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Potential of hydrogel-forming and dissolving microneedles for use in paediatric populations

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ABSTRACT

Development of formulations and drug delivery strategies for paediatric use is challenging, partially due to the age ranges within this population, resulting in varying requirements to achieve optimised patient outcomes. Although the oral route of drug delivery remains the preferred option, there are problematic issues, such as difficulty swallowing and palatability of medicines specific to this population. The parenteral route is not well accepted by children due to needle-related fear and pain. Accordingly, a plethora of alternative routes of drug administration have been investigated. Microneedles (MN) breach the *stratum corneum* (*SC*), the outermost layer of skin, increasing the number of drug substances amenable to transdermal delivery. This strategy involves the use of micron-sized needles to painlessly, and without drawing blood, create transient aqueous conduits in the *SC*. In this study, polymeric dissolving MN and hydrogel-forming MN were fabricated incorporating two model drugs commonly used in paediatric patients (caffeine and lidocaine hydrochloride). The potential efficacy of these MN for paediatric dosing was investigated *via in vitro* and *in vivo* studies. Views pertaining to MN technology were sought amongst school children in Northern Ireland, members of the UK general public and UK-based paediatricians, to determine perceived benefits, acceptance, barriers and concerns for adoption of this technology. In this study, polymeric MN were shown to substantially enhance skin permeability of the model therapeutic molecules *in vitro* and *in vivo*. In particular, hydrogel-forming MN led to a 6.1-fold increase in caffeine delivery whilst lidocaine HCl delivery was increased by 3.3-fold using dissolving MN *in vitro*. Application of caffeine-loaded MN led to a caffeine plasma concentration of 23.87 μg/mL in rats at 24 h. This research also highlighted a strong consensus regarding MN technology amongst schoolchildren, paediatricians and the general public, regarding potential use of MN in the paediatric population. Overall, 93.6% of general public respondents and 85.9% of paediatricians regarded the use of MN as a positive approach.

1. Introduction

The oral route of drug delivery remains the preferred option for patients, due to its convenience, ease of administration and non-invasive nature. Whilst the use of hypodermic needles produces predictable plasma concentration profiles compared to oral delivery and allows delivery of a greater range of drugs (*e.g.* aminoglycosides), it often has poor patient acceptance, primarily due to pain and needle-related phobia (Smith and Meuret, 2012). This invasive means of drug delivery typically requires administration by skilled healthcare personnel, hence, necessary visits to primary care settings, which might be inconvenient and distressful to patients, especially children (De Schepper et al., 2011).

Microneedles (MN) consist of a plurality of micron-sized projections, typically assembled on one side of a supporting base or patch (Prausnitz, 2004). These microprojections generally range in height from 25 μm to 2000 μm and are produced from a range of materials (*e.g.* silicon, glass, polymers) (Donnelly et al., 2011; Gill and Prausnitz, 2007; Prausnitz, 2004) and have the ability to painlessly and without draining blood penetrate the *stratum corneum*, the principal barrier layer of the skin (Donnelly et al., 2011). MN may offer particular benefits to the paediatric population. For example, by avoiding pain during childhood immunisation and needle-related medicine therapy.

The ultimate commercial success of MN-based delivery and monitoring devices will depend upon not only the ability of the

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devices to perform their intended function, but also their overall acceptability by both health care professionals and patients. Accordingly, efforts to ascertain the views of these end-users will be essential in moving forwards. A previous study in this regard was conducted recruiting healthcare professionals and members of the public, who were able to appreciate potential advantages and drawbacks of the use of MN (Birchall et al., 2011). Reduced pain, less tissue damage and reduced risk of transmitting infections and needlestick injuries; the feasibility for self-administration and use in children, needlephobics and/or diabetics were some of the identified advantages. Some concerns regarding effectiveness, a means of confirming successful drug delivery, delayed onset of action, costs of the delivery system, possible accidental use, misuse or abuse were also raised (Birchall et al., 2011). Our previous study used focus groups with children to qualitatively explore the children perspective and thoughts on MN and their use as an alternative approach to blood sampling (Mooney et al., 2014). However, no previous studies have investigated children's views on MN technology as a potential drug delivery tool. Further studies in the area of MN perceptions and acceptability will undoubtedly aid researchers and industry as it moves towards the marketing of MN devices.

In the present study, caffeine and lidocaine hydrochloride were chosen as model drugs to evaluate the feasibility of transdermal delivery of drug molecules using novel laser-engineered polymeric MN for potential paediatric applications. Since MN will need strong approval from end users, such as paediatricians, who will prescribe the products, parents who will administer them to their children, and the children themselves in order to achieve improved therapeutic outcomes for patients, we also sought to ascertain the views of children, paediatricians and members of the general public based in the UK on the potential use of MN for drug delivery, with a particular focus for paediatric applications. Clearly, this will provide a valuable insight on the acceptance and perspectives of the different population groups on MN technology as a potential drug delivery tool for the paediatric population.

