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¹ A proposed model membrane and test method for microneedle ² insertion studies

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A R T I C L E I N F O

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A B S T R A C T

A commercial polymeric film (Parafilm $M^{\textcircled{1}}$, a blend of a hydrocarbon wax and a polyolefin) was evaluated as a model membrane for microneedle (MN) insertion studies. Polymeric MN arrays were inserted into Parafilm $M^{\text{\tiny (B)}}$ (PF) and also into excised neonatal porcine skin. Parafilm $M^{\text{\tiny (B)}}$ was folded before the insertions to closely approximate thickness of the excised skin. Insertion depths were evaluated using optical coherence tomography (OCT) using either a force applied by a Texture Analyser or by a group of human volunteers. The obtained insertion depths were, in general, slightly lower, especially for higher forces, for PF than for skin. However, this difference was not a large, being less than the 10% of the needle length. Therefore, all these data indicate that this model membrane could be a good alternative to biological tissue for MN insertion studies. As an alternative method to OCT, light microscopy was used to evaluate the insertion depths of MN in the model membrane. This provided a rapid, simple method to compare different MN formulations. The use of Parafilm $M^{(1)}$, in conjunction with a standardised force/time profile applied by a Texture Analyser, could provide the basis for a rapid MN quality control test suitable for in-process use. It could also be used as a comparative test of insertion efficiency between candidate MN formulations.

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⁶ 1. Introduction

7 Microneedle (MN) devices are composed of an array of micron-
8 size needles. These systems are currently attracting great interest ⁸ size needles. These systems are currently attracting great interest $\frac{9}{2}$ 9 in transdermal drug delivery research ([Chandrasekhar](#page--1-0) et al., 2013;
10 11 Hanny et al., 1999; *Vim et al.*, 2013; Type Mahmaad et al., 2013). 10 Henry et al., 1998; Kim et al., 2012; [Tuan-Mahmood](#page--1-0) et al., 2013). 11 MN has the ability to pierce the outermost layer of the skin, the stratum cornoum (SC) and create migre conduits that can deliver 12 stratum corneum (SC) and create micro-conduits that can deliver
13 drugs to the deeper layers of the skip from where they can be 13 drugs to the deeper layers of the skin from where they can be observed directly into the systemic circulation (Prayspitz 2004) ¹⁴ absorbed directly into the systemic circulation ([Prausnitz,](#page--1-0) 2004).
¹⁵ Several key physical factors affect MN performance. These are:

15 Several key physical factors affect MN performance. These are:
 $\frac{16}{10}$ type of material, needle beight, tin-radius, hase diameter, needle ¹⁶ type of material, needle height, tip-radius, base diameter, needle $\frac{17}{12}$ geometry and needle density. The penetration denth and the ¹⁷ geometry and needle density. The penetration depth and the 18 fracture force of MN are determined by all these factors (Davis ¹⁸ fracture force of MN are determined by all these factors ([Davis](#page--1-0) 19 et al. 2004) Clearly effective penetration of MN arrays into the ¹⁹ et al., [2004](#page--1-0)). Clearly, effective penetration of MN arrays into the $\frac{20}{\pi}$ skin is the primary pre-requisite for effective drug delivery ²⁰ skin is the primary pre-requisite for effective drug delivery.
²¹ However when developing and testing MN systems it is apparent. However, when developing and testing MN systems, it is apparent

