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# Hollow polymer microneedles array resistance and insertion tests

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ABSTRACT

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.

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## 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 been 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

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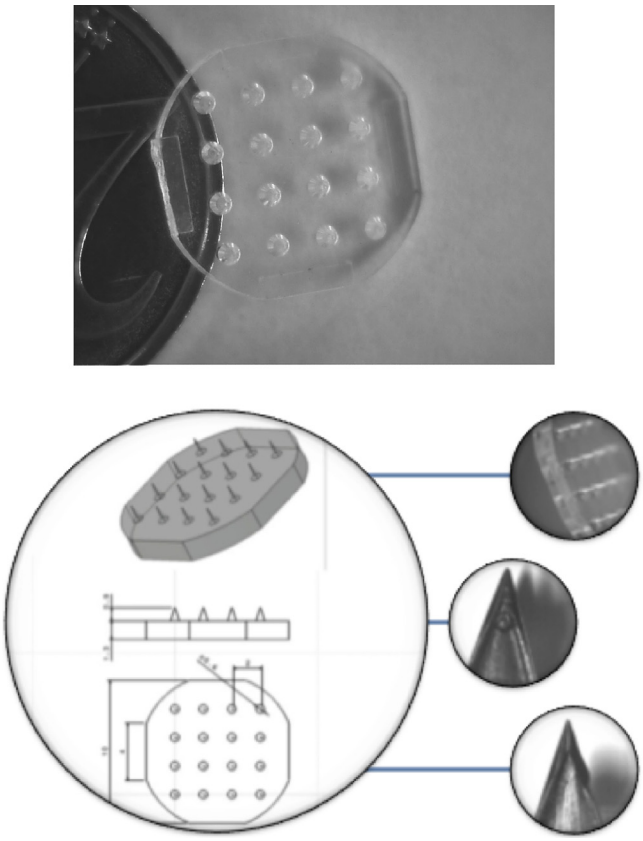

**Fig. 1.** Hollow polymer microneedle array developed at the Université Libre de Bruxelles.

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 needle 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.

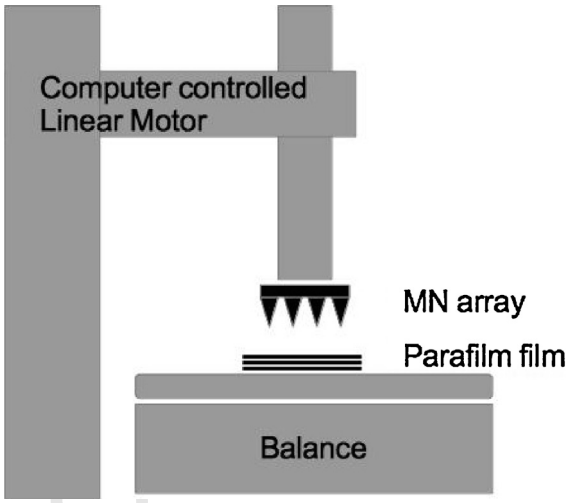


**Fig. 2.** Test bench used to assess MN penetration.

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 ± 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 measurement are performed using a precision scale on which the membrane is deposited.

From Henry et al. (1998), theoretical insertion pressure to pierce skin is $3.183 \times 10^6$ 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 has penetrated the skin, the resistive force falls drastically. From Sausse Lhernould and Delchambre (2011),

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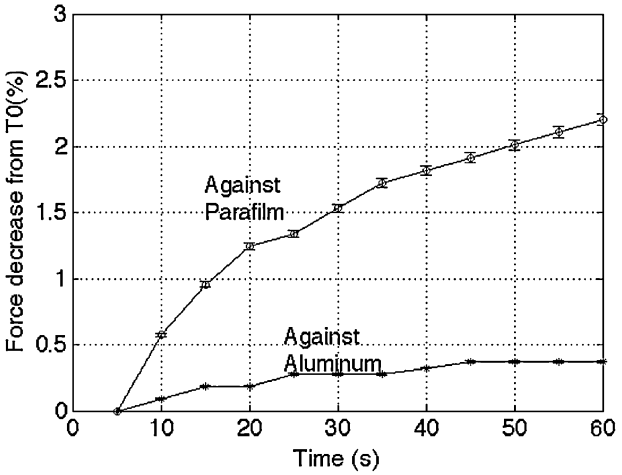


