International Journal of Pharmaceutics 497 (2016) 62–69

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

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

A facile system to evaluate *in vitro* drug release from dissolving microneedle arrays

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ARTICLE INFO

Article history:
Received 7 October 2015
Received in revised form 18 November 2015
Accepted 21 November 2015
Available online 1 December 2015

Keywords:
Microneedles
Release tests
Polymeric films
Transdermal
Quality control

ABSTRACT

The use of biological tissues in the *in vitro* assessments of dissolving (?) microneedle (MN) array mechanical strength and subsequent drug release profiles presents some fundamental difficulties, in part due to inherent variability of the biological tissues employed. As a result, these biological materials are not appropriate for routine used in industrial formulation development or quality control (QC) tests. In the present work a facile system using Parafilm M® (PF) to test drug permeation performance using dissolving MN arrays is proposed. Dissolving MN arrays containing 196 needles (600 μm needle height) were inserted into a single layer of PF and a hermetic "pouch" was created including the array inside. The resulting system was placed in a dissolution bath and the release of model molecules was evaluated. Different MN formulations were tested using this novel setup, releasing between 40 and 180 μg of their cargos after 6 h. The proposed system is a more realistic approach for MN testing than the typical performance test described in the literature for conventional transdermal patches. Additionally, the use of PF membrane was tested either in the hermetic "pouch" and using Franz Cell methodology yielding comparable release curves. Microscopy was used in order to ascertain the insertion of the different MN arrays in the PF layer. The proposed system appears to be a good alternative to the use of Franz cells in order to compare different MN formulations. Given the increasing industrial interest in MN technology, the proposed system has potential as a standardised drug/active agent release test for quality control purposes.

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1. Introduction

Microneedle (MN) devices are currently attracting great interest in transdermal drug/vaccine delivery and patient monitoring (Donnelly et al., 2014a, 2012b; Mooney et al., 2014; Prausnitz 2004; Quinn et al., 2014; Yang et al., 2013). These systems are composed of an array of micron-sized needles that painlessly, and without drawing blood, pierce and bypass the outermost layer of the skin, the *stratum corneum* (SC), which is the principal barrier to transdermal drug delivery (Benson and Watkinson, 2012; Hadgraft, 2002; Prausnitz et al., 2004). MN arrays create micro-conduits through the SC that can be used to deliver drugs to the deeper layers of the skin from where they can be absorbed directly into the systemic circulation, or to deliver vaccines to the skin-resident antigen-presenting cells (Donnelly et al., 2012b; Tuan-Mahmood et al., 2013).

MN technology is, of course, part of the broader transdermal drug delivery (TDD) area. TDD has been an important area of pharmaceutical research and development over the last four decades (Margetts and Sawyer, 2007; Prausnitz et al., 2004; Prausnitz and Langer, 2008). More recently, the market value of TDD has increased significantly from US$12.7 billion dollars in 2005 to an expected US$32 billion in 2015 (Paudel et al., 2010). However, this market is predominantly based on passive diffusion through the SC. This limits the number of molecules to only a small group (less than 20 approved drugs) that share three features: molecular mass <500 Da, relatively high lipophilicity and low required daily dose (<2 mg) (Margetts and Sawyer, 2007). As MN arrays bypass the SC, molecules delivered using this technology do not need to fulfil these requirements (Donnelly et al., 2012b). This makes MN technology an appealing approach to overcome the main limitations of conventional transdermal delivery systems

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http://dx.doi.org/10.1016/j.ijpharm.2015.11.038
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while keeping its key advantages: non-invasive delivery method, avoidance of the first-pass effect, suitability for self-administration and prolonged drug release (Prausnitz and Langer, 2008). MN mediated transdermal drug delivery offers a major expansion of the route.

To date there are no MN transdermal patches on the market due to the difficulty in scale-up of fabrication (Lutton et al., 2015a). In addition, there are no currently accepted regulatory standards for MN products. The lack of MN regulation generates further difficulties regarding mass production, which requires accepted standards to assess product quality (Lutton et al., 2015a).

To date, almost all MN insertion and drug permeation studies have been carried out using biological tissue. A variety of skin models, such as heat separated epidermis, dermatomed skin, full-thickness skin, in addition to synthetic membranes have been used for these purposes (Coulman et al., 2009; Garland et al., 2012; Lee et al., 2008; Verbaan et al., 2007). Biological tissue samples are often heterogeneous, unstable, difficult to obtain and the use of biological materials sometimes presents legal issues. Therefore, these biological materials are not suitable to be routinely used in industrial formulation development or quality control (QC) tests as the tests themselves are not reproducible and, accordingly, cannot be transferred between laboratories. A good alternative to overcome these limitations in MN testing is to replace biological tissues with synthetic materials. The number of research publications detailing the use of artificial membranes in MN testing is limited however. Some examples of studies outlining the use of artificial membranes for MN insertion studies are: (Hamilton, 2011; Koelmans et al., 2013; Larrañeta et al., 2014; Muthu, 2007). Drug permeation studies using artificial membranes have been carried out by the following research teams (Donnelly et al., 2009; Garland et al., 2012; Zhang et al., 2014). Garland et al. (2012) studied the use of different skin models, including biological tissue (dermatomed and full-thickness neonatal porcine skin) and an artificial silicone membrane (Silescol®), to evaluate drug permeation from dissolving MN arrays. Due to the elasticity of the Silescol® membrane, MN arrays did not remain inserted in the membrane but rather were withdrawn from it, thus limiting drug permeation. For this reason, Silescol® membranes cannot be considered a suitable material for MN testing.

