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Sustained epidermal powder drug delivery via skin microchannels☆

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ABSTRACT

Transdermal delivery of hydrophilic drugs is challenging. This study presents a novel sustained epidermal powder delivery technology (sEPD) for safe, efficient, and sustained delivery of hydrophilic drugs across the skin. sEPD is based on coating powder drugs into high-aspect-ratio, micro-coating channels (MCCs) followed by topical application of powder drug-coated array patches onto ablative fractional laser-generated skin MCs to deliver drugs into the skin. We found sEPD could efficiently deliver chemical drugs without excipients and biologics drugs in the presence of sugar excipients into the skin with a duration of ~12 h. Interestingly the sEPD significantly improved zidovudine bioavailability by ~100% as compared to oral gavage delivery. sEPD of insulin was found to maintain blood glucose levels in normal range for at least 6 h in chemical-induced diabetes mice, while subcutaneous injection failed to maintain blood glucose levels in normal range. sEPD of anti-programmed death-1 antibody showed more potent anti-tumor efficacy than intraperitoneal injection in B16F10 melanoma models. Tiny skin MCs and 'bulk' drug powder inside relatively deep MCCs are crucial to induce the sustained drug release. The improved bioavailability and functionality warrants further development of the novel sEPD for clinical use.

1. Introduction

Oral administration remains the most popular route for drug delivery due to its convenience and non-invasiveness [1]. Yet, drugs delivered orally can be extensively degraded in the gastrointestinal tract (GI) and metabolized in the liver before reaching systemic circulation. The GI tract degradation and first-pass metabolism present significant challenges for oral delivery of certain chemical drugs and most of the biologics drugs. Transdermal delivery has been actively pursued for alternative drug delivery with following advantages [2]. Firstly, transdermal delivery bypasses first-pass metabolism and avoids the harsh environment of the GI tract, potentially improving drug bioavailability. Most biologics drugs are compatible for transdermal drug delivery. Secondly, skin has a large surface area and is readily accessible. Thirdly, transdermal delivery can sustain drug release and potentially reduce dosing frequency. Sustained release is also likely to reduce peaking plasma drug levels and drug toxicity. Lastly, transdermal delivery can be needle-free, painless, and self-applicable with good patient compliance.

Despite these advantages, only a limited number of small hydrophobic drugs, like nicotine, fentanyl, and lidocaine, are approved for transdermal delivery [2,3]. This is mainly because the superficial Stratum Corneum (SC) layer of the skin is impermeable to most of the hydrophilic molecules due to its highly compacted lipid structure [4]. While the SC layer is essential to protect from environmental pathogen invasion, it also presents as a formidable barrier for transdermal drug delivery. Different methods, like hydration, chemical enhancers, tape stripping, electric current, and ultrasound, have been explored to disrupt SC layer to facilitate transdermal drug delivery [2,3,5–9]. Despite years of research and development, little success has been achieved in this field either due to low efficient SC ablation or induction of skin irritation or other adverse reactions [2,3].

Lasers have been explored to facilitate transdermal drug delivery [10,11], but face similar challenges as mentioned above. In this regard, a low-fluence laser induces quick skin recovery, but it is unable to efficiently ablate SC layer [10,12]. On the other hand, a high-fluence laser can efficiently ablate SC layer, but has a high risk of skin damage and infection [10,12,13]. This dilemma is efficiently addressed by the advent of an ablative fractional laser (AFL) technology. AFL is based on Fractional Photothermolysis [14], an innovative concept in skin resurfacing field. Instead of illuminating big laser beams with a few millimeters in diameter for full-surface SC ablation, AFL emits an array of focused laser beams with ten to hundred micrometers in diameter to vaporize tiny skin tissues and generate microchannels (MCs) in the skin surface [12, 15,16]. These MCs can span from skin surface to deep epidermal or dermal tissue, depending on laser conditions. The micro-fractional laser ablation spares the majority of the skin and causes minimal skin reactions, leading to complete and fast skin recovery in 2– 3 days [12,15,16]. The efficient SC ablation and quick skin recovery make AFL an attractive technology for transdermal drug delivery.

☆ The authors have no conflict of interest to declare.

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In the last decade, AFL has been found to efficiently enhance transdermal delivery of a variety of hydrophilic molecules, including small chemicals, macromolecules, and nanoparticles [12,15–17]. Different dosage forms, like liquids, gels, lotions, and creams, show good delivery across AFL-treated skin [12,15–17]. In pursuit of a more convenient and controlled delivery platform, we explored powder drug delivery through AFL-generated skin MCs [18,19]. In that study powder drugs were coated onto adhesive patch surface in the same pattern as AFL-generated skin MCs [18,19]. Powder drug-coated array patches were then topically applied onto AFL-generated skin MCs to deliver drugs into the skin via these MCs [18,19]. We found the micro-fractional epidermal powder delivery (EPD) is capable of delivering both small chemicals and macromolecules into the skin with >80% drug doses delivered within 1 h [19]. However, due to the limited surface coating, the amount of drugs that can be delivered per patch is rather low and may not be practical for high-dose drug delivery in humans. To increase the delivery capacity, this study explores the coating of powder drugs into high-aspect-ratio, micro-coating channels (MCCs) and then investigates drug delivery efficiency, pharmacokinetics, and bioavailability in preclinical animal models. We found the volumetric coating significantly improved drug coating capacity and prolonged drug release to ~12 h. Small chemicals can be directly coated for high efficient delivery, while sugar excipients are required to induce high efficient delivery for biologics. Remarkably, the sustained epidermal powder delivery (sEPD) was found to significantly improve drug bioavailability and functionality *in vivo* when compared to oral or injection delivery.

