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Research paper

Production of dissolvable microneedles using an atomised spray process: Effect of microneedle composition on skin penetration

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ABSTRACT

Dissolvable microneedles offer an attractive delivery system for transdermal drug and vaccine delivery. They are most commonly formed by filling a microneedle mold with liquid formulation using vacuum or centrifugation to overcome the constraints of surface tension and solution viscosity. Here, we demonstrate a novel microneedle fabrication method employing an atomised spray technique that minimises the effects of the liquid surface tension and viscosity when filling molds. This spray method was successfully used to fabricate dissolvable microneedles (DMN) from a wide range of sugars (trehalose, fructose and raffinose) and polymeric materials (polyvinyl alcohol, polyvinylpyrrolidone, carboxymethylcellulose, hydroxypropylmethylcellulose and sodium alginate). Fabrication by spraying produced microneedles with amorphous content using single sugar compositions. These microneedles displayed sharp tips and had complete fidelity to the master silicon template. Using a method to quantify the consistency of DMN penetration into different skin layers, we demonstrate that the material of construction significantly influenced the extent of skin penetration. We demonstrate that this spraying method can be adapted to produce novel laminate-layered as well as horizontally-layered DMN arrays. To our knowledge, this is the first report documenting the use of an atomising spray, at ambient, mild processing conditions, to create dissolvable microneedle arrays that can possess novel, laminate layering.

1. Introduction

Microneedle insertion into skin forms temporary micropores in the skin which aid the delivery of drugs that are unable to passively diffuse through the *stratum corneum* [1–3]. First generation microneedles, made from silicon, metals or organic polymers, were designed to create the pore in the skin into which the drug or vaccine diffused [2,4]. More recently, microneedle arrays have been manufactured from biodegradable materials that fully incorporate drugs and vaccines that dissolve in the skin, thereby eliminating sharps waste, such as hypodermic needles, currently required to administer the drug or vaccine [5–7]. Materials such as sugars and polymers have been used to formulate dissolvable microneedles (DMNs) because of the biocompatibility and the release profiles of these materials [8–10]. Compared to coated microneedle devices, dissolvable microneedles can potentially incorporate a higher drug load and they eliminate all sharps waste as the needles dissolve during drug delivery.

Dissolvable microneedles are commonly fabricated by molding processes using a limited range of methods. Complete filling of micromolds with formulation is constrained by high interfacial tension at the micron-scale between the solution and the mold. Incomplete filling results in poor microneedle tip formation, the presence of air bubbles or inability to remove the dissolvable microneedle from the mold. Some methods involve heating the material, so that the molten material can then be poured into the mold or pulled into the microneedles by vacuum or centrifugation [5,7,8,11,13,14]. A key barrier to the successful translation of biodegradable microneedles will be the ability to fabricate these drug delivery systems at large scale; however, the commonly used fabrication methods are predominantly batch methods, which may pose obstacles with respect to scale up for efficient, high-throughput continuous manufacturing processes. For successful development of vaccine

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containing DMNs, the manufacturing process must be compatible with these labile biologics.

To date, DMNs have been manufactured from many biocompatible materials such as sugars, namely maltose [7,11], galactose [15], trehalose, sucrose, mannitol or xylitol [12]), glycosaminoglycans [16], polymers, namely polylactic acid, polyglycolic acid and their copolymer PLGA [8,9,13,17,18], poly(vinyl)alcohol [10], polyvinylpyrollidone (PVP) [14,19,20] and carboxymethylcellulose (CMC) [8,13]. Sugars, such as trehalose or sucrose, are often chosen as microneedle substrates as they can stabilise protein in the amorphous state [3,12,21,22]. Assessment of the crystallinity of sugar DMNs produced provides an indication of the physical and vaccine stability of a drug delivery system. Sugars and celluloses are often hygroscopic and susceptible to the effects of humidity, processing and handling, resulting in physical and chemical degradation of the microneedle and the incorporated active material [15]. It was hypothesised that an external coating on the microneedles could provide a protective barrier preserving the DMN from loss of physical integrity following storage and handling. Skin penetration is a critical attribute that must be achieved by a dissolvable microneedle array. Failure of skin penetration can result from buckling of the microneedles upon application [23]. Penetration of the skin is dependent on microneedle design and the component materials which affect the tensile strength and the microneedle array design [10]. Previous studies that examined DMN skin penetration focussed on fracture force of the microneedle as a measure of mechanical strength in tandem with representative *en face* staining or histology to demonstrate pore formation in the skin [9,10,12]. Here, we wished to quantify the consistency and reliability of microneedle patch insertion into different skin layers as a functional assessment of DMN skin penetration, providing the first confirmation of the effect of selecting different component materials on the ability of the DMN to penetrate the skin.

