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Successful application of large microneedle patches by human volunteers

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ABSTRACT

We describe, for the first time, the design, production and evaluation of large microneedle patches. Such systems, based on 16 individual microneedle arrays (needle height 600 μm), were prepared from aqueous blends of 15% w/w Gantrez® S97 and 7.5% w/w poly(ethyleneglycol) 10,000 Da. Ester-based crosslinking was confirmed by FTIR and mechanical strength was good. Insertion depths in a validated skin model were approximately 500 μm. Ten human volunteers successfully self-inserted the microneedles of these larger patches in their skin, following appropriate instruction, as confirmed by transepidermal water loss measurements. The mean insertion depth ranged between 300 and 450 μm over the area of the large patches. That this was not significantly different to a single unit MN patch self-applied by the same volunteers is encouraging. Microneedle patch sizes much larger than the 1–2 cm^2 will be required if this technology is to be successfully translated to clinic for delivery of drug substances. The work described here suggests that use of such larger patches by patients can be successful, potentially opening up the possibility for a significant expansion of the size of the market for transdermal drug delivery.

1. Introduction

Microneedle (MN) arrays are minimally-invasive devices that are used to penetrate the skin's outermost layer, the *stratum corneum* (SC), which is the principal barrier to topically-applied drugs (Donnelly et al., 2012b; Larrañeta et al., 2016c; Prausnitz 2004). MN arrays are currently of great interest to the pharmaceutical industry, due to the number of advantages they possess over traditional methods of drug delivery, such as oral and parenteral administration. Some of the benefits include the ability to painlessly administer the active pharmaceutical ingredient, bypass of hepatic first pass metabolism and extension of the range of types of drug that can be delivered intradermally and transdermally (Tuan-Mahmood et al., 2013).

A wide variety of substances have been successfully delivered transdermally and intradermally using MN arrays (Donnelly et al., 2012a; Larrañeta et al., 2016a; Prausnitz 2004; Tuan-Mahmood et al., 2013). However, the predominant focus in the field has been on vaccines (Henry et al., 1998; McGrath et al., 2011). This is hardly surprising, given the potential for stable, dry state formulation, the avoidance of needle-stick injuries common with hypodermic syringes, dose-sparing through direct targeting of viable skin's abundance of professional antigen-presenting cells and the self-disabling nature of dissolving MN. Indeed, MN vaccines have the potential to revolutionise vaccination, especially in the developing world. In studies where delivery of therapeutic drug substances using has been exemplified, the focus has tended to be on illustration of the capability of MN in delivering a substance with particular physicochemical characteristics and little mention is typically made of the actual amount delivered or its relevance to therapeutic human doses.

Vaccines tend to be quite potent and so delivery of even microgram quantities of antigen, antigen/adjuvant combination, virus-like particle or even DNA is often sufficient to elicit an immune response, especially when targeted to the viable epidermis and/or dermis. This means that small, postage stamp-sized MN patches that can be inserted into skin by fairly gentle thumb pressure are sufficient to achieve successful vaccination. Our own work has focused strongly on delivery of therapeutically-relevant doses of drugs using MN patches (Donnelly et al., 2012a, 2014b; Kearney et al., 2016). We have measured plasma levels in

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animal models and extrapolated to estimate suitable patch sizes for achievement of therapeutic plasma levels in humans. Since most commonly-used small molecule drugs tend to require oral doses in the range of tens to hundreds of milligrams daily, the patch sizes we have estimated have ranged from 10 cm^2–30 cm^2. Such patch sizes are well within the range of marketed transdermal patches. Indeed, Novartis market Nicotinell® (nicotine) patches of 30 cm^2 (Novartis, 2017), while Janssen market Duragesic® CII (fentanyl) patches of 32 and 42 cm^2 (Janssen, 2017), for example. MN patches of such sizes could clearly not be effectively inserted into skin using a single thumb. Since it is our opinion that patients will be more accepting of a large MN patch that can be applied by hand rather than an applicator device, we sought here, for the first time, to examine the ability of human volunteers to successfully use large MN patches.

2. Material and methods

2.1. Materials

Gantrez® S-97 (Mw = 1.2×10^6 Da), a copolymer obtained from the free acid of methyl vinyl ether and maleic anhydride polymers, was provided by Ashland (Tadworth, Surrey, UK). Poly(ethylene glycol) (PEG, molecular weight 10,000 Da) was purchased from Sigma-Aldrich (Steinheim, Germany). Parafilm M®, a flexible thermoplastic sheet (127 μm thickness) made of olefin-type material and used as a skin simulant for insertion studies, was obtained from BRAND GMBH (Wertheim, Germany). In order to build the MN patch, an adhesive dressing, Tegaderm™ (3M, St Paul, USA), and a pressure-responsive film, Pressurex-micro Green® (Sensor Products Inc., Madison, USA) were used.

