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# Design and physicochemical characterisation of novel dissolving polymeric microneedle arrays for transdermal delivery of high dose, low molecular weight drugs

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ABSTRACT

We describe formulation and evaluation of novel dissolving polymeric microneedle (MN) arrays for the facilitated delivery of low molecular weight, high dose drugs. Ibuprofen sodium was used as the model here and was successfully formulated at approximately 50% w/w in the dry state using the copolymer poly(methylvinylether/maleic acid). These MNs were robust and effectively penetrated skin *in vitro*, dissolving rapidly to deliver the incorporated drug. The delivery of 1.5 mg ibuprofen sodium, the theoretical mass of ibuprofen sodium contained within the dry MN alone, was vastly exceeded, indicating extensive delivery of the drug loaded into the baseplates. Indeed in *in vitro* transdermal delivery studies, approximately 33 mg (90%) of the drug initially loaded into the arrays was delivered over 24 h. Iontophoresis produced no meaningful increase in delivery. Biocompatibility studies and *in vivo* rat skin tolerance experiments raised no concerns. The blood plasma ibuprofen sodium concentrations achieved in rats (263 μg $ml^{-1}$ at the 24 h time point) were approximately 20 times greater than the human therapeutic plasma level. By simplistic extrapolation of average weights from rats to humans, a MN patch design of no greater than 10 $cm^2$ could cautiously be estimated to deliver therapeutically-relevant concentrations of ibuprofen sodium in humans. This work, therefore, represents a significant progression in exploitation of MN for successful transdermal delivery of a much wider range of drugs.



## 1. Introduction

Microneedle (MN) arrays are micron scale, minimally-invasive devices that painlessly by-pass the skin's *stratum corneum* (*SC*), which is the principal barrier to topically-applied drugs. MN arrays have been extensively investigated in recent years as a means to enhance transdermal drug and vaccine delivery. The current trend in MN-based research has involved recognition of the dubious biocompatibility of silicon and the potential for inappropriate reuse of silicon or metal microneedles, which remain fully intact after removal from a patient's skin. Consequently, much recent effort has focussed on MN arrays prepared from drug-loaded gels of FDA-approved biocompatible polymers. Such systems typically dissolve in skin interstitial fluid to release their drug payload.

Dissolving MN arrays have been shown to enhance transdermal and intradermal delivery of numerous substances, including insulin [1,2], 5-aminolevulinic acid [3], sulforhodamine B [4], low molecular weight heparin [5], ovalbumin [6,7], adenovirus vector [7] and a variety of vaccine antigens [8,9]. Synergistic effects of dissolving MN arrays used in combination with other enhancing strategies have been reported recently by Garland et al. [10], where the use of drug-loaded dissolving poly(methyl-vinyl-ether-co-maleic-acid) MN arrays was coupled with iontophoresis.

A schematic depiction of the means by which dissolving MN arrays deliver their payload is presented in Fig. 1(A). The compounds delivered to date by dissolving MNs have typically been of high potency, meaning only a low dose is required to achieve a therapeutic affect (*e.g.* insulin) [11] or elicit the required immune response [8,9]. Accordingly, dissolving MN arrays have proven to be an extremely successful delivery strategy, even though high molecular weight biomolecules are only normally delivered from the dissolving MNs themselves and not the baseplate upon which they are formed [11]. Clearly, the majority of marketed drug substances are not low dose high potency biomolecules. Indeed, many drugs require oral doses of several hundred milligrams

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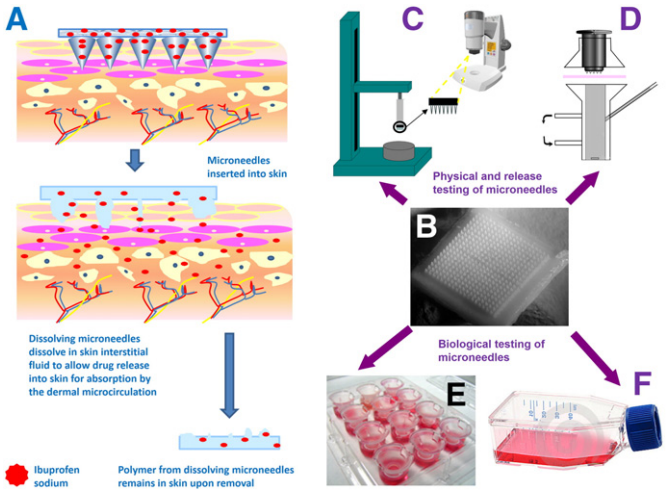


**Fig. 1.** Schematic illustration of the mechanism of drug delivery from dissolving microneedle arrays with containing ibuprofen sodium (A). Digital image of the optimised formulation for dissolving microneedles containing ibuprofen sodium (B). Texture Analyser/light microscopy set-up for investigation of physical properties of microneedles (C) and Franz cell set-up for *in vitro* transdermal drug release studies (D). Indication of biological testing of microneedles in 3D (E) and 2D (F) cell culture models.

per day in order to achieve therapeutic plasma concentrations in humans. Until now, such high doses could not be delivered transdermally from a patch of reasonable size, even for molecules whose physicochemical properties are ideal for passive diffusion across the skin's *stratum corneum* barrier. Therefore, transdermal delivery has traditionally been limited to fairly lipophilic low molecular weight, high potency drug substances. Since most drug substances do not possess these properties, the transdermal delivery market has not expanded beyond around 20 drugs [12–14]. In the present study, we aimed to overcome the current limitations of both conventional transdermal delivery and dissolving MN strategies to deliver, for the first time, therapeutically-relevant doses of a model low molecular weight, high dose drug molecule.

