

Development and *In Vitro* Testing of a Novel Universal Transdermal Drug Delivery Platform to Reduce Medication Nonadherence

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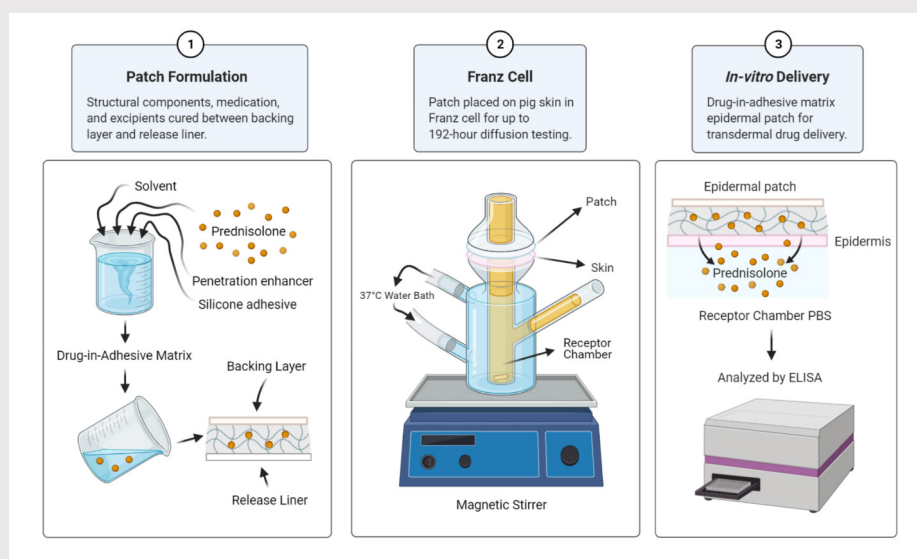
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Abstract

Medication nonadherence results in avoidable symptom exacerbations and hospitalization, causing thousands of deaths and billions of dollars in healthcare costs annually. Although pharmacological therapies are present for chronic diseases, lengthy and complicated medication regimens often have high rates of nonadherence. Transdermal drug delivery is a potential method of reducing medication nonadherence as it allows for long-course medication regimens to be simplified to a one-time epidermal patch. We have engineered a transdermal drug delivery system on a customizable platform to longitudinally deliver a wide variety of soluble small-molecule drugs. As a proof of concept, we have chosen to administer long-course corticosteroids for chronic inflammatory disease *via* epidermal patch. A drug-in-adhesive matrix consisting of the drug, adhesive, solvents, and penetration enhancers, was cured onto a fluoropolymer release liner. The transdermal drug delivery system has an integrated tapering mechanism to avoid end-of-course steroid dependence and can incorporate other small-molecule medications required for cases of polypharmacy. To date, there have been no successful attempts to develop long-term steroid patches for systemic delivery, which may be attributed to issues with patch adhesion and skin irritation over extended periods of time. We have analyzed such challenges and have designed a proof of concept system to overcome these obstacles in order to provide patients with a simple, inexpensive, and effective solution to complicated and long-term treatment regimens.

Graphical Abstract



Keywords: Transdermal; Drug; Delivery; Nonadherence; Prednisolone; Polypharmacy

Introduction

Medication nonadherence, or the patient's failure to follow the therapeutic regimen recommended by their healthcare provider, places an immense avoidable burden on the global health system [1]. The World Health Organization reports that only half of patients in developed countries are adherent to medications for chronic diseases; studies from Gambia and Seychelles report that less than 30% of patients are adherent to antihypertensives, while only 28% of Australian patients are adherent to preventive medication for asthma [2]. Such trends persist worldwide for numerous other chronic diseases, including diabetes, HIV/AIDS, and depression, increasing morbidity and mortality, while placing undue financial strain on healthcare payers. In the United States alone, up to \$300 billion of avoidable health care costs have been attributed to nonadherence, representing up to 50% of treatment failures and 10% of total healthcare costs nationwide [3,4]. Three-fourths of Americans do not take their medication as directed [5], and 125,000 deaths per annum can be attributed to medication nonadherence [6]. Nonadherence to prescribed medication is directly associated with continued deterioration of health [7] and poor therapeutic outcomes [8,9] for countless chronic illnesses [10]. Factors contributing to medication nonadherence include forgetfulness, complacency [11], complicated dosing, cumbersome or long-term regimens [12-14], prohibitively high costs [15], poor understanding of instructions [16], and difficulty of use, among others [17]. Previous studies have recognized simplification of treatment plans [18] and modifying the patient-provider dynamic to improve patient education and resultant compliance [19], but these strategies vary in efficacy by disease and patient health literacy, demonstrating the urgent need for treatments optimized to circumnavigate nonadherence.