**Fig. 3.** Evolution of the measure of the application force with time (in percent).

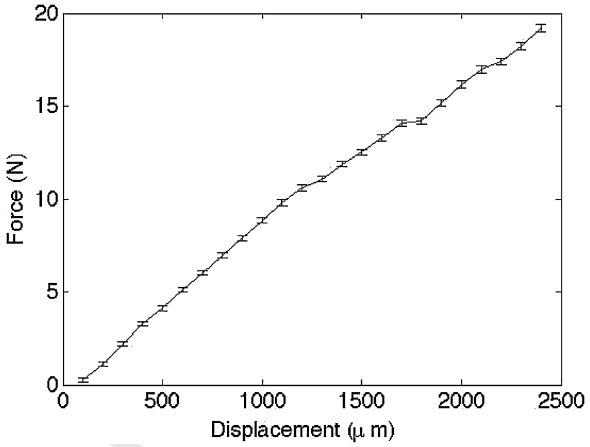


**Fig. 4.** Measurement of needle force during pressing against aluminium block. There is no discontinuity in the process.

the tip of the microneedles is 60 μm, leading to a theoretical force to rupture skin of 0.144 N which seems a very low value and may not be taking into account the bed of nails effect (Sausse Lhernould et al., 2013).

Initial testing was performed in order to determine the precision of the force measurements resulting from the test bench. The microneedle array is projected against the Parafilm® film at 1 m/s and observations of the measured force were made during 60 s, starting 5 s after impact in order to stabilise the balance. Similar tests were performed against an aluminium block. With the Parafilm® film, the force tends to decrease during the whole 60 s by up to 2.5% of the initial value, while against aluminium the measure is stable with less than 0.5% decrease. The elastic response of the Parafilm® film explains the phenomena as we will see further in this article, the microneedles being able to reach deeper layers of Parafilm® film (Fig. 3) with increased holding time. These errors in reading the correct measurements for the force have been included in the evaluation of errors made on measuring the force. Concerning insertion depth, errors may come from a bad observation of effective membrane rupture, but also come from some variation in the parafilm thickness of about ±7 μm.

## 3. Results

### 3.1. Mechanical resistance and blunting of microneedles

Microneedles are aimed at being used as a mean of transdermal drug delivery system. It is thus of the utmost importance that their are made of biocompatible material and resist to insertion into skin. This is why we use medical grade polymer, which not only is already widely used in the biomedical device industry, but is also very resistant.

The first resistance test consisted in pressing the microneedle array against an aluminium block at the speed of 0.1 mm/s. Fig. 4 shows no discontinuity in the process while pressing the MN against the aluminium block meaning that there is no needle fracture (silicium MN show a fracture phenomena (Davis et al., 2004) during similar testing). The polycarbonate needles have a good mechanical resistance. Even under extreme loading they do not break but crush. This is a very important feature because, even when misused, this insures that no needle will stay into the patient dermis. To observe the crushing phenomenon, an elevated force has to be applied. Even at a relatively important force (5.5 N) the needle damage was minor, as illustrated in Fig. 5a. Larrañeta et al. (2014) showed that 20 N was the average force used for users to press on an elevator button). Fig. 5b shows damages after pressing the array with a force of 13 N and Fig. 5c is for a force of 23 N at 1 m/s. Fig. 5d illustrates that by drastically diminishing the insertion speed, needle damages are lowered.