2.2. Fabrication of hydrogel-forming MN arrays

MN arrays were prepared using aqueous blends containing 15% w/w Gantrez® S-97 and 7.5% w/w PEG 10,000. The formulation (0.5 g/cm^2) was carefully syringed onto silicone micromoulds (14×14 needles on a 0.5 cm^2 area, 600 μm needle height). The needle cavities were filled after applying positive pressure (3–4 bar) to the formulation for 15 min. MN arrays were left to dry for 48 h at room temperature and were then crosslinked by esterification through heating at 80 °C for 24 h (Donnelly et al., 2012a, 2014b; Larrañeta et al., 2015; Lutton et al., 2015b). The MN arrays were stored under ambient until assembled into large patches.

2.3. MN array characterization

MN were inspected using a Leica EZ4 D digital microscope (Leica, Wetzlar, Germany) and a Keyence VHX-700F digital microscope (Keyence, Osaka, Japan).

Attenuated total reflectance (ATR) Fourier transform infrared (FTIR) spectroscopy was used to evaluate the crosslinking of MN arrays. The IR spectra were recorded at room temperature using a FTIR Accutrac FT/IR-4100 Series (Jasco, Essex, UK) equipped with MIRacle™ software from 4000 to 600 cm^{-1}, with a resolution of 4.0 cm^{-1}. The obtained spectra were the result of averaging 64 scans.

Axial compression forces (*i.e.* forces applied perpendicular to the needle base) were applied to MN arrays in order to evaluate needle strength. A known load was applied to the MN arrays in axial compression mode of a TA.XT-Plus Texture Analyser (Stable Micro Systems, Surrey, UK). MN arrays were attached to the moving test probe of the Texture Analyser using double-sided adhesive tape. The MN arrays were then pressed against a flat block of aluminium at a rate 0.5 mm s^{-1} until a maximum force of 30 N per array was applied. The change in needle height was evaluated using the Leica EZ4 D digital microscope.

Parafilm® M (PF) film was used as a skin simulant for MN insertion studies, as described previously (Larrañeta et al., 2014). MN arrays were inserted into a sheet assembled from 8 layers of Parafilm® using the Texture Analyser, with the probe lowered onto the artificial membrane at a speed of 0.5 mm s^{-1}, with an exerted force of 30 N per array, held for 30 s. The MN arrays were removed from the polymeric sheet after insertion, the PF sheet unfolded and the number of holes in each layer was evaluated using the Leica EZ4 D digital microscope. In order to ease the detection of the created holes in the PF layers, the sample was placed between two polarizer filters. The thickness of each PF layer was determined previously to be 126 ± 7 μm (Larrañeta et al., 2014) and this knowledge was used to calculate the percentage of MN successfully inserted as a function of depth.

2.4. Assembly of large patches from individual microneedle arrays

Large MN patches were assembled by using the adhesive properties of Tegaderm™ films (10 cm × 12 cm) to attach 16 individual MN arrays (Fig. 1). To the reverse, non-adhesive side of the assembled patches, the pressure-responsive Pressurex-micro Green® indicator sensor films were attached using double-sided adhesive tapes. Pressurex-micro Green® changes colour from white to red when pressures >20 N cm^{-2} are applied. Notably, colour changes are only seen on areas of the film where the pressure exceeds the cut-off. Below this, the microparticles from the red donor layer are not transferred to the white receiver layer. We have previously shown that pressures of approximately 10 N cm^{-2} are sufficient to successfully insert hydrogel-forming MN into human skin *in vivo*. Accordingly, Pressurex-micro Green® serves as a useful patient feedback tool, confirming MN insertion. For larger MN patches, where correct insertion of each individual array will be required for consistent dosing, addition of such site-specific feedback will be vital.

2.5. Volunteer recruitment

Ten healthy volunteers (6 men and 4 women), aged between 20 and 30 years old, with no pre-existing skin conditions were recruited to the study by means of an email circular. Volunteers were asked not to apply cosmetic formulations to their upper arm or forearm 24 h prior to the study and to avoid hot showers/baths or exercise immediately before the study. Volunteers were provided with a patient information leaflet and a volunteer information sheet detailing the aims and objectives of the study, their contribution and, in particular, the risks associated and the confidentiality of the results obtained upon recruitment. The School of Pharmacy Research Ethics Committee, Queen's University Belfast, approved this study. All volunteers were asked to confirm their fully-informed consent by signing an appropriate form prior to participating in the study (See Supporting Information). All data was anonymised and stored on firewalled servers in password-protected files and was scheduled for destruction 2 years after completion of the study. Only the researchers directly involved in the study had access to the data.

2.6. Patient information leaflet and counselling

The patient information leaflet (PIL) used in this study (See Supporting Information) was prepared with particular emphasis on existing PILs for transdermal patches' (*e.g.* BuTrans®). Reference was made to PILs for other products (*e.g.* metred-dose inhalers) that require a more descriptive protocol and the inclusion of