Transdermal Drug Delivery Systems (TDDS) have long been shown to have better adherence over traditional routes of medication administration (e.g. inhaled [20], oral [21]). TDDS saw great improvements in precision and reproducibility of systemic drug administration towards the end of the 20th century [22]. Since the advent of scopolamine (hyoscine) as a topical means to manage seasickness [23], TDDS have been developed using many common drugs, including nitroglycerin [24], clonidine [25], and estradiol [26], among nearly 20 FDA approved drugs [27]. Transdermal patches have been developed for dozens of diseases [22], and therapies for many chronic conditions have taken advantage of transdermal delivery, resulting in positive outcomes for diseases such as Alzheimer's disease [28], HIV [29], attention-deficit hyperactivity disorder [30], and chronic pain [31].

Replacing a pill or inhaler with a transdermal patch has the potential to reduce medication nonadherence by reducing frequency of dosing [22], likelihood of improper use, as well as making it easier to remember, and increasing convenience [21]. Transdermal patches offer numerous benefits over conventional routes of administration: it is noninvasive, pain-free, and self-administered, and eliminates spikes and troughs of drug concentration in the blood, leading to more constant plasma drug concentration [32], thereby allowing for constant systemic effect. Transdermal patches directly introduce the drug into the blood stream, immediately making the drug available for systemic action, increasing bioavailability, bypassing the hepatic first-pass metabolic effect and gastrointestinal tract, and circumventing any contraindications related to gastrointestinal and respiratory routes of administration, such as intestinal complications present in inflammatory bowel diseases [33,34]. Given the ample benefits, transdermal drug delivery is a leading contender for the development of platforms to reduce medication nonadherence, as it would simplify delivery of existing medications.

In the case of chronic respiratory syndromes, improper use of inhalers and complex dosing regimens may increase medication nonadherence. Month-long steroid regimens are often prescribed to prevent exacerbations following Chronic Obstructive Pulmonary Disease (COPD)-related hospitalizations. Up to 50% of COPD patients do not take nebulized treatments - many patients overuse, underuse, forget, or deliberately alter their regimen [35], preferring simpler, less frequent administrations of oral or injected medicine. This makes COPD patients an ideal target population to test a novel TDDS to address medication nonadherence. An adhesive epidermal patch that is waterproof, light, durable, and discreet would reduce aversion from self-medication, and would not require diligent patient activity to ensure regular medication administration. There are currently no specific mechanisms in place to reduce medication nonadherence in patients with long-term steroid prescriptions. Our current model aims to simplify Prednisolone delivery by transporting the drug directly into the bloodstream *via* a noninvasive skin patch. Prednisolone is a viable candidate for transdermal delivery as it is of low molecular weight and moderately lipophilic [36,37]. Prednisolone is the downstream metabolite of the prodrug prednisone. Conventional oral administration of prednisone results in hepatic metabolism into prednisolone, the biologically active form. Using concentrated prednisolone and transdermal administration directly into the bloodstream reduces the first-pass hepatic metabolism effect and reduces the necessity of high pre-metabolic doses, both of which would be necessary when using oral prednisone. prednisolone will be stored and introduced with a cocktail of chemical excipients to ensure skin-safety and reduce systemic side-effects. As transdermal systems offer an affordable and easy-to-use means of reducing medication nonadherence, a TDDS built on a customizable platform to deliver a wide variety of medications could fulfill the needs of countless patients. Using a TDDS to simplify the process of self-medication and reducing patient effort could be an efficient way of reducing medication nonadherence without depending on the patient's health literacy.

