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Perspective: Materials and Electronics Gaps in Transdermal Drug Delivery Patches

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Transdermal drug delivery systems offer a noninvasive method of delivering drugs through the skin surface, which circumvents problems associated with metabolic breakdown, uncontrollable biodistribution after initial drug administration, and limited patient compliance. The most common implement for transdermal drug delivery is the transdermal patch (TDP), which is a flexible, medicated adhesive patche that can be placed on any available skin surface for targeted delivery. In this perspective, we summarize the most recent advancements in transdermal drug delivery patches and highlight gaps that can be filled with advanced sensor development.

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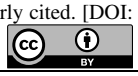

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Transdermal drug delivery systems have drawn much attention as a noninvasive method of delivering drugs through the skin surface, which circumvents problems associated with metabolic breakdown, uncontrollable biodistribution after initial drug administration,[1] and limited patient compliance.[2] The most common implement for transdermal drug delivery is the transdermal patch (TDP), which are flexible, medicated adhesive patches that can be placed on any available skin surface for targeted delivery and disposed after drug administration.[3] Over the past few decades, selected TDPs have matured into the commercial market, including nicotine patches for nicotine cessation, fentanyl patches for pain relief, scopolamine patches for motion sickness, and a variety of skin-care masks for dermal barrier repair. These transdermal patches allow rapid and effective self-administration of a limited set of small-molecule therapeutics, resulting in perceptible alleviation of associated symptoms and, therefore, high patient compliance.

Despite the commercial success and effectiveness of these aforementioned TDPs, the TDP form factor is not widely pursued for emerging therapeutics. The main limitation posed by a TDP is attenuated mass transport through the dermal barrier, the management of which necessitates a number of added physical and chemical considerations during patch/drug design and/or the use of sophisticated electronic control systems. For example, to mildly improve the yield of passive therapeutic diffusion through the dermal barrier, researchers have proposed the use of both microneedles to act as physical permeation enhancers in TDPs and covalently-attached drug structure modifiers to act as chemical permeation enhancers. Sophisticated electronic systems that temporarily disrupt the fidelity of the dermal barrier to allow for active therapeutic delivery are also under investigation. Although these methods can enhance the transdermal delivery of some model therapeutics, there remain many materials and electronics gaps that inhibit further proliferation and practical use of transdermal patches for broad-scope drug delivery.

In this perspective, we summarize the most recent advancements in transdermal drug delivery patches and highlight major areas that, we believe, could benefit from focused materials and technology development efforts.

Current Status

All known TDPs have four basic components: an outer, occlusive backing layer, a solid matrix or liquid reservoir where the drugs are stored, an adhesive layer, and a release liner. Figure 1 depicts the major components of a TDP after the release liner has been removed and the patch applied to the skin. Two major strategies to create the drug storage layer are known: liquid reservoirs and solid matrix clathrates.[4] Liquid reservoir patches, as the name insinuates, contain a liquid reservoir in which solvated drugs are loaded. For solid matrix patches, drug targets are typically clathrated within a polymer membrane.

Backing layer.—The backing film is the furthest away from the skin and serves as a protective layer for the entire TDP while still maintaining high flexibility and support.[4] Materials for the backing layer need to be carefully selected to maintain adhesion to the drug reservoir/matrix while still offering high breathability and flexibility for the user. The backing films are made of chemically inert polymers to prevent side reactions with the drugs, the polymer matrix, and the drug reservoir. The backing layers are roughly 1–10 mm thick, with the preferred thickness falling between 3–6 mm to ensure wearer comfort.[5] This layer consists of synthetic and natural polymers like polyethylene, polyester, gelatin, or various functionalized cellulosics.[6] Synthetic polymers are typically used for their superior mechanical strength, flexibility, and low water vapor transport rate, which helps to increase the diffusivity of the drugs into the skin. However, low water vapor transport rates translate to poor perceived user comfort and, therefore, in certain contexts, bioderived polymers are preferred backing materials to improve user comfort and ensure patient compliance despite comparatively unideal drug diffusivity.[7]

Polymer matrix and drug reservoir.—The drug reservoir or drug-clathrated polymer membrane is located between the backing layer and the adhesive layer. TDPs with liquid drug reservoirs are typically used in conjunction with microneedle arrays to effect cargo delivery. We discuss microneedles in further detail in the subsequent section.