2. Materials and methods

2.1. Reagents

Sulforhodamine B (SRB, 230161), ovalbumin (OVA, A5503), zidovudine (AZT, A2169), mannitol (M4125), sucrose (S9378), trehalose (T5251) were purchased from Sigma (St. Louis, MO). AZT internal standard 3′-azido-3′-deoxythymidine (AZT-IS, MG103) was purchased from Moravek Biochemicals (Brea, CA). Anti-mouse programmed death (PD)-1 (CD279) antibody (clone RMP1-14) and rat IgG2a isotope control were obtained from Bio X Cell (West Lebanon, NH).

2.2. Animals

BALB/c and C57BL/6 mice (male, 6–8 weeks old) were purchased from Charles River Laboratories (Wilmington, MA). Animals were housed in animal facilities of University of Rhode Island (URI) and anesthetized for hair removal, laser treatment, and patch application. All animal procedures were approved by Institutional Animal Care and Use Committees of URI.

2.3. Laser device

An UltraPulse Fractional CO_2 Laser (Lumenis Inc.) was used in this study to generate patch MCCs and skin MCs.

2.4. Patch preparation, coating, and extraction

A 750 μm-thick polycarbonate patch laminated with an adhesive layer was exposed to 5 pulses of AFL laser at 40 mJ energy and 5% coverage to generate 9×9 array of MCCs in 6×6 mm^2 area. Drug powder was repeatedly pushed into these MCCs with a spatula until full. Powder-coated 9×9 array patches were directly applied or cut into four 4×4 array patches and then applied onto AFL-treated skin. Powder array patches were immersed into phosphate buffer saline (PBS) with agitation to extract coated or remaining drugs.

2.5. Patch application

Dorsal mouse skin was exposed to AFL at 5 mJ energy and 5% coverage to generate 4×4 MCs in 2×2 mm^2 skin area unless otherwise specified. Powder array patches were then topically applied on the laser-treated skin with patch MCCs and skin MCs aligned. Patches were then firmly pressed on the skin to ensure a tight patch/skin contact. A narrow bandage was used to keep patches in position before removal at indicated times.

2.6. Gelatin skin model

Gelatin powder from porcine skin (60 bloom, type A, Electron Microscopy Sciences) was dissolved in warm water and then poured into 35 mm Petri dishes to form 5% gel with ~1 cm in thickness.

2.7. In vitro Franz cell system

Franz cell system with orifice diameter of 5 mm and recipient chamber volume of 1.5 ml were custom-made by PermeGear. Patch-applied skin was excised and mounted onto the surface of the recipient chamber. Donor chamber was laid atop and assembled with the help of a clamp. PBS (1.5 ml) was added into the recipient chamber and bubbles were removed to ensure full skin contact with PBS. PBS in the recipient chamber was continuously stirred. At different times, 100 μl solution was removed from the recipient chamber for quantification of drug concentrations. Equal volume of fresh PBS was added back to maintain an equal volume during the entire study.

2.8. Serum SRB quantification

Blood was collected into heparin-containing tubes and quickly centrifuged to separate serum from blood cells. Fluorescence intensity of SRB was measured at 565/585 nm after 1:20 dilution of serum samples into PBS.

2.9. Oral gavage

Oral gavage was performed following a published protocol [20]. In brief, mice were restrained and a sterile plastic mouse-specific feeding tube (Cadence Science, Inc.) was inserted and advanced into the stomach. Solutions were slowly injected and feeding tube was pulled out afterwards.

2.10. LC-MS/MS quantification of AZT

Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was used to quantify AZT levels as reported [21]. Patch extracts and AZT standards (5, 20, 50, 100, 200, 400 ng/ml) were mixed with 100 ng/ml AZT-IS. Serum samples were diluted by 20 times, mixed with 100 ng/ml AZT-IS, filtered through 10 kDa cutoff Amicon filter. Samples were loaded into an AB Sciex 4500 QTRAP LC-MS/MS equipped with Shimadzu LC-20AD pumps and a QTRAP 4500 System. A Synergi Hydro-RP 80A, 2.0 × 150 mm, 4 μm particle size analytical column (Phenomonex, Torrance, CA) was used for sample separation. Acquisition was performed in multiple reaction monitoring (MRM) mode using m/z 268/127 for AZT and 271/130 for AZT-IS detection. A standard curve was generated by plotting peak area ratios of AZT to AZT-IS against AZT concentrations and used to quantify AZT levels in unknown samples.

2.11. Insulin biotinylation

Insulin (Humalog, insulin lispro injection, Eli Lilly & Co, Indianapolis, IN) was biotinylated using EZ-link Sulfo-NHS-biotinylation kit (Thermo Scientific, Rockford, IL) by following manufacturer's instructions.