Components

We have developed a discreet, durable transdermal drug delivery patch with an integrated tapering mechanism that will allow patients to apply a single patch for the entire duration of their medication regimen. By reducing the amount of patient interaction with the medication, and by essentially allowing the patient to forget about the therapy, we eliminate the major causes of medication nonadherence, which include forgetfulness and conscious decision-making in medication administration.

Drug-in-adhesive matrix

The drug-in-adhesive matrix is composed of several components: the corticosteroid used is prednisolone (MilliporeSigma, St. Louis, Missouri, USA), a metabolite of prednisone, that is commonly used as anti-inflammatory or immunosuppressant medication for numerous systemic conditions. The adhesive is BIO-PSA MD7-4602 silicone adhesive (Dow Corning, Midland, Michigan, USA) as it provides a high tack, non-toxic base for our TDDS and is commonly used in the clinical setting [38,39]. Ethyl acetate (MilliporeSigma, St. Louis, Missouri, USA) is used to dilute the adhesive, control viscosity, and make the mixture homogenous before it is evaporated off by degassing. A small amount (<10%) of DMSO (MilliporeSigma, St. Louis, Missouri, USA) is used to dissolve prednisolone into the solution as well as to enhance skin permeability [33,40-43]. Polyoxyethylene (20) oleyl ether (MilliporeSigma, St. Louis, Missouri, USA) is a penetration enhancer and plasticizer, which allows for control of the consistency of

the solution. Isopropyl myristate (MilliporeSigma, St. Louis, Missouri, USA) is another penetration enhancer used in our TDDS to further push medication into and past the skin [33,44,45].

Using proprietary combinations of these ingredients in our matrix allows us to control dosages that are released over allotted periods of time. Further layering of different concentrations of each component allows for time-mediated delivery of various concentrations of the drug. As we can modulate both the concentrations within each layer and the layering order, we can deliver numerous sequential doses of medication all in a single patch. Higher concentrations of prednisolone can be delivered and subsequently tapered to lower dosages as the layers pass into the skin. We can also vary the width of each layer of drug-in-adhesive matrix, as well as concentration of medication, penetration enhancers, and other excipients, offering control over temporal administration of a particular dose. With two or more drug-in-adhesive matrices, as medication is delivered through the skin, layers of progressively lower drug concentrations will pass into the bloodstream over time. The formulation is easily customizable as each excipient and non-pharmacologic component interacts amicably with a wide variety of corticosteroids.

Dressing

Tegaderm is a dressing widely used in clinical settings, often to secure and protect intravenous lines and catheter sites, as well as to cover wounds. We are using Tegaderm (3M, Maplewood, Minnesota, USA) to secure the patch to the site of application. Tegaderm conforms well to the skin that it is applied to, and increases skin hydration to promote transdermal penetration [46]. This ensures a watertight seal while protecting the TDDS from the environment. The Tegaderm material is flexible and comfortable, allowing the patient full range of mobility; at the same time, durability of the patch is not sacrificed.

Backing layer

The backing layer we have chosen is the 3M Scotchpak 9723 Backing Polyester Film Laminate (3M, Maplewood, Minnesota, USA). The backing layer was specifically chosen because of its inherent properties and interactions with our drug-in-adhesive matrix, including good oxygen and moisture-vapor transmission [39]. This means that comfort for the patient is improved as the skin on which the TDDS is applied will not dry out as easily as with other backing layers. The backing layer also has high enhancer resistance, improving transdermal drug delivery. The backing layer is heat sealable, and formulated to resist leaching of the drug.

Release liner

The release liner we have chosen is the 3M Scotchpak 9755 Fluoropolymer Coated Polyester Film (3M, Maplewood, Minnesota, USA). The fluoropolymer coating allows for complete separation of our drug-in-adhesive matrix from the liner when the patch is peeled, assuring that no medication is lost in the process of preparing and applying the patch. The liner has also been found to maintain chemical stability and is compatible with our chosen silicone adhesive [38,47].

Tapering

The drug delivery tapering mechanism is integrated into the TDDS by layering drug-in-adhesive matrices of varied drug concentration in a single TDDS, so that the patient does not have to remember to replace the patch with a lower dosage patch in order to achieve tapering. The components of the TDDS, including the high tack adhesive, that will prevent reduction of adhesion to skin over time, and a flexible and

breathable backing layer that allows for long term comfort, address the FDA's main concerns about TDDS in today's market [48].