Drug-clathrated polymer gels and membranes are comparatively predominant. Drug-clathrated polymer membranes have been shown to accommodate loading capacities of ca. 1% weight per unit volume (w/v)[8,9] at membrane thicknesses of ca. 0.10 mm.[10] These membranes are comprised of natural and synthetic polymers, such as poly(ethylene glycol), chitosan, and various poly(acrylates).[7] These polymers offer high biocompatibility, provide mechanical support and acceptable drug solvation/containment, and can control the rate of drug diffusion/release into the stratum corneum via tunable chemical/physical interactions with the cargo.[3] The diffusion rate of the drug cargo within/through the membrane has been modulated via host-guest electrostatic interactions or mechanical swelling/shrinking of the matrix due to osmotic pressure.[11]

Drug-loaded hydrogels are frequently employed due to their highly-crosslinked and porous structures. This porosity allows the

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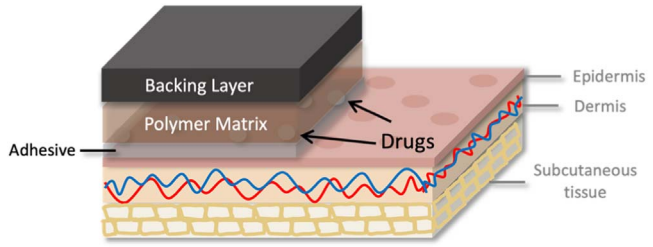

Figure 1. The major components of a transdermal patch when placed on the skin.

drugs to be loaded into the gel matrix at higher concentrations.[12] Specifically, hydrogels can exhibit drug-loading capacities of upto 50% higher than other conventional drug delivery systems.[13] Further, since the porosity of hydrogel matrices can be tuned over a wide range, control over the rate of drug diffusion can be effected with carefully selected synthesis and processing parameters. The types of polymers used in hydrogels consist of both synthetic and natural polymers, like poly(ethylene glycol) and chitosan.[14]

A secondary rate-controlling membrane can also be used to control the rate of drug delivery/diffusion into the skin, while the drug-loaded gel/membrane simply serves as a high-capacity storage layer. Such a secondary membrane controls the rate of the drug permeation via the drug's solubility in the membrane and/or the membrane's thickness. Additionally, the porosity of the membrane can control the diffusivity of the drugs through the patch.

Adhesive layer.—The adhesive layer is meant to attach to the skin under light pressure, maintain a strong attachment throughout the wear cycle, and extend the entire patch.[15] Pressure-sensitive adhesives (PSAs) that can stick to the skin with a small amount of applied pressure are most prevalent in TDPs. To qualify as a PSA, polymer films need to display a tackiness of approximately 0.1 MPa to ensure proper attachment to the skin, according to Dahlquist's criterion of tack.[16] Poly(acrylate)s, silicones, and poly(isobutylene)-copolymers are some of the most common types of adhesives used in TDPs. These polymers are typically used due to their strong mechanical properties and the balance of viscosity and elasticity that supports Dahlquist's criterion of tack.[17]

Since the adhesive layer is located between the drug reservoir or drug-clathrated polymer membrane and the skin, adhesives used in TDPs need to allow (or, in the least not inhibit) transport of the drug cargo from the polymer membrane/reservoir into the skin. Adhesive poly(isobutylene)s consist of a mixture of both low and high molecular weight polymers. This decreases the amount of free fraction void volume and leads to low molecular mobility within the film, which, in turn, leads to low diffusivity of drugs through the adhesive layer. Silicones are often selected as adhesives for their biocompatibility, chemical inertness, ease of fabrication and tunable tackiness. However, the solubility and mobility of many (water-soluble) drugs in (hydrophobic) silicones is poor. Poly(acrylate)s are miscible with many different types of drugs, making this class of polymers a very common adhesive in TDPs.[18]

Sometimes, the drugs can be loaded within the adhesive itself to simplify the overall structure of the TDP. However, incorporating drugs into the adhesive can cause changes in the chemical properties of the adhesive. For example, Suksaeree et al. created PSAs with drugs loaded inside the adhesive with high loading, but poor cumulative release.[19] Thus, the incorporation of the drugs in the adhesive creates a variety of challenges for the TDP and the selected drug.

