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Bioresponsive transcutaneous patches

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Transdermal drug delivery systems that utilize transcutaneous patches of arrayed microneedles have attracted increasing interest in medical practice as an alternative method to hypodermic injection. Over the past ten years, research has focused on leveraging physiological signals associated with diseases or skin-specific tissues to create bioresponsive patches that release drug directly in response to an internally-generated stimulus. This review surveys the recent advances in the development and use of bioresponsive transcutaneous patches for on-demand smart and precise drug delivery, exploiting different physiological signals including pH, serum glucose levels, and enzyme activity. The clinical potential of these devices, including challenges and opportunities, is also discussed.

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Introduction

Hypodermic injection is a widely used delivery technique for most biotherapeutics and represents a low-cost and rapid delivery approach [1]. However, injections are often associated with poor patient adherence and may lead to injection phobia and distress [2•,3–5]. An attractive alternative to hypodermic injection is to deliver therapeutics across the skin using transcutaneous patches [2•,3,6]. Typically, these transcutaneous patches incorporate arrays of microneedles (MNs) that are designed to penetrate skin's outer stratum corneum layer to enhance delivery capabilities [2•,7–9]. Since the needles are micron-size, they can deliver almost any drug or small particulate formulation as well as facilitate localized tissue delivery [2•]. Critically, transcutaneous patches are a more appealing approach to patients as this method of drug delivery is painless and can be self-administered [2•,3,6].

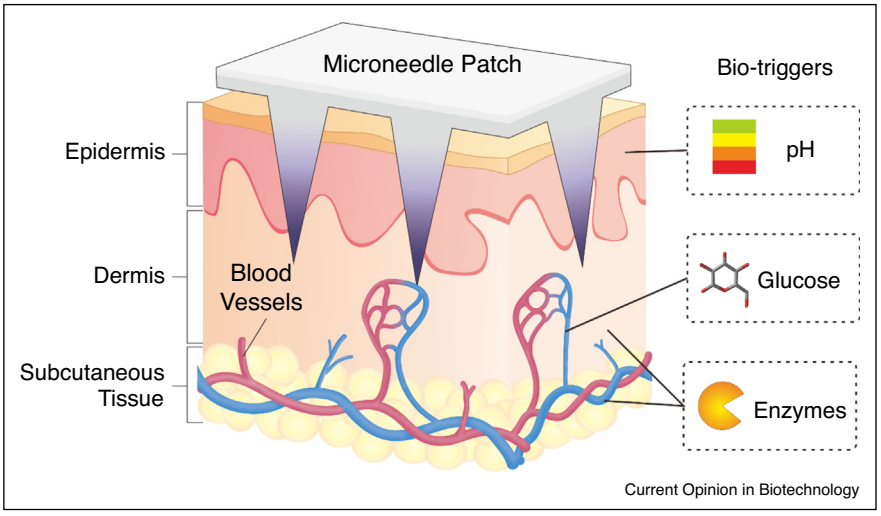
Recently, transdermal patch models that incorporate stimuli-responsive MNs which release drug in response to an internally-generated stimuli have been proposed for smart and precise drug release [10–13]. Compared to delivery systems triggered by external stimuli like electric field [14,15], light [16,17], or mechanical force [18], the MN patches activated by a physiological signal provide self-regulated delivery of drug in response to the abnormal physiological signals, thereby maximizing therapeutic efficiency and minimizing side effects or toxicity [19].

For instance, glucose-responsive MNs can be triggered to release insulin in response to abnormally high glucose levels in vascular and lymph capillary networks while showing basal insulin release in euglycemic conditions, achieving a smart closed-loop system for insulin delivery [20•]. Herein, we will summarize and classify recent advances in the development of bioresponsive transcutaneous patches, including pH-responsive, glucose-responsive, and enzyme-activated systems (Figure 1), and discuss the advantages, limitations of these current formulations. Future challenges and opportunities in terms of clinical translation will also be discussed.