that there are limited techniques to evaluate this aspect. Most are $\frac{22}{12}$ based on the measurement of transepidermal water loss (TEWL) 23
(Badren at al. 2000; Bal at al. 2009) or in the viry elimination of the 24 ([Badran](#page--1-0) et al., 2009; Bal et al., 2008) or in the visualization of the 24
mismograps are tod effect be application of a due to the skip surface 25 micropores created after the application of a dye to the skin surface 25
(Ob at al. 2008; Regis at al. 2005; Merbeca at al. 2009; Merg at al. 26 (Oh et al., 2008; Park et al., 2005; [Verbaan](#page--1-0) et al., 2008; Wang et al., 26
2006), An elternative to these techniques is to take a higher of the 27 [2006](#page--1-0)). An alternative to these techniques is to take a biopsy of the $\frac{27}{10}$
MM giarged tiesue and section it wing histological techniques $\frac{28}{10}$ MN pierced tissue and section it using histological techniques 28
(Badran at al. 2000; Wang at al. 2006; Widera at al. 2006) In this 29 (Badran et al., 2009; Wang et al., 2006; [Widera](#page--1-0) et al., 2006). In this 29
latter case, the subsequent treatment of the skip could change the 30 latter case, the subsequent treatment of the skin could change the 30
structure of the micropores. Previously, optical coherence tomor structure of the micropores. Previously, optical coherence tomog-
 $\frac{31}{2}$
 $\frac{32}{2}$ raphy (OCT) has been demonstrated as a good option to evaluate 32
the insertion of MN (Coulman et al. 2011; Donnelly et al. 2010) It the insertion of MN (Coulman et al., 2011; [Donnelly](#page--1-0) et al., 2010). It 33
is a non-invasive technique and in addition to note diameter, the 34 is a non-invasive technique and, in addition to pore diameter, the 34
nenetration denth of the MN can be readily obtained

EXECUTE penetration depth of the MN can be readily obtained. The metric of the MN insertion studies have tunically been performed in 36 MN insertion studies have typically been performed in 36
slogical tissue and this can present some disadvantages in that 37 biological tissue and this can present some disadvantages, in that 37
tissue samples are often betarogeneous unstable and difficult to 38 tissue samples are often heterogeneous, unstable and difficult to 38
obtain. In addition, the use of higherical materials cometimes 39 obtain. In addition, the use of biological materials sometimes 39
presents legal issues Importantly many of the reported methods 40 presents legal issues. Importantly, many of the reported methods, $\frac{40}{11}$ although valuable during the product development phase, are too $\frac{41}{2}$ complex to be suitable as a standard, routine quality control (QC) 42
mothod, for MN. Thus, for QC applications, it is dosirable to 43 method for MN. Thus, for QC applications, it is desirable to 43 approximations by using an artificial material in place 44 overcome these limitations by using an artificial material in place

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 45 of skin. Critically, this will allow the speed and repeatability of experiments to be improved. There are many reports on the use of 46 experiments to be improved. There are many reports on the use of 47 experience for 47 diffusion studies generally $\frac{47}{18}$ artificial membranes for drug diffusion studies generally
 $\frac{48}{18}$ (Ng et al. 2012) and specifically for MN mediated transdermal 48 (Ng et al., [2012](#page--1-0)) and, specifically, for MN mediated transdermal
 49 drug delivery (Donnelly et al., 2009; Carland et al., 2012; Zhang $\frac{49}{100}$ drug delivery ([Donnelly](#page--1-0) et al., 2009; Garland et al., 2012; Zhang
50 et al., 2014). Artificial membranes are widely used for bypodermic 50 et al., [2014](#page--1-0)). Artificial membranes are widely used for hypodermic
 51 enedle mechanical testing and bench tests have been developed ⁵¹ needle mechanical testing and bench tests have been developed
 $\frac{52}{2}$ and standardiced for this purpose (Medrine et al. 2003) However $\frac{52}{100}$ and standardised for this purpose [\(Vedrine](#page--1-0) et al., 2003). However, 53 to the best of our knowledge, studies on artificial membranes for 54 ⁵⁴ MN insertion or mechanical characterization are scarce ([Hamilton,](#page--1-0) $\frac{55}{2011}$, $\frac{1}{2010}$, $\frac{1}{2010}$, $\frac{1}{2010}$, $\frac{1}{2010}$, $\frac{1}{2007}$, $\frac{1}{201}$, $\frac{1}{2010}$, $\frac{1}{2010}$, $\frac{1}{2010}$, $\frac{1}{2010$ 55 2011; [Koelmans](#page--1-0) et al., 2013; Muthu, 2007). The implementation of 56 are arrived for insertion attributed and also 56 an artificial membrane method for insertion studies can also
 57 arguidates land important comparison tool between different 57 provide valuable and important comparison tool between different
 58 types of MM expans 58 types of MN arrays.