The second resistance test aimed at determining the process of needle blunting when microneedles may be used for several insertions. This may be required to treat wider skin surface such as in view of dermatological treatments. For this test, the microneedle array was pressed against the 1 mm Parafilm® membrane, and held during 10 s, with a force of 5 N and speed of 1 m/s, and observed under a microscope after each insertion. Repeatible insertion of MN into the Parafilm® film shows a slight decrease of effectiveness after 10 insertions tending to show that needle sharpness may have been damaged due to blunting. This however is very difficult to visually observe as illustrated Fig. 6a (needle after 1 insertion) and b (needle after 10 insertions).

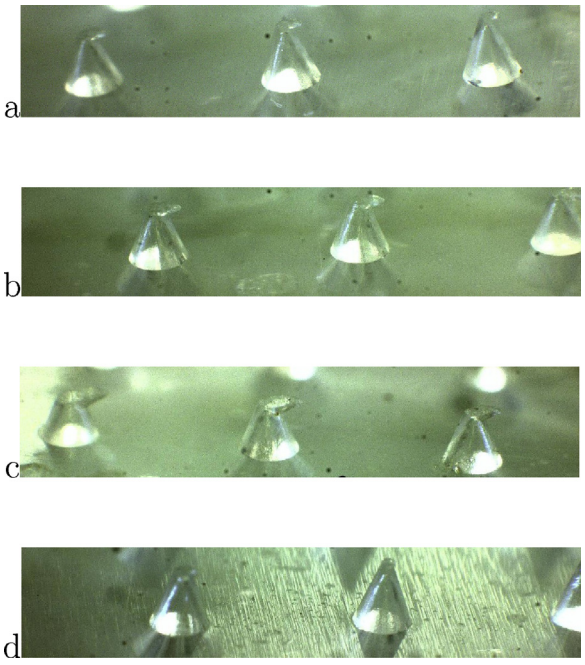


**Fig. 5.** Visual observations of polymer MN damages after pressing the array against an aluminium block at (a) $F = 5.5$ N, (b) $F = 13$ N, (c) $F = 23$ N with an impact speed of 1 m/s, (d) $F = 23$ N with impact speed of 1 mm/s.

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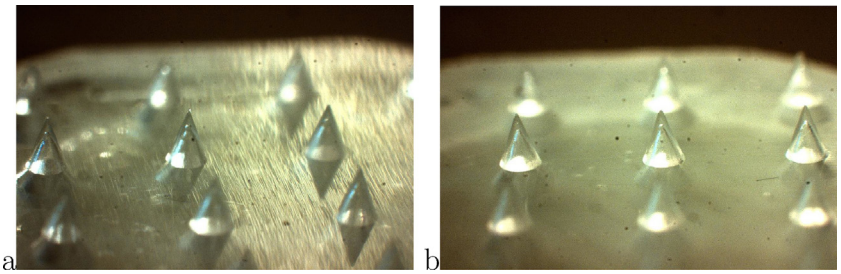

**Fig. 6.** Visual observations of needles (a) after 1 insertion, (b) after 10 insertions under a force of $F = 15$ N, at insertion speed 1 m/s and pressed against the Parafilm® for 10 s.

### 3.2. Manual application

Manual application of the microneedle array on Parafilm® layers seems to be efficient based on visual observation alone. However, closer observation through a microscope shows that there are indeed visual mark of the needle presence but, in many cases, the membrane only deformed but did not rupture. With an insertion force of approximately 10 N, by pressing with the thumb, only the 2 first Parafilm® layers were efficiently pierced meaning that insertion depth reached 250 μm. The third layer shows important deformations with the 16 needles clearly marked but did not rupture. The fourth layer was partially deformed. These observations tend to confirm the necessity to apply microneedle arrays using an impact insertion method, i.e. projecting the MN array at a minimum speed against the membrane in order to get efficient MN penetration. The second observation concerning the manual application is that it is very difficult to apply the same force in a repeatable way, meaning that, the correct insertion of MN array may vary from time to time or depending on users. This information is also important to underline the fact that, even when very sharp needles are used, and an impact application may not be required to effectively pierce membranes, it is important to assist the user with an applicator in order to reach each time the same insertion depth.