In the past, we proposed the use of Parafilm M® as a model for MN insertion studies (Larrañeta et al., 2014). Continuing with the use of artificial membranes for MN characterization/testing in this work, a facile method using Parafilm M® to test drug permeation using dissolving MN arrays is proposed. A series of dissolving MN arrays were prepared containing representative models of either a low molecular weight active (methylene blue) or a macromolecule (fluorescein isothiocyanate–dextran). Permeation of these molecules was evaluated *in vitro* using the proposed method and compared with conventional Franz cells permeation experiments.

2. Material and Methods

2.1. Materials

Gantrez® S-97 (M_w = 1,500.000), a copolymer of methylvinylether and maleic acid polymers, was provided by Ashland (Surrey, UK). Poly(ethyleneglycol) (PEG, M_w = 10,000), poly(vinyl alcohol) (PVA, M_w = 9000–10,000, 80% hydrolyzed) and Methylene blue were obtained from Sigma–Aldrich (Dorset, UK). The isothiocyanate–dextran (FITC-dextran 70, M_w = 63,000–77,000) was obtained from TdB Consultancy AB (Uppsala, Sweden) and polyvinylpyrrolidone (PVP, M_w = 58,000) was obtained from Ashland (Surrey, UK). Parafilm® M, a flexible thermoplastic sheet (127 μm thickness) made of olefin-type material was obtained from Brand GMBH (Wertheim, Germany).

2.2. Mehtods

2.2.1. Preparation of MN arrays

Aqueous blends containing Gantrez® S-97 (20% w/w), PEG 10,000 (7.5% w/w) and the selected molecules were individually used to fabricate MN arrays. Table 1 shows the formulations used in this study. This formulation was poured into laser-engineered silicone micromould templates, centrifuged for 15 min at 3500 rpm, allowed to dry under ambient conditions for 48 h. This process was followed for the preparation of dissolving MN arrays. In order to prepare hydrogel-forming MN arrays, a crosslinking step (80 °C for 24 h) was carried out after the MN arrays were dry (Donnelly et al., 2012a,2014b). Additionally the hydrogel-forming MN arrays formulation only containing Gantrez® S-97 and PEG 10,000. All the arrays (1 cm^2) contained 14 × 14 needles with the following dimensions: 600 μm needle height and 300 μm width at the base.

2.2.2. Release experiments

MN arrays were inserted in a single PF layer using a TA.XTPlus Texture Analyser (Stable Micro Systems, Surrey, UK) in compression mode (Larrañeta et al., 2014). MN arrays were placed on the surface of the PF membrane and the probe lowered onto the MN array at a speed of 0.5 mm s^{-1} until the required force was exerted (40 N). Forces were held for 30 s. Once the target force was reached, the probe was moved upwards at a speed of 0.5 mm s^{-1}. PF was then folded around the baseplate of the MN array and thermally sealed, thus creating a hermetic “pouch” (Fig. 1A). A UK twenty pence coin was applied to the back part of the system as sinker (Diameter = 21.4 mm; Weight = 5.0 g; Thickness = 1.7 mm; Composition: 84% copper and 16% nickel) was applied to the back part of the system. The experiment was slightly modified for the release of hydrogel-forming MN arrays. This specific type of MN arrays was inserted in the PF and the backing layer containing MB was attached to the baseplate (Donnelly et al., 2012a). The diffusion of water will cause controlled swelling of the MN arrays creating an *in situ* hydrogel conduit. This will allow the liberation and diffusion of MB from the patch through the hydrogel MN into the release medium (Donnelly et al., 2012a). The release experiment was carried out by placing two of these closed PF/MN array systems inside a beaker containing 30 mL of phosphate buffer solution (PBS, pH 7.4) (Fig. 1B) in a thermostatic bath at 32 °C with a stirring speed of 52 strokes/min). Samples (1 mL) were extracted at defined time intervals and replaced with an equal volume of PBS.

2.2.3. Franz cell permeation studies

A single layer of PF was placed on a sheet of dental wax and then a MN array was inserted into the PF using a TA.XT-plus Texture Analyser (Stable Micro Systems, Surrey, UK) as described before. The PF sheet with the MN arrays inserted was placed and secured to the donor compartment of the diffusion cell using cynoacrylate adhesive. Once MN arrays were in place, donor compartments were mounted onto the receptor compartments of the Franz cells

Table 1
Composition of different formulations (%w/w).

Compound	F1	F2	F3	F4
Gantrez® S-97	20.0	20.0	–	–
PEG 10,000	7.50	7.50	–	–
PVP 58 kDa	–	–	–	40.00
PVA 9-10 kDa	–	–	20.00	–
Methylene blue	0.50	–	0.37	0.73
FITC-Dextran 70 kDa	–	1.00	–	–
Water	72.00	71.50	–	59.27

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