⁵⁹ In this work, we propose the use of a polymeric film as a model
 60 for MN insertion studies A comparative study between the 60 for MN insertion studies. A comparative study between the 61 insertion of MN into this material and excised poenatal persine 61 insertion of MN into this material and excised neonatal porcine 62 ckin was carried out. OCT was used as a tool to qualitate the 62 skin was carried out. OCT was used as a tool to evaluate the incertion of MN inside the tissue taking into account aspects such 63 insertion of MN inside the tissue, taking into account aspects such 64 as the insertion force. Additionally, the force that patients use to 64 as the insertion force. Additionally, the force that patients use to 65 annly MN arrays to their skin was evaluated. To the best of our ⁶⁵ apply MN arrays to their skin was evaluated. To the best of our 66 knowledge there are no studies relating test conditions to actual ⁶⁶ knowledge, there are no studies relating test conditions to actual 67 real life use of MN in the context of skin insertion by patients a key ⁶⁷ real life use of MN, in the context of skin insertion by patients, a key
⁶⁸ factor in designing a reliable OC test method factor in designing a reliable QC test method.

⁶⁹ 2. Materials and methods

⁷⁰ 2.1. Materials

⁷¹ Gantrez[®] S-97 (M_w = 1.2 \times 10⁶), a copolymer obtained from the 72 free acid of methyl vinyl ether and maleic anhydride polymers, was
 73 provided by Ashland (Tadworth, Surrey UK), Poly(ethyleneglycol) ⁷³ provided by Ashland (Tadworth, Surrey, UK). Poly(ethyleneglycol)
74 (BEC) 10,000 Da was obtained from Sigma, Aldrich (Boole, Dorset ⁷⁴ (PEG) 10,000 Da was obtained from Sigma–Aldrich (Poole, Dorset, ⁷⁵ UK), Parafilm M^{\circledR} a flexible thermoplastic sheet (127 um) ⁷⁵ UK). Parafilm M[®], a flexible thermoplastic sheet (127 μ m thickness) made of olefin-type material was used as skin simulant ⁷⁶ thickness) made of olefin-type material, was used as skin simulant
77 **03** for insertion studies, was obtained from PPAND CMPH (Mortheim) ⁷⁷ **Q**3 for insertion studies, was obtained from BRAND GMBH (Wertheim, 78 of G or m) N obtains no produce the from foil was provided ⁷⁸ Germany). Deka[®] poly(urethane) needle testing foil was provided
⁷⁹ by Melab CmbH (Leopherg Germany) by Melab GmbH (Leonberg, Germany).

$\frac{81}{82}$ 2.2.1. Preparation of MN arrays
 $\frac{82}{82}$ To fabricate MN agueous bl.

⁸² To fabricate MN, aqueous blends containing Gantrez[®] S-97 (20%⁸³ u/w) and PEC 10,000 (7.5% u/w) were micromoulded in laser $\frac{83}{10000}$ w/w) and PEG 10,000 (7.5% w/w) were micromoulded in laser-⁸⁴ engineered silicone micromould templates, as previously ⁸⁵ described (Donnelly et al., 2010, 2011; [Migalska](#page--1-0) et al., 2011; $\frac{86}{100}$ [Garland](#page--1-0) et al., 2011; Singh et al., 2009, 2010). Three different MN
 $\frac{87}{1000}$ geometries were used (Table 1). Light misroscope images of the $\frac{87}{100}$ geometries were used (Table 1). Light microscope images of the $\frac{88}{100}$ two main MN arrays used in this work can be seen in Fig. 14. $\frac{88}{10}$ two main MN arrays used in this work can be seen in [Fig.](#page--1-0) 1A.
 $\frac{89}{100}$ Alternatively, two different fermulations were used to propage. ⁸⁹ Alternatively, two different formulations were used to prepare
 $\frac{90}{25}$ either brittle (propared by adding codium carbonate 2.5% w/w.to ⁹⁰ either brittle (prepared by adding sodium carbonate 3.5% w/w to $\frac{91}{100}$ the original formulation) or floyible (prepared by replacing BEC in ⁹¹ the original formulation) or flexible (prepared by replacing PEG in $\frac{92}{100}$ the original formulation with 10% w/w glucatine) MN arrays. In the ⁹² the original formulation with 10% w/w glycerine) MN arrays. In the $\frac{93}{100}$ proparation of brittle and flovible formulations the MN was not 93 preparation of brittle and flexible formulations the MN was not
94 crosslinked (Donnelly et al. 2012a) crosslinked ([Donnelly](#page--1-0) et al., 2012a).