### 3.3. Assisted application

The thickness of Parafilm® film is 127 μm. We thus used 8 layers of Parafilm® to simulate a membrane with 1016 μm thickness. We believe that the insertion force cannot be dissociated from the insertion speed in order to get efficient membranes penetration. We thus realised several insertion tests at 0.1 N, 1 N and 10 N with insertion (which is in accordance with values used in Donnelly et al. (2011)) speeds of 0.5 m/s, 1 m/s, 2 m/s and 5 m/s and made observations.

The first general observation that we made was that, with optimised insertion parameters, insertion depth reached a maximum value for insertion forces above 20 N corresponding to 5 pierced layers, meaning a maximum insertion depth of 635 μm. Most of the time, with forces up to 20 N, the maximum insertion depth was equivalent to 4 layers meaning 508 μm. These observations are in good agreement with Larrañeta et al. (2014).

Three parameters have been investigated: insertion speed, insertion time (time while MN is held against the membrane) and insertion force. A membrane is considered to be pierced when there is clearly a visual indication of a hole. Sometimes the membrane is only deformed by the microneedles array, in that case the membrane is not considered to have been pierced. The holes left in the first layers of the membranes are a lot wider than in the underlying layers which is due to the needle diameter increasing while getting closer to its basis. Fig. 7 illustrates the holes left by the MN array on, (a) the first layer, (b) the second layer, (c) the third layer and (d) the forth pierced layer.

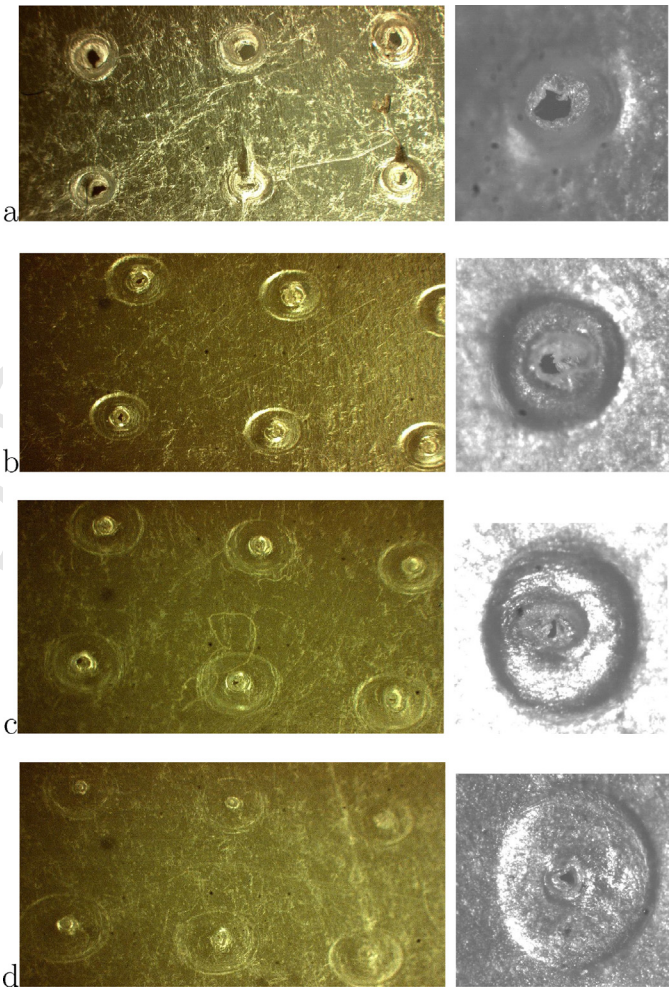

**Fig. 7.** Holes left on the different layers of membrane (a) 1st layer, (b) 2nd layer, (c) 3rd layer, (d) 4th layer.

First we tested the influence of insertion force by pressing the MN array against the membrane at a constant speed of 1 m/s and holding the insertion for 10 s. Results can be found in Fig. 8.

From these observation a maximum depth corresponding to 5 Parafilm® layers, around 600 *mu*m layers can be achieved.