Formulation and Testing

Patients have shown through numerous studies over a broad range of different medical conditions that the adherence rate to TDDS-based delivery systems is up to 90.3%, over 20% greater than other forms of drug delivery [20]. Clinical trials are necessary to confirm that our specific TDDS also reduces medication nonadherence in the target patient population.

The prednisolone, penetration enhancers, and other excipients were dissolved into the silicone adhesive. The current prototype is a drug-in-adhesive matrix, where all components are incorporated into monolithic strata between the release liner and the backing layer (Table 1). The 3M backing layer and release liner and the Dow Corning adhesive are the most effective components currently available on the market (highest tack, medical grade, most durable, compatible with excipients). Other TDDS currently use similar Dow Corning adhesives, with different solvents (heptane vs. ethyl acetate) and different bases (acrylic vs. silicone), and similar release liners (fluorosilicone vs. other fluoropolymer).

The patch solution is cured onto the backing layer, and a removable release liner was placed atop in order to maintain sterility and adhesion. The release liner was tested through repeated peeling to verify that the drug/adhesive solution maintains attached to the backing layer (data not shown). The surrounding Tegaderm dressing ensures that the patch will securely adhere to the skin of the patient for one week. The adhesive properties of the patch augment those of the Tegaderm assuring the entire system will be secured properly through physical activity. Moreover, the waterproof properties of the Tegaderm dressing further ensure strong adhesion to the skin for over seven days of daily activity (Figure 1).

Table 1: Transdermal drug delivery system components. Listed are the materials comprising the drug-in-adhesive matrix, as well as the materials used as the dressing, backing layer, and release liner. Each component is the current industry standard or next-generation equivalent in transdermal drug delivery system manufacturing, from companies such as 3M and Dow Corning which supply adhesives and liners for current FDA-approved transdermal drug delivery systems.

Component	Function	Category	Supplier
Prednisolone	Medication	Drug-in-Adhesive Matrix	MilliporeSigma
BIO-PSA MD7-4602 Silicone Adhesive	Adhesive	Drug-in-Adhesive Matrix	Dow Corning
Ethyl acetate	Solvent	Drug-in-Adhesive Matrix	MilliporeSigma
Dimethyl sulfoxide	Solvent	Drug-in-Adhesive Matrix	MilliporeSigma
Polyoxyethelene (20) oleyl ether	Penetration enhancer	Drug-in-Adhesive Matrix	MilliporeSigma
Isopropyl myristate	Penetration enhancer	Drug-in-Adhesive Matrix	MilliporeSigma
Tegaderm	Securement	Dressing	3M
Scotchpak 9723	Polyester film laminate	Backing Layer	3M
Scotchpak 9755	Fluoropolymer-coated polyester film	Release Liner	3M