2.2.2. Human manual force measurements 95
The forces that 20 volunteers applied using their thumbs were 96 The forces that 20 volunteers applied using their thumbs were 96
resured using a TA YIPlus Texture Applycer (Stable Micro 97 measured using a TA.XTPlus Texture Analyser (Stable Micro 97
Systems Surrey UK) The selected volunteers were 10 males 98 Systems, Surrey, UK). The selected volunteers were 10 males 98
and 10 females aged between 20 and 35 years. The volunteers were 99 and 10 females aged between 20 and 35 years. The volunteers were $\frac{99}{100}$
asked to apply the same force they would use to push an elevator $\frac{100}{100}$ asked to apply the same force they would use to push an elevator button or to press a stamp onto an envelope, using their right ¹⁰¹ thumb and a 30 s application period, as shown in [Fig.](#page--1-0) 1B. The 102
Turtum Application we seed in tension mode to register the force 103 Texture Analyser was used in tension mode to register the force 103
survey. Three different nonproters were determined from these 104 curves. Three different parameters were determined from these 104
example the meximum minimum and example forme analized 105 curves: the maximum, minimum and average forces applied 105
during this time internal (Fig. 16) during this time interval [\(Fig.](#page--1-0) $1C$).

2.2.3. Insertion of MN arrays 107

Full this linear negative large parties of the considered a good Full thickness neonatal porcine skin can be considered a good a state of hair considered a good a state burn of hair consequences and physical a state of the human claim terms of hair consequences and physical a state of t model for human skin in terms of hair sparseness and physical 109
proporties (Mayor 1006) It was obtained from stillborn piglets and properties (Meyer, 1996). It was obtained from stillborn piglets and 110
oxciood <24.0 b after high Full thickness ckin (≈ 0.5 mm) was then excised <24.0 h after birth. Full thickness skin (\approx 0.5 mm) was then 111
stored in aluminium foil at 20.0 °C until further use Two sections stored in aluminium foil at -20.0 °C until further use. Two sections 112
of skip were placed together, with the dermal side contacting each of skin were placed together, with the dermal side contacting each 113
other, such that the stratum corneum surface was exposed at either other, such that the stratum corneum surface was exposed at either side, giving a total skin thickness of about 1 mm. This was then utilised for the OCT assessment of MN penetration. 116
As an alternative to peopatal porcine skip Parafilm M^{\circledR} (PF) film

As an alternative to neonatal porcine skin, Parafilm $M^{(8)}$ (PF) film 117
decay needle, testing polyurathano, film, were used as skin 118 and a needle testing polyurethane film were used as skin 118
cimulante A shoot of Danglin was folded to get an eight layer 119 simulants. A sheet of Parafilm was folded to get an eight-layer 119
film (\approx 1 mm thickness) and a poly(urathane) needle testing film 120 film (\approx 1 mm thickness) and a poly(urethane) needle testing film (20 A) was used as received (0.4 mm thickness). The 121 (Deka[®]) was used as received (0.4 mm thickness). The ¹²¹
skin/Parafilm[®] was then-placed onto a sheet of expanded poly ¹²² skin/Parafilm[®] was then placed onto a sheet of expanded poly 122
(othylone) for support ¹²³ (ethylene) for support.