Second we investigated the number of holed left on the 4 first layers for different forces and at speed of 1 m/s, the MN array being held against the membrane for 10 s. Results can be found in Fig. 9.

From these observation, a force of 12 N is sufficient to reach a depth of 500 μm with the 16 needles in a repeatable way.

We repeated the previous experiment, inserting the MN with a force of 2.5 N, a speed of 1 m/s but this time varying the time the MN array is pressed against the membrane. Results can be found in Fig. 10.

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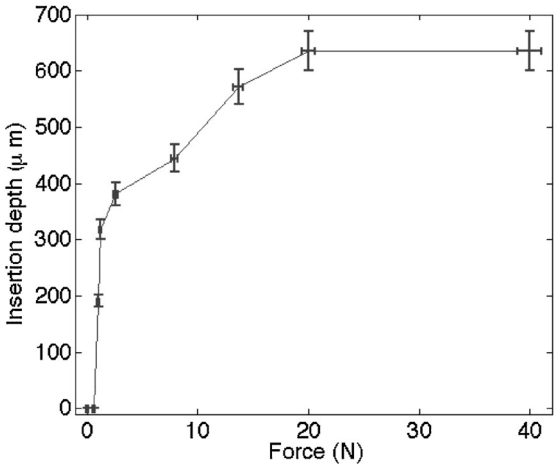


**Fig. 8.** Insertion depth as a function of insertion force by pressing the MN array at 1 m/s against the membrane and holding 10 s.

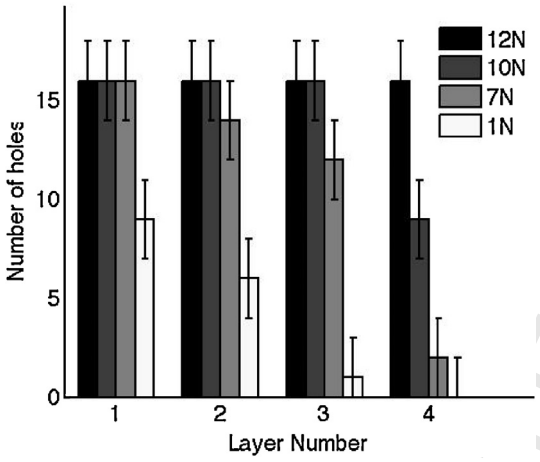


**Fig. 9.** Number of holes observed into the 4 first layers for insertion force up to 12 N for a speed of 1 m/s and holding time of 10 s.

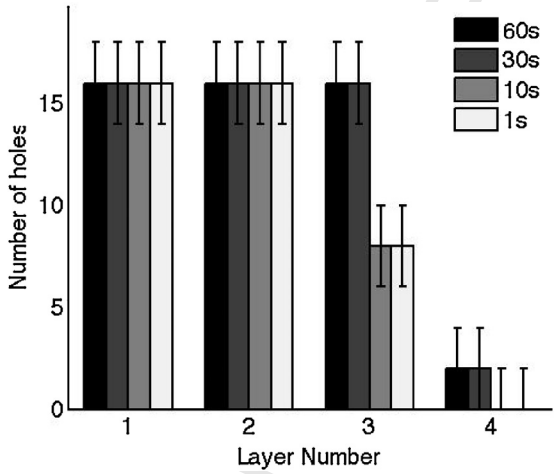


**Fig. 10.** Number of holes observed into the 4 first layers for insertion times varying from 1 s to 1 min with a force of 2.5 N and speed of 1 m/s.

From these observations, it is better to hold the MN array pressed against the membrane for at least 10 s against the membrane in order to efficiently pierce it.