pH-responsive transdermal patches

Normal skin is slightly acidic, with a pH ranging from 4.0 to 7.0, which provides a barrier to bacteria, viruses and other potential contaminants [21]. In particular, the acid mantle secreted by sebaceous glands maintains the epidermis pH at approximately 5.5 [22]. The acidic properties of skin enable the use of pH-sensitive patches for on-demand transdermal drug delivery. For example, MNs filled pH-responsive poly(lactic-co-glycolic acid) (PLGA) hollow microspheres were developed and reported to sequentially co-deliver multiple drugs to skin tissue by Ke *et al.* [23]. In this system, hollow PGLA microspheres encapsulated an aqueous core containing red-fluorescent dye Cy5 as a model drug and sodium bicarbonate ($NaHCO_3$) loaded via a double-emulsion method. The Cy5-loaded microspheres and a second

Figure 1



Typical physiological signals (bio-triggers) for bioresponsive transcutaneous patches.

model drug, Alexa 488, were further encapsulated together in polyvinylpyrrolidone (PVP) MN arrays. Upon application to the skin, the PVP rapidly dissolved within minutes, simultaneously releasing the Alexa 488 dye. The acidic environment of the skin stimulated $NaHCO_3$ in the PLGA microspheres to generate CO_2 bubbles, thereby creating the channels in the PLGA shell and releasing the Cy5. Researchers demonstrated the sequential release of the two dyes into the porcine cadaver skin *ex vivo* using fluorescence microscopy. pH-sensitive surface modification was also reported in the fabrication of pH-sensitive microneedles. Here, MNs were coated with ovalbumin, a model antigen, and a pH-sensitive pyridine surface [24]. Upon insertion into the acidic skin conditions, reduced electrostatic interactions allowed the ovalbumin to be efficiently released. Layer-by-layer assembly of polyelectrolytes has also been shown to achieve pH-triggered drug release through weakened electrostatic binding that occurs between the negatively and positively charged layers in the physiological pH [25,26].

Glucose-responsive transdermal patches

Since MNs inserted into skin can directly contact the dermal microcirculation, these MNs can sense serum biomarker levels and changes thereof in a real-time manner [8,27]. For patients with diabetes who are tasked with frequent monitoring of blood glucose levels and timely injection of insulin as part of diabetes self-management [28,29], insulin-loaded MNs with glucose-responsive moieties are desirable for achieving closed-loop insulin delivery. Based on this concept, Yu *et al.* have developed a 'smart insulin patch' that effectively releases insulin in response to hyperglycemic conditions for diabetes treatment [20•]. In this study, glucose-responsive vesicles containing insulin and the glucose-specific enzyme (GOx) were loaded into the tips of MN arrays. These vesicles were formed from hypoxia-sensitive hyaluronic acid (HA) conjugated with a hydrophobic group that could be bio-reduced to hydrophilic under hypoxic conditions (2-nitroimidazole). In hyperglycemic conditions, oxygen consumption from the enzymatic conversion of glucose to gluconic acid generated a local hypoxic environment, which resulted in the reduction of 2-nitroimidazole to hydrophilic 2-aminoimidazole, disassembly of the vesicles, and subsequent insulin release. Researchers demonstrated this glucose-responsive insulin-delivery system was able to quickly 'sense' and correct elevated blood glucose levels of chemically induced type 1 diabetic mice to the normal state within 0.5 hour and maintain euglycemic conditions for several hours thereafter.

Furthermore, Gu group have also designed an MN patch integrated with insulin-secreting pancreatic *beta*-cells and loaded with glucose-signal amplifiers for glucose-responsive insulin delivery [30•]. Instead of direct insulin release from glucose-responsive vesicles, these vesicles were encapsulated with GOx, α-amylase as well as glucoamylase and acted as synthetic glucose-signal amplifiers. In high glucose concentrations, α-amylase and glucoamylase were released and hydrolyzed the α-amylose that loaded in MNs into glucose. This amplified glucose signal further diffused into the externally positioned *beta*-cell capsules on the base of MN patch, prompting secretion of insulin for diffusion into the vascular and lymph capillary networks. This model showed extended therapeutic efficacy compared the MNs without glucose-signal amplifiers, where one patch was shown to effective control on blood glucose levels for 6 hours in diabetic mouse.