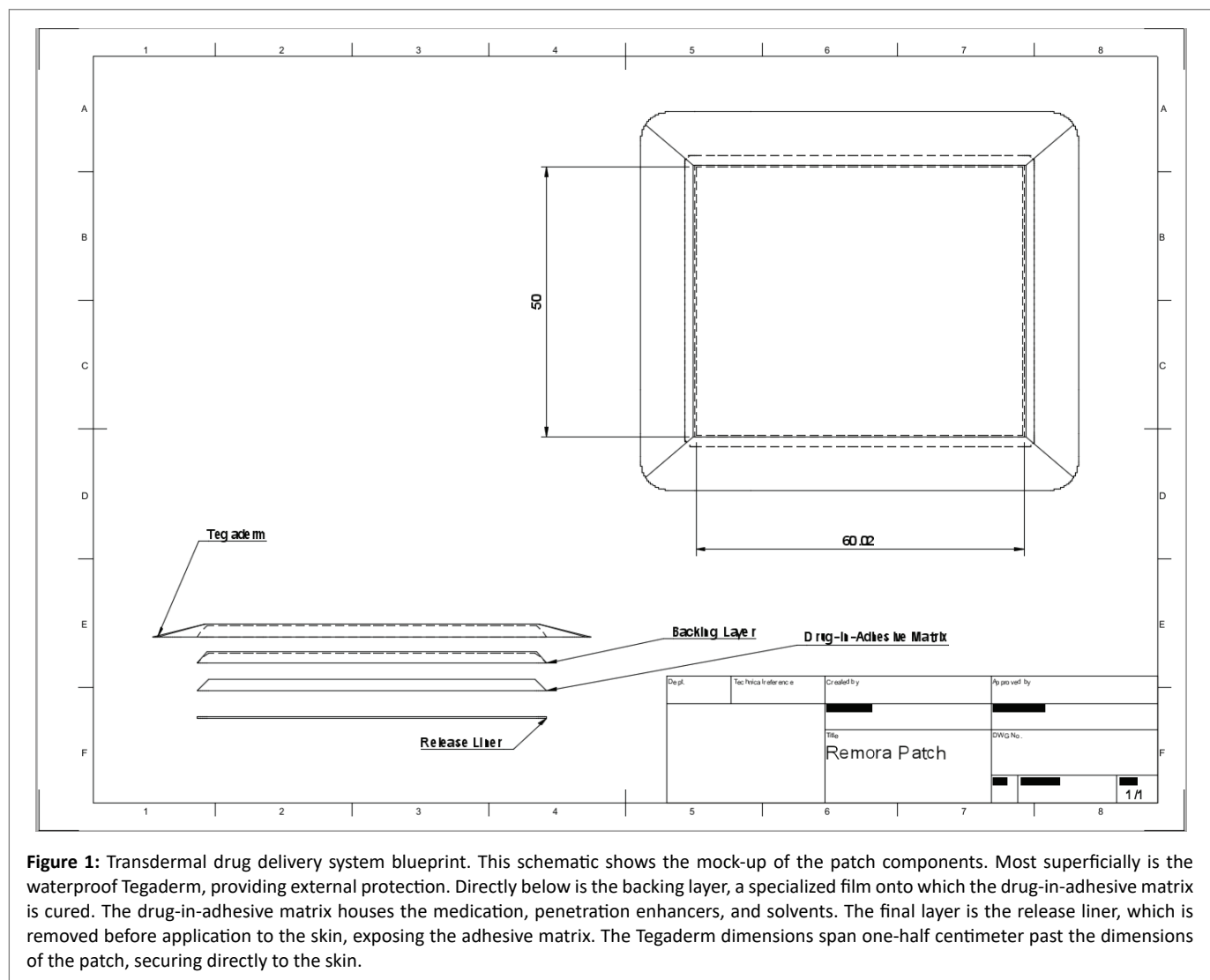


Figure 1: Transdermal drug delivery system blueprint. This schematic shows the mock-up of the patch components. Most superficially is the waterproof Tegaderm, providing external protection. Directly below is the backing layer, a specialized film onto which the drug-in-adhesive matrix is cured. The drug-in-adhesive matrix houses the medication, penetration enhancers, and solvents. The final layer is the release liner, which is removed before application to the skin, exposing the adhesive matrix. The Tegaderm dimensions span one-half centimeter past the dimensions of the patch, securing directly to the skin.

The final TDDS prototype was placed on pig skin (Midwest Research Swine LLC, Glencoe, Minnesota, USA) for 1 week. The adhesive properties of the patch were maintained for at least seven days, as the patch was forcibly peeled off the skin for removal at this time-point (repeated twice more with similar results).

To test the medication administration ability of this system, *in vitro* testing was conducted by placing a 1 cm² square patch on top of pig skin within a Franz Cell simulating physiological conditions at 37°C with a constant flow of phosphate buffered saline. Preliminary efficacy of the TDDS was determined over short periods of time. Samples were taken out of the cell at various time points and prednisolone concentrations were analyzed *via* Enzyme Linked Immunosorbent Assay (ELISA, MyBioSource, San Diego, CA, USA). The prednisolone ELISA kit is a competitive assay that comes pre-coated with a monoclonal anti-prednisolone antibody and utilizes a prednisolone-HRP conjugate as an inhibitor antigen. Samples are co-incubated with the conjugated prednisolone-HRP antigen, allowing for the prednisolone in the sample or the HRP conjugate to competitively bind to the well-bound antibody. After decanting and washing, an HRP substrate enzyme is added to the wells initiating a reaction that results in a blue colored complex. A stop solution is then added in order to halt the reaction, resulting in a yellow colored complex. Using a microplate reader,

the wells are measured spectrophotometrically at 450 nm. The intensity of the color is inversely proportional to the concentration of prednisolone, which is found using a standard curve plotted from the measurements of the provided concentration standards, allowing for the quantification of prednisolone concentration.

