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Review

Current advances in the fabrication of microneedles for transdermal delivery

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ABSTRACT

The transdermal route is an excellent site for drug delivery due to the avoidance of gastric degradation and hepatic metabolism, in addition to easy accessibility. Although offering numerous attractive advantages, many available transdermal systems are not able to deliver drugs and other compounds as desired. The use of hypodermic needles, associated with phobia, pain and accidental needle-sticks has been used to overcome the delivery limitation of macromolecular compounds. The means to overcome the disadvantages of hypodermic needles has led to the development of microneedles for transdermal delivery. However, since the initial stages of microneedle fabrication, recent research has been conducted integrating various fabrication techniques for generating sophisticated microneedle devices for transdermal delivery including progress on their commercialization. A concerted effort has been made within this review to highlight the current advances of microneedles, and to provide an update of pharmaceutical research in the field of microneedle-assisted transdermal drug delivery systems.

Contents

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1. Introduction

Avoiding the emotional trauma and pain associated with injections, the risk of needle-stick injuries, increasing patient compliance, controlling plasma levels, improving bioavailability, and reducing overall doses have all made transdermal drug delivery systems an effective alternative to the available parenteral and oral routes. In addition, Transdermal Drug Delivery Systems (TDDSs) offer the advantage of avoiding hepatic/gastrointestinal metabolism, hepatotoxicity, palatability issues and disease transmission [1–4]. Although many methods such as the use of ultrasound, electric fields, chemical enhancers, and thermal methods have been used to successfully delivery active substances [5], the enhancement in the permeability of the delivered active across the skin has resulted in limited success, particularly in compounds with a high molecular weight. The past decade has seen exceptional progress in microneedle device design and fabrication by both academic and industrial researchers alike, with some devices currently in clinical development and some awaiting FDA approval. In addition to device fabrication, integration and cost issues, many other issues are apparent from a pharmaceutical research point of view, such as optimal dose finding and minimizing adverse reactions. Even though great progress has been made over the years, these issues alone warrant the need for significant research and development efforts [6]. Microneedle array (MNA) technology is an evolving technique combining the ease of a transdermal patch and the effectiveness of hypodermic syringes through the use of multiple microscopic projections from a backing plate to facilitate penetration of actives into the skin, and thus MNAs provide a unique methodology of painless drug transport [7,8]. Arrays of microneedles are developed as a solid, a dissolvable or as a microneedle device comprising cannulae [9]. The microneedles are usually designed in arrays in order to improve the surface contact with the skin [10,11]. The following Sections 1.1 and 1.2 will provide a brief general introduction of the potential paradigm shift in drug delivery technology, which is claimed by utilizing microneedles. Further, in this review the different types of microneedles and their methods of use will be explained in Section 2, while an overview on advances in fabrication techniques will be given in Section 3. Finally, we will provide an update on the efforts of microneedle technology commercialization, highlighting the current state of the art of pharmaceutical research in the field of microneedle-assisted transdermal drug delivery systems in Section 4.

1.1. Transdermal delivery

The skin consists of three layers, i.e. epidermis, dermis and subcutaneous fat layer (subcutis), collectively serving as an external physical barrier (Fig. 1), with the real barrier to transdermal diffusion being specifically the stratum corneum [12]. Delivery from hypodermal administration results in the compound being deposited either intramuscularly (IM), subcutaneously (SC) or intradermally (ID). Due to microscopic projections on microneedle arrays, compounds can be delivered either precisely into or just beyond the epidermis [13].

1.2. Microneedles vs. hypodermic needles

Even though hypodermic needles are the norm for parental delivery, there are however, several disadvantages [14–16]:

- Pain and needle phobia, leading to poor patient compliance
- If re-used, possibility of transmitting disease and dosing needs trained personnel
- Erratic delivery, rapid degradation/poor absorption, leading to poor bioavailability and thus requiring a higher drug amount to achieve the therapeutic dose
- The possibility of needle-stick injuries

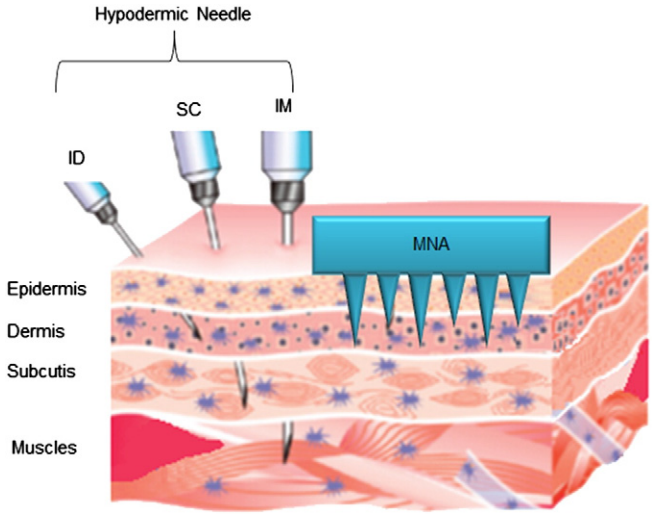

Fig. 1. Classical and transdermal needle-driven delivery in relation to the anatomy of the skin (adapted with permission [13]).

- Potentially dangerous biological waste and sharp disposal hazard
- Possibility of hematoma formation or bleeding

Delivery using microneedles is pain-free in comparison to hypodermic needles, as due to their small size, the minimally invasive microneedles are capable of reducing the stimulation of nerves and thus evading the generation of the pain sensation [14,17–20]. Besides the aspect of pain-free delivery, numerous other advantages of microneedles are presented in reference to the existing hypodermic injection in existing literature, including: minimal skin trauma following microneedle insertion [21]; no bleeding or introduction of pathogens associated with microneedle use [22–25] appropriateness and a comparatively effortless application or ease of use for non-skilled and/or self-administration [20,21,26]; reduced risk of needle-stick injury and cross-contamination [20] as well as the increased ease in disposal [8]. In certain cases, diffusion alone is an inadequate mechanism to penetrate the stratum corneum preventing optimal drug delivery and numerous procedures have been developed to aid drug delivery in such instances. It must be stated that diffusion is not the only factor controlling delivery through the stratum corneum: permeability; aqueous/lipid solubility ratio; and molecular size are critical as well in facilitating permeation [27]. Martanto et al. [23] have tested the hypothesis of compressed dermal tissue trapped within a hollow microneedle after insertion offering resistance to flow through the microneedle and into the skin. Results have concluded that skin infusion can be increased by retracting the microneedle. One of the most attractive applications of the microneedle arrays is to use them for transcutaneous vaccination [2,28,29]. Since transcutaneous immunization is limited by poor macromolecular skin permeation, as a vaccination tool, microneedle arrays could offer easier and painless administration, in addition to reducing vaccination costs [30]. Furthermore, vaccine delivery via the skin or via other mucosal membranes may improve effectiveness and result in better cellular immunity by eliciting immune responses at the virus entry site. Research has suggested that the transport mechanism appears non-dependant on cellular uptake functions, allowing for physical methods to be applied to all cell types at all stages of the cell cycle, resulting in a biologically nontoxic and minimally invasive process [31]. The perceived disadvantages that may occur with the use of microneedles include the possibility of inflammation in the surrounding tissues, and the fact that there is a certain likelihood of the microneedles to break off and be left under the skin. Due to the small size of microneedles the latter may occur unnoticed causing unforeseeable adverse reaction. A recent survey by Birchall et al. [32] demonstrated that both the public and healthcare professionals support the introduction of