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Device-assisted transdermal drug delivery☆

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ABSTRACT

Transdermal drug delivery is a prospective drug delivery strategy to complement the limitations of conventional drug delivery systems including oral and injectable methods. This delivery route allows both convenient and painless drug delivery and a sustained release profile with reduced side effects. However, physiological barriers in the skin undermine the delivery efficiency of conventional patches, limiting drug candidates to small-molecules and lipophilic drugs. Recently, transdermal drug delivery technology has advanced from unsophisticated methods simply relying on natural diffusion to drug releasing systems that dynamically respond to external stimuli. Furthermore, physical barriers in the skin have been overcome using microneedles, and controlled delivery by wearable biosensors has been enabled ultimately. In this review, we classify the evolution of advanced drug delivery strategies based on generations and provide a comprehensive overview. Finally, the recent progress in advanced diagnosis and therapy through customized drug delivery systems based on real-time analysis of physiological cues is highlighted.

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1. Introduction

The growing demand for patient-friendly therapies has led to the development of transdermal drug delivery that has several advantages over conventional drug delivery methods. For instance, transdermal delivery enables sustained and controlled drug release, and promotes patients' compliance and convenience with its non-invasiveness and painlessness [1]. In particular, transdermal route is a good alternative

Abbreviations: RF, radiofrequency; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; MSN, mesoporous silica nanoparticle; NP, nanoparticle; PCM, phase change material.

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to needle injection or oral intake of medication. Transdermal delivery often requires a lower dosage of drugs than oral administration. With a short diffusive pathway to reach vasculature, transdermal mode helps the patients to circumvent side effects due to digestion and metabolism of the drug in the gastrointestinal tract. Transdermal delivery is painless and non-invasive, the advantage which is prominent against intravenous or intramuscular administration. The non-invasiveness allows repeated administrations of the drug over the same region of the body for a long-term treatment, and thus provides patients with compliance and convenience.

However, transdermal drug delivery is not a flawless drug transport method. The stratum corneum, the outermost barrier of the skin against foreign materials, imposes an obstacle to the transdermal diffusion of drugs [2]. Since only a few small-molecule drugs with high lipophilicity can naturally permeate through the hydrophobic stratum corneum, a vast majority of hydrophilic drugs have been ruled out against transdermal delivery. Even after the drug successfully penetrates the stratum corneum, it may be degraded prematurely by epidermal enzymes, resulting in decreased bioavailability. Latency in the onset of action as well as a lack of pharmacokinetic control may also undermine the reliability of the transdermal delivery.

The endeavor for a better transdermal delivery has evolved towards overcoming such limitations, and the innovation has been seen in several generations, namely, focusing on drug formulation, external actuation, and minimally invasive microneedles. The first generation of transdermal delivery focused on refining the drug formulation to maximize its diffusion through the skin as manifested by emulsions, nanocarriers, and chemical enhancers. The second generation has sought external forces, such as heat and electricity, to energetically fuel the drug to cross the epidermal layers and reach the vasculature. The third generation incorporated microneedles, which puncture the outer skin layer but preserve the dermis, to provide the drug with a physical shortcut bypassing the epidermal barriers. The breakthroughs of previous generations have greatly improved the efficiency of transdermal drug delivery.

Although the betterment of transdermal delivery so far has focused on maximizing the delivery efficiency, transdermal drug delivery is yet to see another breakthrough by adopting a paradigm shift towards personalized therapy [3–5]. Furthermore, transdermal delivery is set to adopt an advanced paradigm of device-assisted personalized therapy where the precise control of the amount and duration of a drug dose in response to the patient's physiological condition is a key to maximizing the therapeutic efficacy (Fig. 1a and b). The controlled and on-demand administration of a drug tailored to the needs of each patient requires extensive innovation. Wearable devices may be a viable and useful strategy because they can collect an assortment of physiological [6–15], electrophysiological [16–21], and biochemical [22–27] cues, and thereby, facilitate drug delivery *via* energetic actuations.

