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Research Paper

Monitoring the penetration process of single microneedles with varying tip diameters

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ABSTRACT

Microneedles represent promising tools for delivery of drugs to the skin. However, before these microneedles can be used in clinical practice, it is essential to understand the process of skin penetration by these microneedles. The present study was designed to monitor both penetration depth and force of single solid microneedles with various tip diameters ranging from 5 to 37 μm to provide insight into the penetration process into the skin of these sharp microneedles. To determine the microneedle penetration depth, single microneedles were inserted in human ex vivo skin while monitoring the surface of the skin. Simultaneously, the force on the microneedles was measured. The average penetration depth at 1.5 mm displacement was similar for all tip diameters. However, the process of penetration depth was significantly different for the various microneedles. Microneedles with a tip diameter of 5 μm were smoothly inserted into the skin, while the penetration depth of microneedles with a larger tip diameter suddenly increased after initial superficial penetration. In addition, the force at insertion (defined as the force at a sudden decrease in measured force) linearly increased with tip diameter ranging from 20 to 167 mN. The force drop at insertion was associated with a measured penetration depth of approximately 160 μm for all tip diameters, suggesting that the drop in force was due to the penetration of a deeper skin layer. This study showed that sharp microneedles are essential to insert microneedles in a well-controlled way to a desired depth.

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1. Introduction

The skin provides an important physical barrier to the environment. It is rich in immune-responsive cells, such as Langerhans cells and dermal dendritic cells. Consequently, it provides a promising location for vaccination. By administrating the vaccine directly to the epidermal and dermal layers of the skin, a lower dose of antigens may be required to achieve a comparable immune response to subcutaneous or intramuscular vaccination with a hypodermic needle (Chen et al., 2010, 2011; Fernando et al., 2010; Gelinck et al., 2009; Quan et al., 2010). Vaccination with microneedles represents a promising method to deliver antigens into the skin. These projections with a length of less than a millimetre can be fabricated from various materials in a wide range of geometries (Donnelly et al., 2010a; Kim et al., 2012; van der Maaden et al., 2012). Microneedles are used in multiple ways. For example, hollow microneedles can be used to inject fluids into the skin. By contrast, solid microneedles can either create micropores in the stratum corneum after which drugs can be topically applied (poke and patch) or they can release the vaccine into the skin after their insertion. Using this last approach two methods are in development, coated microneedles and dissolvable microneedles.

An important challenge in using microneedles to deliver vaccines into the skin in a reproducible manner is to effectively and reproducibly penetrate the skin. Therefore, microneedle penetration of the skin has to be fully characterised, including the inter-subject variation in skin mechanical properties and the various geometries of the microneedles. It is of paramount importance to obtain sufficient control on the depth of penetration of the microneedle into the skin since only the part of the microneedle within the skin will deliver the drug. In addition, the penetration depth may be important to specifically target Langerhans cells or dermal dendritic cells residing in the epidermal and dermal layer of the skin, respectively. Activation of these different cells may result in a different immune response (Banchereau et al., 2009; Romani et al., 2010).

During microneedle application, the skin is first indented before penetration occurs. As a result, many studies reveal that the insertion depth of microneedle arrays range widely from 10 to 80% of the microneedle length (Chu and Prausnitz, 2011; Coulman et al., 2010; Crichton et al., 2010; Donnelly et al., 2010b; Kalluri et al., 2011; Lee et al., 2008; Li et al., 2009; Matriano et al., 2002; Roxhed et al., 2007). Various factors affecting microneedle penetration depth have been examined. The penetration depth of a microneedle array increases with application velocity (Crichton et al., 2010) and application force (Donnelly et al., 2010b). Microneedle length also influenced the penetration depth, in contrast to microneedle interspacing. Accordingly, most studies have employed microneedles in an array, with a high velocity or large force to ensure effective penetration of the skin. However, the penetration mechanism of a single microneedle is still yet to be fully clarified.

Clearly the application force is critical. A previous study reported that insertion force of relative blunt microneedles, with tip diameters ranging from 60 to 160 μm, ranged from 0.08 to 3.04 N and was linearly dependent on tip frontal area (Davis et al., 2004). These relatively high insertion forces motivated the design of sharper microneedles, with a resultant reduction of insertion force measured for microneedle arrays (Khanna et al., 2010; O'Mahony, 2014; Roxhed et al., 2007).

Evidently, penetration depth as well as penetration force are important factors in controlled application of microneedles. However, the mechanism of microneedle penetration and the relation between penetration force and depth are still not well understood. Therefore, the present study was designed to monitor both penetration force and depth of single microneedles, manufactured to a range of tip diameters. In particular, it was designed to examine the influence of tip diameters on the nature of the penetration mechanisms and the absolute values of the penetration parameters.

2. Materials and methods

2.1. *Microneedle fabrication*

Single solid microneedles were fabricated in a controlled manner by pulling glass rods with a diameter of 1 mm (World Precision Instruments, Inc, Sarasota, FL, USA) with a micropipette puller (P-97, Sutter Instruments Company, Novato, CA, USA) (Martanto et al., 2006a). Microneedles varying systematically in tip diameter were produced by tuning the input parameters of the micropipette puller. In addition, in some cases the microneedle was cut to the desired tip diameter using a microforge (MF-830, Narishige, Japan). Four sizes of microneedles were produced with tip diameters of 5, 15, 24, and 37 μm with a resolution of 1 μm. For each microneedle, an image was made with a digital microscope to determine its shape (Fig. 1). The tip angle between differently sized microneedles varied from 11 to 21 degrees. The tip length of the microneedles was approximately 3.3 mm.

2.2. *Preparation of human skin samples*

Abdominal human skin was obtained from 8 female patients, aged between 35 and 55 years, from the Catharina Hospital, Eindhoven, the Netherlands, according to Dutch guidelines of secondary used materials. The skin was transferred to the laboratory and processed within 4 h of excision. For processing, the skin was stretched on a stainless steel plate, using multiple forceps, and cleaned with ethanol (Geerligs et al., 2011a; Lamers et al., 2013). Subsequently, skin slices of 1.20 ± 0.23 mm thickness (mean ± standard deviation), which contained the stratum corneum, viable epidermis, and dermis, were obtained using a dermatome (D42, Humeca, Enschede, the Netherlands). These slices were cut into squares of approximately 3 by 3 cm. Thereafter, speckles of Graphit 33 were sprayed on the skin samples to increase contrast of features during imaging.

Natural pretension in the skin leads to shrinkage during the cutting process. As the penetration can be influenced by the tensions within the skin samples (Butz et al., 2012), the in vivo state should be mimicked as closely as possible. This was achieved by attaching a metal ring of 7.5 g weight with an inner diameter of 15 mm on the unstretched skin samples