2. Materials and methods

2.1. Chemicals

Poly(methylvinylether/maelic anhydride) (Gantrez® AN-139) was provided by Ashland, (Kidderminster, UK). Acetic acid (glacial), poly(ethyleneglycol) (PEG) 10,000 daltons, sodium hydroxide, methylene blue, caffeine (anhydrous), lidocaine hydrochloride (HCl) monohydrate and 7-(β-hydroxyethyl)theophylline) (7-BHT) were obtained from Sigma–Aldrich (Steinheim, Germany). Caffeine 5 mg/mL Solution for Injection (For Intravenous and Oral Administration) was purchased from Martindale Pharma® (Newport, UK). Sodium dihydrogen phosphate dihydrate and acetonitrile (ACN) (isocratic HPLC grade) were obtained from VWR® (Leuven, Belgium) and tetrahydrofuran from Merck (Darmstadt, Germany). All other chemicals were of analytical reagent grade.

2.2. Preparation of dissolving MN

Silicone MN mould templates (11 × 11 and 19 × 19 MN/array, 600 μm in height, 300 μm of base diameter) were laser-engineered as described previously (Donnelly et al., 2011). Aqueous blends containing 20% w/w poly(methylvinylether/maelic acid) (PMVE/MA) and 2% w/w caffeine or 6% w/w lidocaine HCl were cast in the moulds as previously described (Donnelly et al., 2010, 2011; Garland et al., 2012b; Migalska et al., 2011). To study the influence of different pH of lidocaine-loaded dissolving MN, an extra batch of dissolving MN was prepared by neutralising the acidic PMVE/MA aqueous blend to pH 7 by adding sodium hydroxide pellets (pH 209 bench top pH meter, Hanna® Instruments, Rubano, Italy) prior to lidocaine HCl addition. Following drying for 48 h at room temperature, a heated scalpel was used to remove the side walls (Garland et al., 2011).

2.3. Preparation of hydrogel-forming MN

Hydrogel-forming MN were prepared from aqueous blends containing 15% w/w PMVE/MA and 7.5% w/w PEG also using 11 × 11 and 19 × 19 MN moulds, as previously described (Donnelly et al., 2010, 2011, 2014; Migalska et al., 2011). Upon preparation, MN were dried at room temperature for 48 h. Following MN crosslinking at 80 °C (Laboratory oven VENTI-Line, VWR International, Leicestershire, UK) for 24 h, sidewalls were removed using a heated scalpel (Garland et al., 2011).

2.4. Preparation of caffeine loaded patches

Adhesive patches were prepared from aqueous blends consisting of 10% w/w PMVE/MA, 5% w/w tripropyleneglycol methyl ether (TPM) and 3% w/w caffeine for *in vitro* studies. Following centrifugation to remove the air incorporated during the preparation of the blend by Jouan C312 laboratory centrifuge, DJB Labcare (Buckinghamshire, UK) at 3500 rpm for 15 min, an aliquot of 2.7 g was cast into 30 × 30 mm^2 silicon moulds and left to dry for 48 h, as previously described (Donnelly et al., 2012).

2.5. In vitro *transdermal permeation studies*

Transdermal permeation and the ability to deliver hydrophilic drugs from the 3 delivery systems was studied. Namely, 11 × 11 dissolving MN, caffeine-loaded patches coupled to 11 × 11 hydrogel-forming MN, hereinafter named "integrated hydrogel-forming MN", and single drug-loaded patches (without MN) delivery was investigated *in vitro* across dermatomed (300–400 μm) neonatal porcine skin (previously shown to be a suitable skin model for prediction of *in vivo* performance of MN (Garland et al., 2012b)) by using a modified Franz-cell setup (Donnelly et al., 2010, 2011; Migalska et al., 2011). Systems composed of MN were applied by using a custom spring-activated applicator at a force of 11.0 N per array (Donnelly et al., 2010), whilst adhesive patches were applied using gentle pressure (Donnelly et al., 2011). The release medium was phosphate buffered saline (PBS, pH 7.4).

2.6. Analysis of caffeine and lidocaine HCl in PBS

Caffeine and lidocaine HCl were quantified using isocratic HPLC methods (Agilent Technologies 1200 Series, Stockport, UK). Caffeine quantification was achieved using a C18 Spherisorb® ODS2 (4.6 × 150 mm, 5 μm particle size) analytical column (Waters Associates, UK). The mobile phase consisted of a ratio of 90:10 of 0.52% v/v acetic acid aqueous solution and a mixture of 50% ACN and 50% tetrahydrofuran at a flow rate of 1 mL/min. Sample injection volume was 50 μL and run time 10 min. The column was thermostated at 35 °C and UV detection was set at 273 nm. Lidocaine HCl was quantified using a C18 Bondapak™ (3.9 × 300 mm, 10 μm packing) analytical column (Waters Associates, UK). The mobile phase consisted of 55% 0.02 M phosphate buffer pH 6 and 45% ACN at a flow rate of 1 mL/min. Sample injection volume was 20 μL and run time 13 min. UV detection was performed at 265 nm. Chromatograms obtained for both caffeine and lidocaine HCl were analysed using Agilent ChemStation® Software B.02.01. Least squares linear regression analysis and correlation analysis were performed on the calibration curve produced, enabling determination of the equation of the line, its coefficient of determination and the residual sum of squares. An