and patch durability.

Biological Background

Prednisolone is a corticosteroid used to treat many inflammatory and autoimmune conditions. It decreases inflammation by suppressing leukocytes, reducing capillary permeability, and decreasing the amount of antibodies at the site of inflammation; it is commonly used to treat arthritis, autoimmune disorders, skin conditions, cancer, allergies, and asthma [7]. It is the metabolized form of prednisone, a drug commonly prescribed as oral tablets, with dosages ranging from 5mg to 60mg. The first pass effect greatly reduces the concentration and amount of prednisolone absorbed, anywhere from 50% to 90% [8]. Oral prednisone medication must initially pass through the liver, where it is metabolized into a smaller amount of active prednisolone. Transdermal delivery will introduce prednisolone directly into the bloodstream, bypassing the first pass effect and increasing bioavailability. Transdermal delivery reduces the need for higher doses while maintaining the quality of the drug and potentially increasing the speed of care.

Figure 3: The structure of the prednisolone molecule

Figure 4: Pharmacokinetics comparison of concentration levels of tulobuterol used as a reference between oral and transdermal delivery. [5]

Engineering Principles

This project relies on the diffusion of prednisolone through the skin, comparable to the pharmacokinetics of similar oral medication. Diffusion can be modelled based on Fick's first law, with the variables of diffusivity (diffusion coefficient), concentration, and position determining flux. Flux, reported in terms of volume ($\text{m}^3 \text{m}^{-2} \text{s}^{-1}$), mass ($\text{kg m}^{-2} \text{s}^{-1}$), or diffusion rate ($\text{mol m}^{-2} \text{s}^{-1}$) per area, will be determined after the diffusion coefficient for prednisolone dissolved in solution is calculated – depending on exact chemical composition of the prednisolone mixture with preservatives, alongside its ability to diffuse through skin, the Polyethylene glycol/Propylene glycol solvent, and any chemical enhancers will vary. Other relevant design constraints are lag time, the time it takes the permeant to cross the membrane and diffuse into the receptor fluid and reach steady state, and consistent unchanging movement of the permeant across the membrane.

$$J = -D \frac{\partial c}{\partial x}$$

Figure 5: Fick's Laws of Diffusion, the standard mathematical expression is being used to determine medication concentration.

Figure 6: Comparison between oral medication and transdermally introduced medication.

Figure 7: A diffusion test chamber, to test prednisolone diffusion.

Procedure (in progress)

Experiment 1: Skin Transwell Studies, *in vitro*

- Chemical Assays of prednisolone to have a fingerprint of its structure.
- Test control to make sure experimental design is successful.
- Test solutions with varying levels of solvents (propylene glycol (PG) and DMSO) plus prednisolone, minimizing solvent.
- Apply to human keratinocyte cell line (HaCat) and evaluate for cytotoxicity via trypan blue exclusion at 2, 8, 24, and 48 hours.
- Float pig skin on growth medium, and place in clamp system to create air interface.
- Place in diffusion well and apply solutions to apical surface and take samples from the lower chamber (containing media) at 30min, 1, 4 and 24 hours. At 24 hours, homogenize skin.
- Measure the amount of drug that completely crossed the epithelial barrier and the amount that was retained in the skin, using mass spectrometry and NMR, assure that prednisolone maintained its structure.
- Calculate flux based on area and diffusion rate using Fick's Law, and diffusion coefficients and visualizations using MATLAB.

Experiment 2: Patch Prototypes

Attempt to create a sample patch that can retain the suspended solution.

- Create a patch with drug output and efficient systemic uptake, aiming to optimize flux into the body. Collaborate with UCSD engineering and materials science professors to maintain simplicity.
- Experiment with microcontrollers for constant drug administration and tapering.
- Emulate current patch technologies, including emulsions and gels.

Future Testings: In Vivo Testing, Clinical Trials

Test out solution in live mice to simulate human models with completed patch

- Hairless Mouse (shaving and balding agent, cervically dislocated).
- Apply patch with various dosages of prednisolone solution.
- Take blood samples from mice every 30 min, 1, 4, and 24 hours.
- Simulate COPD and asthma exacerbations through ablation and or abnormal air conditions.
- Measure efficacy of transdermal medication at time intervals.
- Calculate LD50 and assure safety for future human trials.

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