Journal of Drug Delivery Science and Technology 29 (2015) 16–23

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

journal homepage: www.elsevier.com/locate/jddst

Review

Transdermal delivery of drugs with microneedles: Strategies and outcomes

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ARTICLE INFO

Article history:
Received 20 February 2015
Received in revised form
28 April 2015
Accepted 1 May 2015
Available online 20 May 2015

Keywords:
Transdermal
Drug delivery
Microneedles
Strategies
Clinical trials
Outcomes

ABSTRACT

Transdermal drug delivery has a number of advantages. These include avoidance of presystemic metabolism, absence of gastric irritation and enzymatic degradation, convenience, painlessness, non-invasiveness and improved patient compliance [3–6]. Despite these advantages, it is challenging to deliver molecules across the skin. Researchers have used external force to drive compounds through the skin. Several strategies are used to achieve this goal including chemical penetration enhancers, sonophoresis, iontophoresis and microneedles. Microneedles are micrometer-sized needles that are used to porate the skin for drug delivery. These needles are long enough to penetrate the stratum corneum but too short to stimulate pain receptors that are located in the dermis. Considerable progress has been made in the design and development of microneedles. Several strategies have been adopted for the fabrication of different types of microneedles. This paper reviews the strategies used in developing micorneedles and outcomes from clinical trials.

1. Introduction

Over the past four decades, considerable progress has been recorded in the development of transdermal drug delivery systems containing small molecular weight compounds [1–4]. Some of these products are now used in clinical practice (examples are fentanyl and nicotine patches) but there are still considerable challenges to be overcome. During this same period, a large number of biotechnology compounds have been discovered but there are huge problems with the delivery of macromolecules. The difficulty in getting drugs to cross the skin is caused by the formidable barrier presented by the stratum corneum. This outermost layer of the epidermis measuring between 10 and 15 μm in thickness is made from high density (1.4 g/cm^3 in the dry state) and low hydration (10–20%) cell layers [5]. The corneocytes, which is composed of cross-linked keratin fibres, are about 0.2–0.4 μm thick and about 40 μm wide. Corneocytes are elongated, flattened and non-nucleated cells [5] consisting of 70–80% keratin and 20% lipids within a thick cell envelope [2]. There are 6–20 layers of flattened, interleaved, partially desiccated, keratinized cells (corneocytes) in the stratum corneum [6]. The corneocytes are held together by corneodesmosomes. The stratum corneum lipids are mainly ceramides, cholesterol and fatty acids. These are assembled into multi-lamellar bilayers. There are at least 11 classes of fatty acids and sphingoid moieties [5,7]. These are combinations of non-hydroxy-, α-hydroxy, ω-hydroxy and esterified ω-hydroxy fatty acids containing dihydrosphingosines, sphingosines, phytosphingosines and 6-hydroxy-sphingosines [5,7].

The use of ruthenium tetroxide as a post-fixation agent made it possible to preserve and visualize stratum corneum lipids in their saturated state. Subsequent electron microscopy studies demonstrated an unusual lamellar arrangement of a repeating pattern with electron translucent bands in a broad-narrow-broad sequence [8]. Studies carried out using Fourier transform infrared spectroscopy (FTIR) showed mobility and the lateral packing of the lipids in the stratum corneum making it possible to differentiate between hexagonal (gel-phase) and an orthorhombic sublattice [9,10]. Using small angle X-ray diffraction, a series of sharp peaks indicating the presence of a lamellar phase with a periodicity of approximately 13 nm, called the long periodicity phase (LPP), was demonstrated. With wide angle X-ray diffraction studies, it was also possible to observe the presence of an orthorhombic sublattice with a transition from an orthorhombic to a hexagonal subphase occurring between 20 and 40° C [8]. Transdermal delivery is challenging due to the multiphase, multiscale intricate nature of skin microstructure and the complex interplay of partitioning and diffusion [6]. The anatomical and chemical complexity of the stratum corneum and

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http://dx.doi.org/10.1016/j.jddst.2015.05.001
1773-2247/

the need to overcome this barrier has spurred a significant volume of work in the transdermal drug delivery field. An interesting approach to dealing with this obstacle is the use of microneedles.

2. Microneedles

Microneedles are micrometer-sized needles which are used to porate the skin for drug delivery [11–13]. These needles are long enough to penetrate the stratum corneum but too short to stimulate pain receptors that are located in the dermis [14–16]. Microneedles have a number of advantages including painlessness, reduced risk of infection, minimal invasiveness, ease of disposal and the ability to increase transcutaneous flux of medications [17–19]. Haq et al. have reported that over 40 million injections are given daily. Approximately 15 billion injections are administered in a year [20]. Because of needle phobia (the pain associated with injections), some patients avoid seeking medical assistance [20]. Microneedles significantly reduce these problems since they do not stimulate pain receptors.

Although the use of microneedles is considered advantageous, nevertheless several concerns have also been raised regarding their use. There are valid concerns that creating microscopic pores in the skin can lead to bacterial and fungal infections. Also, ingress of allergens can result in hypersensitivity reactions. In addition, there are potentials for misuse and abuse of microneedles [19]. More importantly, the use of microneedles does not always result in the achievement of therapeutic drug concentration [19,21].