In this review, we recapitulate the major breakthroughs of four generations of transdermal drug delivery strategies, providing the reader with the detailed advantages and challenges of each generation. In accordance with a growing interest in controlled drug release for personalized medical treatment, we also emphasize the recent progress on wearable devices that support device-assisted transdermal drug delivery. This review concludes with case presentations to demonstrate the wearable biosensors and advanced transdermal delivery schemes that are seamlessly integrated. Thereby, we hope to present a novel potential protocol and foundation for the next generation of personalized therapy.

2. Advancement of transdermal drug delivery systems

Among the anatomical layers and appendageal structures of the skin (Fig. 2a), the epidermis and its outermost stratum corneum are the most challenging barriers to transdermal delivery [28,29]. The brick-and-mortar assembly of keratinocytes and intercellular lipids renders the epidermis impregnable to most foreign materials. Therefore, a cursory observation of transdermal delivery can regard it as a counterintuitive strategy for delivering a drug systematically. However, a detailed analysis reveals that transdermal delivery provides a number of advantages over oral intake or hypodermic injections. Compared with oral delivery, transdermal delivery requires a lower dosage and has fewer side effects because transdermal diffusion circumvents the digestion and first-pass metabolism of the active drug in the gastrointestinal tract and liver [30]. Moreover, transdermal delivery is less painful, minimally invasive, and convenient to patients so that the compliance with drug administration increases to a great extent. Because such advantages offset the drawbacks of transdermal delivery, studies continue to develop reliable

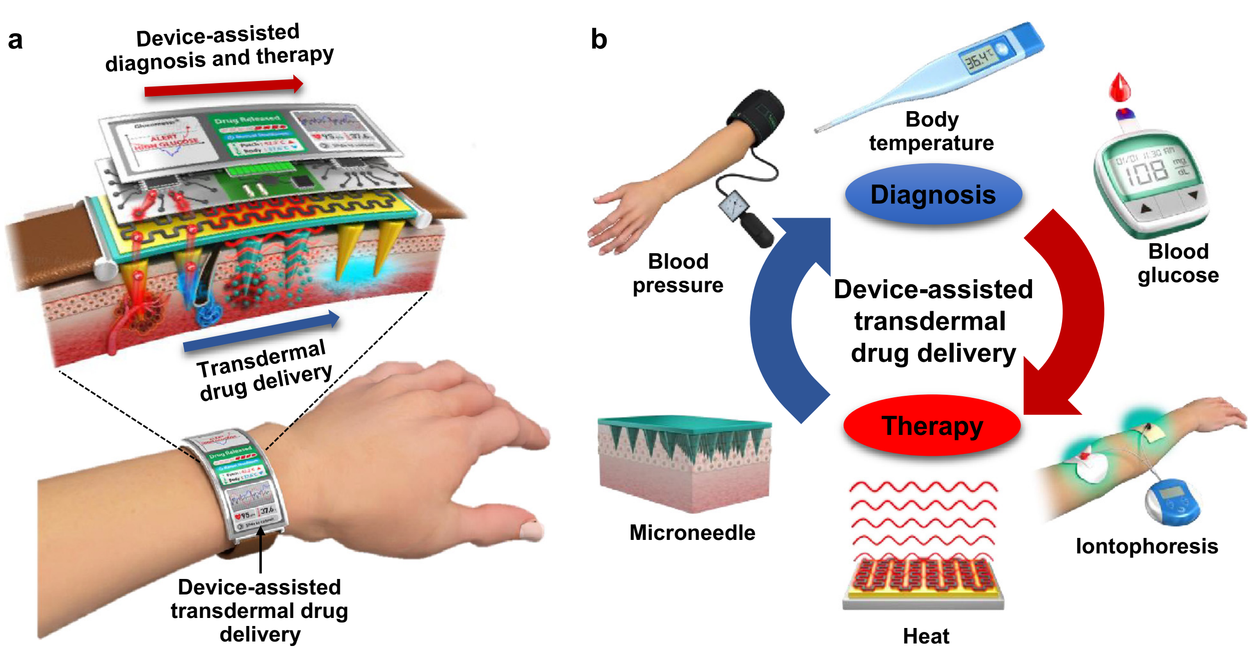

Fig. 1. (a) Schematic illustration of the device-assisted transdermal drug delivery for patient-customized skin-based therapy. (b) The wearable device system conducts real-time monitoring of vital signs and actuates transdermal drug delivery according to individual health condition.