124 Two insertion methods were carried out: manual and Texture 124
alwer insertion For manual insertion different volunteers were Analyser insertion. For manual insertion, different volunteers were 125
requited to apply the MN arrays following the same instructions as recruited to apply the MN arrays following the same instructions as 126
in the force measurement, experiment. The Texture Applycer in the force measurement experiment. The Texture Analyser 127
incention was performed wing a TA YTPlus Texture Analyser insertion was performed using a TA.XTPlus Texture Analyser ¹²⁸
(Stable Migre Systems, Surrey, UK) in sempression mode, MN (Stable Micro Systems, Surrey, UK) in compression mode. MN 129
arrays were placed on the surface of the skin artificial mombrane 130 arrays were placed on the surface of the skin/artificial membrane 130
and sticky tape (Office Depot, Boca Patop, USA) was carefully and sticky tape (Office Depot, Boca Raton, USA) was carefully 131
annlied on the upper surface without annlying force (Fig. 1D). The applied on the upper surface without applying force ([Fig.](#page--1-0) 1D). The $\frac{132}{2}$ probe was lowered onto the skin/artificial membrane at a speed of 0.5 mm s⁻¹ until the required force was exerted. Forces were held for 30 s and varied from 10 N to 50 N per array. Once the target force was reached, the probe was moved upwards at a speed of 0.5 mm s⁻¹.

2.2.4. Optical coherence tomography 138

Inserted MN arrays were immediately viewed wing an EX1201 139 Inserted MN arrays were immediately viewed using an EX1301 ¹³⁹
T. Microscope (Micholsop Diagnostics I td., Kont. J.W.), The swept 140 OCT Microscope (Michelson Diagnostics Ltd., Kent, UK). The swept-
source Fourier domain OCT system has a laser centre wavelength of [141] source Fourier domain OCT system has a laser centre wavelength of 141
1205.0 + 15.0 pm facilitating real time high recolution imaging of 142 1305.0 \pm 15.0 nm, facilitating real-time high-resolution imaging of 142
the unner claim layers (7.5 um lateral and 10.0 um vertical 143 the upper skin layers $(7.5 \,\mu\text{m})$ lateral and $10.0 \,\mu\text{m}$ vertical 143
resolution). The skin was scanned at a frame rate of up to 15 144 resolution). The skin was scanned at a frame rate of up to 15^{144}
B scans (2D cross sectional scans) per second (scan width = 2.0 145 B-scans (2D cross-sectional scans) per second (scan width = 2.0 μ μ = μ). The 2D images were analyzed using the imaging seftuare μ = 146 mm). The 2D images were analysed using the imaging software 146
Imagel® (National Institutes of Hoalth Bothosda USA) The scale of 147 ImageJ[®] (National Institutes of Health, Bethesda, USA). The scale of 147
the image files obtained was 1.0 nivel = 4.2 um thus allowing 148 the image files obtained was 1.0 pixel = 4.2μ m, thus allowing 148
accurate measurements of the depth of MN penetration and the 149 accurate measurements of the depth of MN penetration and the ¹⁴⁹
width of pere created. Three replicates were performed, and the ¹⁵⁰ width of pore created. Three replicates were performed, and the ¹⁵¹ insertion depths of 25 MN were measured in total.

¹⁵² 2.2.5. MN insertion testing using light microscopy

MN arrays were inserted using a Texture Analyser, as described a model in the into eight-layer folded PF sheets. In these cases, sticky tape a model in the sticky tape and the into eight-layer folded PF sheets. In these ca above, into eight-layer folded PF sheets. In these cases, sticky tape 154
was not used. After the insertion, the MN arrays were removed 155 was not used. After the insertion, the MN arrays were removed 155
from the polymeric sheet. The PE was upfolded and the number of 156 from the polymeric sheet. The PF was unfolded and the number of 156
halos in asab layer was avalyted wing a Laise EZ4. D dirital 157 holes in each layer was evaluated using a Leica EZ4 D digital

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