International Journal of Pharmaceutics 480 (2015) 152–157

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

Hollow polymer microneedles array resistance and insertion tests

Marion Sausse Lhernould*, Michel Deleers, Alain Delchambre

Université Libre de Bruxelles – Bio Electro and Mechanical Systems, Av. F.D. Roosevelt 50, CP165/56, 1050 Brussels, Belgium

A R T I C L E I N F O

Article history:
Received 1 December 2014
Received in revised form 8 January 2015
Accepted 10 January 2015
Available online 13 January 2015

Keywords:
Microneedles
Microneedles array
Transdermal drug delivery
Insertion
Membrane penetration

A B S T R A C T

Microneedles are developed in order to become the transdermal administration method of the future. They however still face numerous challenges. This paper addresses the challenge to effectively insert the microneedle arrays into membranes. A recently proposed model membrane and test method for microneedles insertion, published in International Journal of Pharmaceutics, is used in this aim. A moulded 4 by 4 hollow polymer microneedle array developed at the Université Libre de Bruxelles is tested for insertion using this model. Results show that the array is extremely resistant to insertion, it can withstand very high forces and even multiple insertions without blunting. Different insertion tests were performed on a folded in eight Parafilm® film because it exhibits excellent similarity to porcine skin. The insertion force, the insertion speed and the holding time of the array against membranes must be optimised in order to get efficient reliable insertions at, at least, 500 μm depth.

1. Introduction

Hypodermic needles are an effective way to by-pass the stratum corneum and inject drugs through the skin but are associated to pain and discomfort. Injections with hypodermic needles may also induce hypersensitivity, bruising and bleeding at the site of administration, and may result in high contaminations risks. All these inconveniences make hypodermic needles very unpopular. Besides these patient comfort aspects, there are important constraints linked with their use, such as accidental needles stick injury and necessity to train medical staff to their use.

With the advent of microneedles (MN), patients and medical staff will be given an alternative to hypodermic injections. By their micro-size, microneedles are long enough to break the defensive barriers of the skin for allowing drug delivery, but short enough to avoid encountering a nerve, or a pain receptor residing beneath the skin outer layer. Moreover, because they do not have a direct contact with blood vessels, they dramatically diminish contamination risk. Microneedles allow to reach the dermis of patient in a non invasive way and allow drugs to be absorbed directly in the systemic circulation (Prausnitz, 2004). When they are hollow they allow injection of liquids into the skin.

Regarding manufacturing matters, the first microneedles were made out of silicon (Roxhed et al., 2008) and metal (Kim and Lee, 2006). These choices are justified by their mechanical properties and their biocompatibility potential. However inconveniences, like high production costs or fragility, required finding another option, and polymer was proposed. Polymer presents several advantages fitting well with microneedles production, like proven biocompatibility, biodegradable option, or adequate mechanical properties. Our laboratory developed hollow polymer microneedles, which are 900 μm microns tall structures in a 4 by 4 arrays, with a pitch to pitch distance of 2 mm. Detailed description of manufacturing and mechanical properties can be found in Sausse Lhernould and Delchambre (2011).

Davis et al. (2004) measured the insertion force for metal microneedles with a tip radius between 30 and 80 μm and found results varying between 0.08 N and 3.04 N. Using needles with a tip diameter between 55 and 115 μm, Park et al. (2006) report forces between 0.8 N and 1.29 N. Recently developed ultrasharp microneedles (Roxhed et al., 2007), with 0.1 μm tip radius, show the ability to insert into skin with a force less than 10 mN. To the best of our knowledge, this is the smallest insertion force reported in literature for microneedles. On the contrary (Henry et al., 1998) report insertion forces up to 10 N. Recent studies from Martanto et al. (2006), Wang et al. (2006) show the possibility to decrease necessary insertion force by rotating the needle.

Nature should always be a great inspiration source. Mosquitoes are exceptional in their ability to pierce human skin, Kong and Wu (2009) report measurements and prediction of insertion force for the mosquito fascicle penetrating into human skin. Reported forces are very low, in general at least three orders of magnitude lower than the reported lowest insertion force for an artificial microneedle. The insertion mechanism is very complex, the mosquito first

* Corresponding author. Tel.: +32 26502814; fax: +32 26502482.
E-mail address: msausse@ulb.ac.be (M.S. Lhernould).

http://dx.doi.org/10.1016/j.ijpharm.2015.01.019
0378-5173/

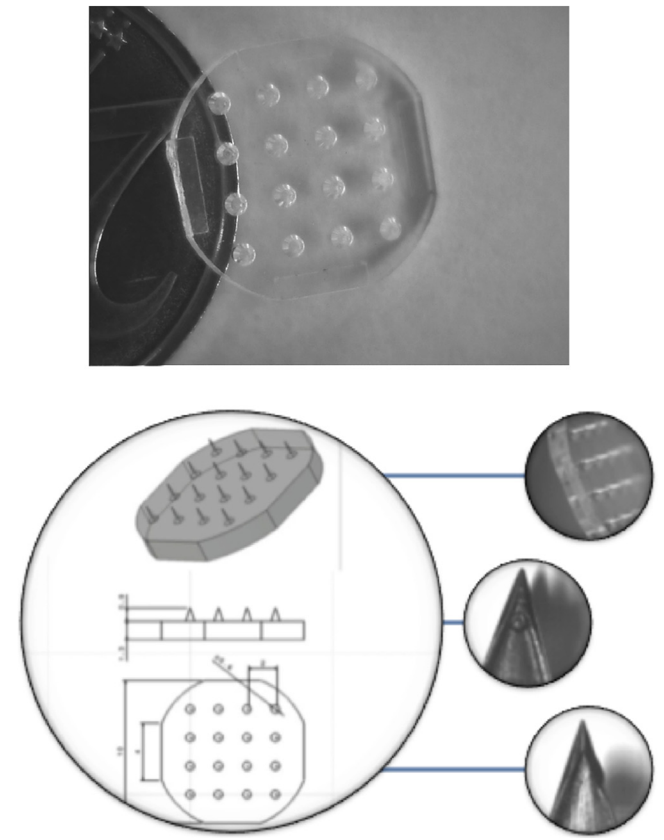

Fig. 1. Hollow polymer microneedle array developed at the Université Libre de Bruxelles.