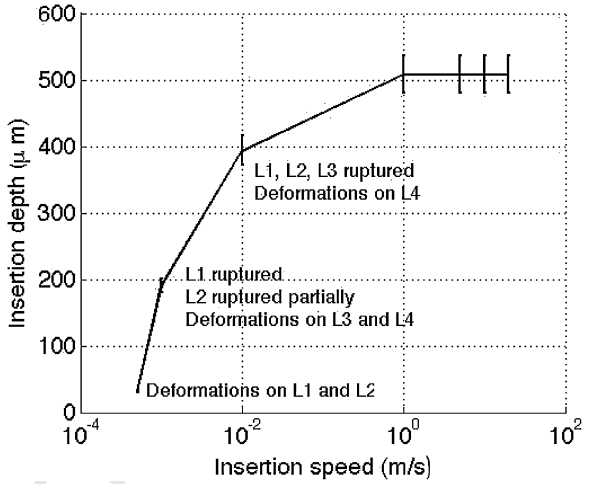


**Fig. 11.** Number of holes observed into the 4 first layers for insertion speeds varying from 0.1 m/s to 10 m/s with a force of 12 N and holding time 10 s.

We repeated once more the experiment above, this time varying the insertion speed, maintaining the array pressed for 10 s with a force of 12 N and monitoring the number of layers pierced. Results can be found in Fig. 11.

From theses observations, a 1 m/s force is mandatory in order to optimise piercing capabilities of our array.

## 4. Discussion

Using a new testing method using Parafilm® layers this article puts into evidence the importance of several parameters on the efficiency of a 4 by 4 polymer microneedle array. While insertion force is the most crucial parameter in order to insert the 900 μm high MN into a membrane, we have also put into evidence the importance of holding insertion for several seconds. Insertion speed is also an important parameter in order to optimise effective piercing of the membranes.

Concerning the developed 16 hollow polymer MN array, the first observation is that manual insertion is not possible in order to get an efficient and repeatable insertion. We thus recommend the use of an applicator able to control speed and insertion forces. This probably applies to all MN arrays, the insertion of microneedles might otherwise become a technical medical act to get a reliable insertion, which is not the aim of such devices.

An insertion force of 12 N is mandatory to effectively penetrate the membrane with a repeatable 500 μm depth. This data is true for a holding time of a least 10 s and an insertion speed of at least 1 m/s. Under 10 s there is a risk that the MN have not completely penetrated due to the elastic response time of the membrane. Also, with slower insertion speed, the MN do not pierce the skin as efficiently. However we also observed that, while increasing the insertion speed provides easier insertion, it also results in more damages to the needles. A compromise must thus be found and we believe that 1 m/s is a recommendable insertion speed.

Observations of multiple insertion of the polymeric microneedles has been carried out and showed that the blunting phenomenon does not significantly affect the insertion efficiency up to ten insertions. We would however not recommend the multiple use of the MN since it has been designed to be manufacturable at very low cost, it should be changed after each insertion.

This study confirms the necessity to use an applicator when inserting microneedle arrays into membranes, not only to avoid the so called bed of nails effect using impact insertion but also in order to obtain repeatable insertions. An insertion device does not only insure constant insertion force and thus insertion depth but it also

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helps the insertion process by maintaining the array pressed again the skin and by controlling the insertion force. Experiments to manually insert the MN array using hands resulted in non consistent results.

## 5. Conclusion

We have developed a hollow polymer MN array that might be fabricated at large scale and low cost because of its innovative fabrication method that implies micro-molding. The biocompatible polymeric materials not only insures excellent biocompatibility for the patients but is also extremely resistant considering insertion into the skin. It can withstand very high forces and does not break but crushes making the MN very safe for the patients as they can not be broken and stay into the skin.

Different insertion tests were performed on a folded in eight Parafilm® film that show excellent resemblance to porcine skin. Not only was the force of insertion investigated but also the insertion speed and the holding time of the array against skin. Results demonstrate that the insertion force is the most important parameter but can be compensated by optimising insertion speed and holding time. Each MN array will have its specific optimised parameters depending on needle number, needle spacing and needle sharpness.

While the insertion force for our MN is already largely acceptable regarding patient comfort, it can be drastically decreased by sharpening the micro needle tips. This is the subject of our future work.

## Acknowledgement

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