Prednisolone concentration increased over a tested seven day period in which our prototype TDDS delivered medication through pig skin and into the receptor chamber of the Franz Cell. Measurements were taken in triplicate and averaged once quantified at time points of hours 0, 1, 2, 4, and 8. Prednisolone was delivered at a constant rate over this period, indicated by a positive linear trend of prednisolone concentration within the receptor chamber.

To further explore the efficacy and long term ability of the TDDS, samples were taken over week-long period to be further analyzed through Mass Spectrometry (MS). MS accurately detects and quantifies molecules and chemical compounds through the measurement of mass-to-charge ratio of ions. The liquid samples from the Franz Cell receptor chamber were charged before being accelerated within the mass spectrometer and subsequently deflected by a magnetic field. The molecules of the sample can be correlated using known standards. Samples were taken from the Franz Cell at hours 2, 4, 8, 36, 72 (day

3), 144 (day 6), and 192 (day 8) and analyzed using MS courtesy of a partner laboratory. Concentrations of prednisolone were plotted against their time points and a model of the transdermal activity of the TDDS was created using semilogarithmic, nonlinear regression (Figure 2). Over a week-long period, prednisolone concentration within the Franz Cell began to flatten out after a brief period of relatively quick transdermal activity.

Discussion and Conclusion

Our TDDS is a unique extension of the already existing generic transdermal medication delivery system. Previously patented TDDS currently in the market do not offer tapering and flexibility with the use of different dosages and medications, novel inclusions in our TDDS prototype. There exist no specific nonadherence-reducing systems in place for long-term steroid regimens. Currently, the standard method of delivering prednisone is through oral tablets, which patients often forget to take - our TDDS is a replacement for this method of administration. The first-pass hepatic metabolism effect also requires that oral pills contain more medication than our TDDS, as drug concentration is greatly reduced when it is passes through the digestive tract and liver. There are presently fewer than 30 transdermal drug delivery systems on the market, most commonly for birth control and to alleviate nicotine addiction-our TDDS is implementing a therapeutic for an extremely common corticosteroid with a complex tapering regimen, and will eventually encompass other long-term medications with high rates of nonadherence, a market void that has not been filled, even with documented evidence of higher adherence to TDDS than traditional therapies.

Non-esterized prednisolone has been shown to have negligible binding within the skin in mouse models [49]. Although transdermal delivery of steroids such as estradiol and testosterone have been well studied, local effects of prednisolone will need to be evaluated in animal models and clinical testing of our TDDS as few studies have evaluated

any dermal side-effects of prednisolone. Matrix patches are typically associated with fewer skin reactions than earlier reservoir patches due to improved air circulation and absence of alcohol-based solvents [50]. Studies on similarly designed TDDS delivering hormones have established low risk of skin irritation, pruritis, urticaria, and did not notice local effects of the medication [51-53]. Mild sub-acute irritation and erythema have been observed in patch formulations lacking drug as well, indicating that occlusion by the patch itself may contribute to skin irritation, while any local dermal effects by the drug were reversible [54]. As prednisolone can be used as a topical anti-inflammatory (although hydrocortisone is preferred), local adverse dermal effects are rare, and reported in less than 4% of cases [55]. Data from the National Poison Data System evaluating TDDS safety suggests that Fentanyl-containing patches are more likely to be abused and are more highly associated with death, a drug that is not present in the described TDDS [56].

Pharmacokinetic parameters obtained from transdermal prednisolone administration in rats have shown that a 3mg/10cm²/patch, testing 30cm² patches (about 9 mg prednisolone per patch), delivers the same peak plasma concentration as a 10 mg/kg oral dose of prednisolone [57]. The oral formulation peaks in plasma concentration at 1000 ng/mL within the first hour and diminishes to <50 ng/mL within 5 hours. The patch maintains a plasma concentration between 100-1000 ng/mL over the course of 24 hours, with a peak after 7 hours and a gradual decline afterwards.