anchors down its fascile tip on the top skin layer, then uses its toothed maxillae of the fascicle to saw its way into the tissue using a vibration frequency. This, with the nanometer size of the fascicle tip, probably explains the very low insertion forces.

While looking at the problematic of microneedle insertion, one should always also keep in mind the phenomenon referred to as bed of nails effect. When needles are placed too close to each other, they fail to pierce the skin. While the phenomena is not very documented concerning microneedles insertion, some paper mention it (Teo et al., 2006; Stoeber and Liepmann, 2005; Yung et al., 2012; Sausse Lhernould et al., 2013).

Inserting microneedles requires often using an assisting device to ease the insertion and allow to insert the microneedles in a repeatable homogeneous way, as suggested by van der Maaden et al. (2014). This explains why many applicators have been designed (Singh et al., 2011). The matter of optimizing microneedle arrays in view of easing the insertion has been previously addressed in Lhernould (2013), showing the importance of the microneedles tip surface on the insertion process. This paper focuses on understanding the influence of different insertion parameters independent of the micro needle array itself: insertion speed, insertion force, and insertion time.

2. Materials and methods

2.1. Hollow polymer microneedle array description

The microneedle arrays are 4 by 4 structures (Fig. 1). The needles are conical with an internal conical cavity. They are fabricated using injection moulding of a biocompatible polymer. These structures are interesting in terms of mechanical resistance and low production costs. The height of the needles is 900 μm with a 600 μm base diameter and a 60 μm tip diameter. The presence of an internal cavity results in a 80 μm wall thickness.

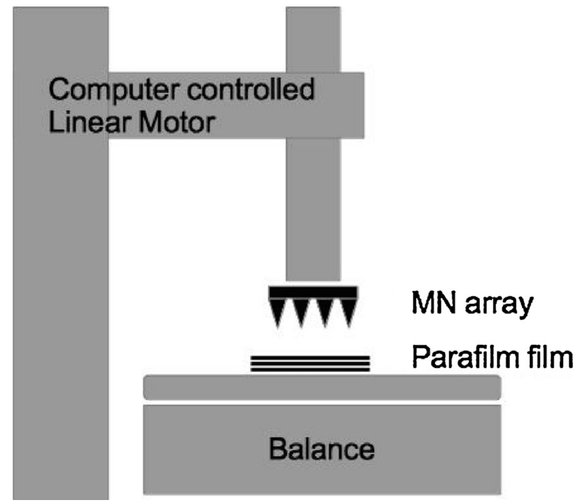

Fig. 2. Test bench used to assess MN penetration.

The microneedles have a conical geometry with an internal cavity, which is also conical. The hole is placed on the side in order to allow fluid to leave the cavity and exit with fewer resistance due to skin clogging. In a first fabrication step, a partially hollow microneedle is obtained using injection molding, thanks to a two inserts mold. Such a design allows modifying the clearance between both inserts until an appropriate configuration allows the material (polycarbonate) to flow and fill the cavities. Microneedles are thus hollow thanks to the cleared conical volume inside. In a second step, post-processing is needed in order to open the fluidic channels through the needle wall. Direct ablation by excimer laser beam (focused beam or through a mask) is the used solution for the micro drilling operation. The fabrication process allows high production rates at low costs (Sausse Lhernould and Delchambre, 2011).

2.2. Insertion of microneedle array

In their recent study (Larrañeta et al., 2014) showed good similarity between Parafilm® film layers and porcine skin, demonstrating that simple insertion tests can be reliably performed on Parafilm® films. One layer being 127 μm, the film is folded into eight layers in order to reach a thickness of around 1 mm. The microneedles array is inserted into the eight membrane layers using a linear motor. After insertion, the MN array is removed from the bench and unfolded, allowing to evaluate the number of holes left in each layer (using a binocular microscope). One layer being 127 μm $\pm$ 7 μm, the insertion depth can be deduced. Careful attention has been paid to control that the membrane is effectively ruptured as sometimes it may only have been deformed under microneedles pressure. Results take into account the fact that it is possible that not all needles have ruptured the membrane as will be illustrated in the results paragraph.

The insertion test bench uses a linear motor to project the microneedle array at controlled velocity and force, and maintains the MN array against the membrane for a defined time, as illustrated in Fig. 2. Force measurements are performed using a precision scale on which the membrane is deposited.

From Henry et al. (1998), theoretical insertion pressure to pierce skin is 3.183×10^6 Pa. The insertion force thus linearly increases with the tip surface of the microneedle (Davis et al., 2004). This is confirmed by Bodhale et al. (2010) who go even further, stating that once the microneedles have penetrated the skin, the resistive force falls drastically. From Sausse Lhernould and Delchambre (2011),