Reports have appeared in the literature documenting the fabrication, characterization and uses of microneedles [22–25]. In 1976, Gerstel and Place filed a patent for a drug delivery device based on microneedles [26]. However, there were technical challenges connected with the realization of this idea. It was when microfabrication technologies matured that Henry et al. were able to fabricate silicon microneedles for transdermal drug delivery [16]. The authors demonstrated an increase in the skin permeability of a model drug, calcein, by 4 orders of magnitude [16]. There are different modes of application of microneedles (Fig. 1). 'Poke and patch', 'coat and poke','poke and release 'are some of the ways in which microneedles can be used [25,27]. In "poke with patch"microneedles are used to make holes and then a transdermal patch is applied. When using "coat and poke," the needles are first coated with drug and then inserted into the skin. In 'poke and release', drugs are released from biodegradable, or dissolving microneedles into the skin. These mechanisms are observed when using solid microneedles. The ultraviolet (UV)-curable polymer SU-8 photoresist has also been used to fabricate polymeric microneedles. Typically, photolithography is used with optically curable polymers, which are then used as master structures for fabrication [28]. There is also 'poke and flow' mode for hollow microneedles. In this case, the drug solution flows through the microneedle bore. Deep reactive ion etching, laser micromachining and wet etching have all been used to make hollow microneedles [28]. Chen et al. documented the use of ovalbumin -loaded microneedles. When these microneedles were embedded in rat skin in vivo, histological examination showed that the microneedles gradually degraded and prolonged ovalbumin (OVA) exposure at the insertion sites for up to 14 days. Compared to traditional intramuscular immunization, rats immunized by a single microneedle dose of OVA showed a significantly higher OVA-specific antibody response [29]. Donnelly et al. have also described hydrogel-forming microneedle arrays [14,30,31]. These microneedles rapidly take up skin interstitial fluid upon skin insertion to form continuous hydrogel conduits from attached drug reservoirs. Microneedles can be fabricated from a wide variety of materials including silicon, metals and polymers.

2.1. Silicon microneedles

Silicon microneedles are typically fabricated by photolithography, thin-film deposition and reactive ion etching techniques [16,32,33]. Thin-film deposition may be carried using physical or chemical vapor techniques. In physical vapor deposition (PVD), the film is formed by atoms directly transported from source to the substrate through gas phase [34]. PVD may be in the form of evaporation or sputtering. In chemical vapor deposition (CVD), the film is formed by chemical reaction on the surface of substrate [35]. There are different forms of CVD-low pressure, plasma-enhanced and atmospheric-pressure CVD. In photolithography (Fig. 2), a light-sensitive polymer (photo-resist) is exposed to ultraviolet (UV) light to define a desired pattern [36]. Initially, UV light with wavelengths in the range of 193–436 nm is illuminated through a photomask. Photomask is an opaque plate which allows light to cross only in a defined pattern. In the exposed area, the polymer chains of photo-resist break down making it more soluble in a chemical solution called the developer. Subsequently, the exposed photo-resist is removed to form the desired photo-resist pattern [16,32,33]. After deposition and patterning of patterns on a silicon (Si) substrate, the portion of the Si wafers not covered by these patterns can also be etched away by an isotropic reactive ion etching [16,33]. Etching may be wet or dry. In wet etching, a liquid-phase ("wet") etchant such as potassium hydroxide solution is used [37] while dry etching refers to the bombardment of the material by ions from plasma of reactive gases such as oxygen or fluorocarbons [16,32].

The advantage of silicon microneedles is that it can easily be fabricated using existing microelectromechanical systems (MEMS) technologies. The disadvantage is that silicon can break easily raising the prospect of creation of biohazardous waste.

2.2. Metal microneedles

Metal microneedles can be made from different metals including stainless steel [17,38,39] (Fig. 3) and titanium [40–43]. These microneedles can be fabricated by using laser

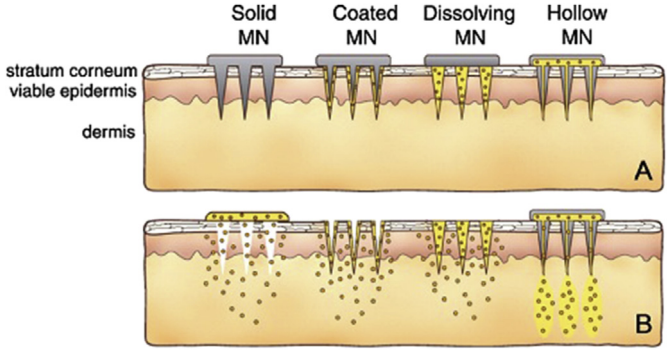

Fig. 1. Different types of microneedles - solid, coated, dissolving and hollow (reproduced with permission from reference [28]).

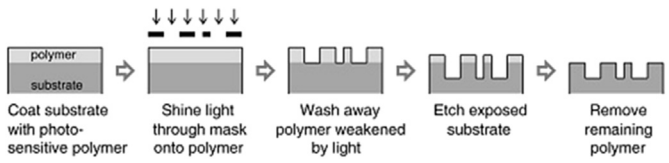

Fig. 2. Etching of microchannels into a substrate using photolithography (reproduced with permission from reference [36]).