Current platforms for TDDS include iontophoretic systems, which use an electrical current to drive transdermal drug delivery; these are currently in development and require either a triboelectric nanogenerator or power supply to modulate drug delivery [58]. Microneedle technologies have successfully delivered vaccines but are more complicated to manufacture and require microscopic penetration of the stratum corneum [59]. Proniosomal patches offer benefits over liposome-based TDDS, but are currently rudimentary and have not been shown to be effective with a wide variety of drugs [60,61]. Current technology in transdermal steroid delivery, outside of matrix-based patches, is currently comprised of liposome-mediated delivery and nanoparticle formulations [62,63]. Drug-in-adhesive matrices are easier to manufacture and are backed by decades of research and development; furthermore, their individual components are more widely available and less expensive due to commercial competition and non-proprietary availability.

We expect that this TDDS would be reimbursable by Medicare and Medicaid. Currently oral prednisone pills are either fully or partially covered by Medicare Part D. Because prednisone is a widely used drug that treats numerous different conditions, prednisone is often covered by Medicare. Medicare Part D plans specify coverage over drugs that fall into six categories: antidepressants, antipsychotics, anticonvulsants, antiretrovirals (AIDS treatment), immunosuppressants and anticancer. Prednisone and its metabolite prednisolone are both anti-inflammatory drugs and therefore fall under the category of immunosuppressants. TDDS which are no longer covered by Medicare/Medicaid are transdermal drug delivery systems that are not primarily aimed to alleviate debilitating conditions such as systemic inflammation, as our TDDS will.

Validation of our prototype and clinical usage of our platform will require: further *in-vitro* testing of liquid chromatography-mass spectrometry of the release liner to ensure absence of steroid, digital adhesion testing in order to quantify the adhesive properties of the

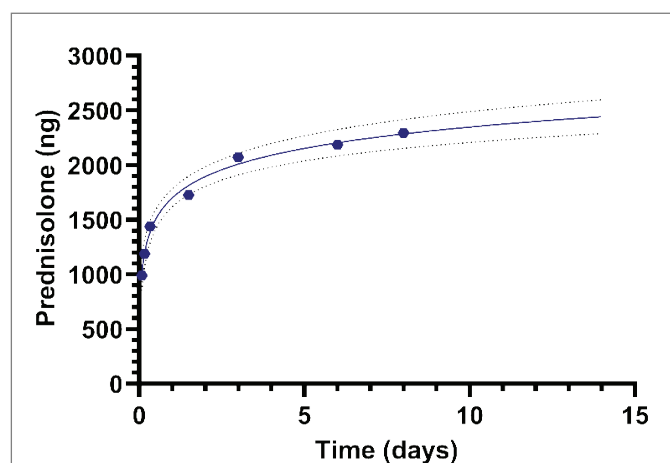


Figure 2: Prednisolone concentration over time in Franz Cell Receptor Chamber. Samples were taken from the Franz Cell at hours 2, 4, 8, 36, 72 (day 3), 144 (day 6), and 192 (day 8) and were analyzed and quantified *via* mass spectrometry. The plotted points signify actual concentration of Prednisolone within the sample at the respective time point. The solid line is the graphed, semilogarithmic, nonlinear regression model of TDDS transdermal activity with equation $Y = 1699 + (648.5) * \log(X)$, with the dotted lines indicating confidence bands in-between which the likely location of the true curve can be found at 99% confidence level.

TDDS at a variety of time points, mass-manufacturing technique to produce sufficient units to begin *in vivo* testing, and animal testing and subsequent clinical trials.

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Declarations

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Conflicts of interest/Competing interests

P.A. has received research support from the National Institutes of Health, has received research support and consultancy fees from and has been on advisory boards for AstraZeneca and GlaxoSmithKline; has received consultancy fees from Ambrx; receives royalties from UpToDate; and has received honoraria from WebMD/Medscape, AHK, Prime CME, Rockpointe, MJH Life Sciences, and Vindico. G.R., A.Z., S.V., and N.L. report no conflicts of interest or competing interests.

Authors' contributions

G.R., A.Z., S.V., and P.A. contributed to the conception, design, and experimental execution and manuscript writing and editing. N.L. contributed to the experimental execution of this manuscript.

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