## 2. Materials and methods

### 2.1. Chemicals

Polyethylene glycol (PEG, MW 10,000 Da), ibuprofen sodium, poly(vinyl alcohol) (PVA, MW 31,000–50,000 g/mol), polyvinylpyrrolidone (PVP, MW 40,000 g/mol), alginic acid sodium salt and the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) cell viability reagent were purchased from Sigma Aldrich, Dorset, UK. Eudragit® S (MW 125,000 g/mol) and Eudragit® L (MW 125,000 g/mol) were obtained from Rohm GmbH & Co.KG, Pharma Polymers, Darmstadt, Germany. Poly(lactic acid) (PLA) was purchased from Futerro, Escanaffles, Belgium. Isocratic HPLC grade methanol and acetonitrile were purchased from VWR International, East Grinstead, UK. L-132 lung epithelial cells were purchased from the American Type Culture Collection (ATCC) and EpiSkin™ was purchased from Skin Ethic Laboratories, Lyon, France. The human IL-1α ELISA kit and Bradford assay kit were purchased from Pierce, Rockford, IL, USA. Gantrez® AN-139, a co-polymer of methyl vinyl ether and maleic anhydride (PMVE/MAH, MW 1,080,000 Da) and Gantrez® MS-955, a mixed sodium and calcium salt of methyl vinyl ether and maleic anhydride copolymer (PVM/MA, MW 1,000,000 Da) were gifts from Ashland, Kidderminster, UK. All other chemicals used were of analytical reagent grade.

### 2.2. Microneedle array fabrication

Laser-engineered silicone micromould templates were used in micromoulding of MN arrays and were microfabricated using a previously-reported approach [15]. The arrays were composed of 361 (19 × 19) needles perpendicular to the base, of conical shape and 600 μm in height, with base width of 300 μm and interspacing of 50 μm. The array area was approximately 0.49 $cm^2$. In order to test the compatibility and suitability of a number of different polymers as potential matrices in the formation of polymeric MN arrays with high loadings of incorporated ibuprofen sodium, various aqueous gel formulations were prepared, as summarised in Table 1. Approximately 300 mg of the relevant polymer gel/drug preparation was poured into the silicone moulds and these were centrifuged for 15 min at 550 ×*g*. Following centrifugation, the MN arrays were dried in the moulds at room temperature for 48 h. The MN arrays were then carefully removed from the moulds and assessed visually for mechanical strength and formulation homogeneity.

### 2.3. Fabrication of PMVE/MA microneedle arrays incorporating ibuprofen sodium

After numerous iterations, MN arrays prepared using the free acid co-polymer poly(methylvinyl ether/maleic acid) (PMVE/MA), produced by aqueous hydrolysis of the PMVE/MAH supplied as described previously [11,15,16], were found to have superior properties to other compositions (Fig. 1B). To prepare such arrays, relevant masses of ibuprofen sodium and a 30% w/w PMVE/MA gel, the pH of which had been altered to 7.0 using sodium hydroxide (NaOH) pellets, were added together so as to generate a formulation of polymer gel:drug in the ratio 70%:30%. This formulation was then poured into the silicone micromoulds, centrifuged for 15 min at 550 ×*g* and again allowed to dry under ambient conditions for 48 h.

### 2.4. Rheological characterisation of PMVE/MA gels containing ibuprofen sodium

In order to consider the processability of gels with such high drug loadings, continuous flow rheological assessment of the gels was performed using a TA Instruments AR 1500 Rheometer (TA Instruments, Elstree, Herts, UK) fitted with a 40 mm diameter steel parallel plate. Flow rheology was conducted at 25 °C in continuous ramp mode with the shear rate increased from 0 to 50 1/s. Viscosity was determined by application of the Power law.

### 2.5. Determination of water content of PMVE/MA microneedles incorporating ibuprofen sodium

The percentage water content of the ibuprofen sodium-loaded PMVE/MA MN arrays was determined with a Q500 Thermo Gravimetric Analyser (TA Instruments, Elstree, Herts, UK). Samples of 5.0–10.0 mg were heated from ambient temperature to 600 °C at a heating rate of 10 °C $min^{-1}$. Nitrogen flow rates of 40 ml $min^{-1}$ (balance purge gas) and 60 ml $min^{-1}$ (sample purge gas) were maintained for all samples. The data from thermogravimetric analysis experiments was analysed with TA Instruments Universal Analysis 2000 software, version 4.4A (TA Instruments, Elstree, Herts, UK).

### 2.6. Mechanical testing of microneedle arrays

MN arrays were subjected to mechanical tests for compression and skin insertion. The mechanical properties were evaluated using a TA-XT2 Texture Analyser (Stable Microsystems, Haslemere, UK) in compression mode, as described previously [15] (Fig. 1C). MN arrays were visualised before and after application of the compression load using a