Release liner.—The release liner acts as a protective layer for the adhesive and is intended to be removed right before the patch is applied to the skin. The release liner is carefully selected to ensure limited reactivity with the rest of the TDP and the drug cargo. Most release liners consist of a release coating and a substrate. The release coating is typically silicone-based or contains fluoropolymers, while the substrates are usually poly(ester) based. These compounds are typically chosen as release liners because they are chemically inert and prevent drug diffusion from the TDPs until they are removed.[20]

Future Needs and Prospects

Delivery mechanisms.—Transdermal drug delivery requires the administration of the drugs through the outer layer of the epidermis, the stratum corneum, and further into the second layer of skin, the dermis, where they can be distributed into the rest of the body. Known iterations of TDPs deliver targets via two major mechanisms: active and passive delivery. Passive delivery depends on unsupervised diffusion of drugs into the stratum corneum and, subsequently, absorption into the dermis, where a dense capillary network is expected to distribute the drug cargo systemically.[21] Due to physiochemical limitations, only a small set of therapeutics can be delivered passively. Comparatively recent efforts in active delivery leverage sophisticated electronics to apply external stimuli that increase the permeability of the stratum corneum, enhancing drug absorption.[1] Such electronics-enhanced active delivery systems promise to effect transdermal delivery of a wide range of therapeutics and vaccines, including small-molecule, peptide and nucleic-acid cargoes, making them potentially-transformative medical implements. In this section, we summarize recent materials and electronics advances in passive and active transdermal drug delivery systems, respectively.

Passive delivery.—One of the major problems associated with passive delivery lies in the unsupervised nature of drug diffusion from the patch and into the stratum corneum. To introduce a modicum of control during this process, cargoes can be chemically bonded to or entrapped within a functionalized and/or nanostructured matrix that responds to specific chemical stimuli (pH or temperature changes, for example), allowing for drug untethering, and subsequent diffusion, only under certain physiochemical contexts.[22,23] While still affecting delivery via passive diffusion, such stimuli-responsive methods allow increased release control and may augment drug permeability.

Depending on their structure, many drug targets are unable to penetrate the stratum corneum without the help of enhancers. Prodrugs, liposomes and vesicles have been demonstrated as chemical enhancers in TDPs.[24] Microneedles can be used as physical permeation enhancers that pierce through the stratum corneum to facilitate delivery. Microneedles can be either solid (coated with a drug-clathrated polymer film) or hollow with a drug reservoir.[25] Although durable metal microneedles are reported, polymer-based microneedles are more commonly used to afford flexible microneedle patches.[26] Poly(lactic acid), poly(acrylate)s, and poly(vinyl alcohol) have been used to create microneedle patches.[27] For example, Lim and Tiew et al. created microneedles capable of delivering a high molecular weight peptide, acetyl-hexapeptide-3, using a microneedle patch.[28] Although microneedles increase the permeability through the stratum corneum, one of the major problems with microneedles is their limited loading capacity due to their small size. Additionally, although microneedle arrays increase the permeation of drugs through the stratum corneum, triggered release and/or dosing control remains unresolved.

Active delivery.—The shift toward increasingly active delivery systems stems primarily from the constraints posed by the types of drugs that can be effectively delivered via passive methods: drugs that can be delivered via passive diffusion are limited to molecular weights <500 Da and partition coefficients (log P) of ca. 2.[29] These limitations effective exclude nascent, important therapeutics from being delivered transdermally via passive diffusion.

Some of the most popular types of active methods for TDPs rely on the external application of light, electromagnetic fields, current or

sound waves to perturb the physical structure of the stratum corneum and, therefore, increase its permeability.[1] Some examples of active delivery methods include iontophoresis, electroporation, and sonophoresis. Iontophoresis increases the permeation of the drugs by applying a low electric current of 0.1–1.0 mA cm^{-2} to the skin, either continuously or through pulses.[29] Depending on the specific therapeutic, the movement of the cargo through the skin is motivated by the electronic repulsion of the drug and the cathode or anode.[30] To date, iontophoresis has been shown to deliver drugs of molecular weights up to ca. 13.6 kDa.[29] Electroporation involves application of a strong electric field, 50–500 V, on the skin for a short amount of time.[29] This large, applied voltage disrupts the stratum corneum allowing for easier diffusion of charged drugs into the skin.[31] Sonophoresis uses sound waves of approximately 20 kHz-16 MHz to reduce the resistance of the stratum corneum and enable drug diffusion.[29] Unlike electroporation and iontophoresis, sonophoresis does not rely on the electrical charge of the drugs to deliver the drugs into the skin. Additionally, these active delivery methods have been paired with passive delivery TDPs for increased permeation or higher loading capacity while actively driving the drugs into the skin.[32] A common feature of all aforementioned active delivery systems is that background drug diffusion is effectively negligible in the absence of the applied stimulus, which allows for greater dosage control.

Areas of opportunity.—We identify three main opportunities to improve the efficacy, scope and practical applicability of transdermal delivery patches. Materials development is still needed to better control drug release rates over the expected wear time of a disposable patch. Active monitoring via accurate and unfoulable sensors paired with responsive drug dosing strategies will enable on-time interventions without the need for medical supervision. Low form-factor, lightweight electronics will enable imperceptible transdermal patches that promise to increase use and patient compliance.

Electronics needs.—To achieve miniaturized active delivery TDPs, further advancements in flexible, biocompatible charge storage and power delivery systems are needed. The aforementioned active delivery patches have high power demands that, in their present iterations, are fulfilled by bulky external power sources.[33,34] Some examples of miniaturization for active delivery systems have been recently reported. Ching et al. reported an integrated circuit for electroporation through a portable TDP powered by two 9 V batteries with an output voltage of 2–300 V.[35] Additionally, An et al. created conductive hydrogels with a portable and disposable reversible electrodialysis battery for an iontophoresis-based delivery system.[36] However, most batteries and control systems used for on-skin electronics remain rigid, heavy and/or bulky. Further, the biosafety and water/sweat/salt tolerance of these electronics components is yet to be reasonably established.

Sensors for real-time monitoring and unsupervised dosing.—Recently, there have been advancements in flexible, on-skin biosensors capable of efficiently sampling sweat and similar interstitial fluids and selectively revealing/quantifying the presence of certain analytes, such as glucose, lactic acid and some xenobiotics.[37] However, TDPs that marry such point-of-care diagnosis with therapeutic delivery (i.e., theranostics) are yet to be developed. Many on-skin biosensors are still subject to significant signal drift that reduces their accuracy over time and precludes their integration with drug delivery systems.[38]

On the drug delivery side, the drug loading capacity of most known TDPs is still insufficient to effect a practical therapeutic response. There have been few examples of increased loading capacity in TDPs recently: for example, Zhang et al. developed a new hydroxyphenyl-modified poly(acrylate) adhesive that facilitated long-term, sustained drug delivery, thanks to its increased loading capacity.[39] Although the loading capacity for TDPs is on the rise, they are still majorly lacking. Iontophoresis-based microneedles can deliver methotrexate at approximately 65 μg ml^{-1};[40] however, oral consumption of methotrexate requires approximately 15 mg/week at starting dosages for treatment.[41]

Most reported TDPs are subject to initial burst effects, which are both highly inflammatory to the wearer and preclude reported TDPs from being coupled to electronic control systems.[42] Exposure to such "bursts" of drugs inevitably initiates an inflammatory cascade response in the body, which can lead to potentially life-threatening complications and, in the least, decreased patient compliance. Patches with microneedles and added electronics pose a heightened risk of skin irritation and inflammation.[42] Potential issues also arise where multiple timed dosages and/or large dosages are needed to treat chronic conditions. Not only are the concentration and time profiles directly related to irritation, but residual drugs on the skin after removing the patch can lead to inflammatory responses.[43]

To be combined with on-skin biosensors for long-term, unsupervised use, better control over the concentration and duration of cargo release (i.e., drug dose) is needed, in addition to larger drug reservoirs. Such closed-loop theranostic patches must ensure accurate sensor functionality and strict control of cargo release over the lifetime of the patch. Recently, Parilla et al. reported a closed-loop TDP that integrates a microneedle array with a biosensor for supervised delivery of methotrexate.[40] However, such active-feedback TDPs are in their nascency and further research and development is needed to produce practical systems.

Conclusions

Transdermal delivery patches that marry point-of-care diagnosis with therapeutic delivery (i.e., theranostics) are yet to be developed. Materials development is still needed to minimize initial burst effects and better control drug release rates over the anticipated wear time of a disposable patch. Active monitoring via accurate and unfoulable sensors paired with responsive drug dosing strategies will enable on-time interventions without the need for medical supervision. Low form-factor, lightweight electronics will enable imperceptible transdermal patches that promise to increase use and patient compliance.

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