Our aim is to develop a DMN fabrication method that could be transferred to a scaled-up GMP-compliant process using common pharmaceutical processes that would enable the subsequent clinical application of such a drug/vaccine delivery technology. Spray-coating is a robust and scalable coating technique that is well established in the pharmaceutical industry. We previously explored and developed this process to film-coat silicon microneedle arrays [24] and furthermore to successfully coat silicon microneedles with live vaccines that retained *in vivo* potency [3]. To date, spraying has not been used to fill molds and produce biodegradable, dissolvable microneedles. We hypothesised that high interfacial tension between the solution and the mold could be overcome by disrupting the cohesive forces of the aqueous solution with the shear produced in the nozzle cap during atomisation, producing fine droplets which are deposited onto the surface of the mold contours. This enables complete wetting of the microneedle mold and tip during filling, removing the requirement for a centrifugation or vacuuming step.

The focus of this study was to determine the applicability of the spraying process to DMN fabrication and to determine if spray-fabricated DMN reliably penetrate skin. We demonstrate the effect of the material of construction on the degree of skin penetration by the DMNs fabricated. We also demonstrate that by altering spraying parameters and solution formulation, horizontal and laminate-layered DMN can be fabricated. Finally, in contrast to a vacuum fabrication method [12], we demonstrate that a single sugar formulation forms an amorphous glass when sprayed into microneedle molds. To our knowledge, this is the first report of laminate-layered DMN. The atomising spray fabrication method, initially investigated as a potentially scalable method, is therefore a versatile method that can produce dissolvable microneedle arrays with composite layers of desired orientation and physical characteristics.

2. Materials and methods

2.1. Manufacture of PDMS microneedle molds

Master silicon microneedle arrays were manufactured from a silicon disc (100 mm diameter) using a wet-etching process as previously described [4]. The dimensions of microneedles on the array were 280 μm in height at a density of 144 needles per 1 cm^2. Molds were manufactured from polydimethylsiloxane (PDMS), (Sylgard 184, Dow Corning, Belgium). The PDMS, mixed in a 10:1 v/v ratio of elastomer to curing agent, was degassed in an 800 Mb vacuum for 20 min and poured over the microneedle arrays before curing at 100 °C for 1 h. The resultant mold was then peeled away from the array.

2.2. Measurement of the viscosity of solutions and the contact angle of water and the PDMS mold

Kinematic viscosity of all solutions was measured using a Vibro Viscometer SV-10 (A & D Company Ltd., and Japan) at 20 °C. The viscometer measures viscosity by controlling the amplitude of the sensor plates immersed in a sample and measuring the electric current to drive the senor plates. The two sensor plates resonate at a constant frequency of 30 Hz. The viscosity of the solution causes a damping effect which reduces the amplitude. The viscosity is calculated from the power required to keep the sensors vibrating at the original amplitude. Contact angle measurements were performed using a Contact Angle System OCA, (Dataphysics, Germany) at room temperature.

2.3. Manufacture of homogenous dissolvable microneedle arrays

A 970 S8 two substance nozzle (Düsen-Schlick, Germany) with a 0.5 mm orifice was used to produce an atomised spray. The nozzle was connected to a compressed air source and a liquid feed, as described previously [3,24]. The liquid feed contained the material for DMN construction dissolved in deionised water at a concentration of 5% w/v. The materials investigated were D-(+)-trehalose dihydrate, D-(−)-fructose 99%, D-(+)-raffinose pentahydrate min. 98%, carboxymethylcellulose sodium salt low viscosity, 0.1% w/v glycerol (added to the CMC) (all Sigma Life Sciences, USA), polyvinyl alcohol (PVA) (Mowiol 13-88, Kuraray, Japan), polyvinylpyrrolidone (PVP) (Kollidon 17PF, BASF, Germany), hydroxylpropylmethylcellulose (HPMC) (Methocel® E5 Premium LV, Colorcon, UK) and sodium alginate (Protanal LF120M, FMC BioPolymer, Norway) at a concentration of 0.35% w/v.

The following parameters were used to obtain a suitable atomised spray; an atomisation air setting of 2, air pressure of 0.25 bars, liquid input rate of 1.5 ml/min controlled using an Aladdin AL-2000 syringe driver (World Precision Instruments, USA) and a gun-to-surface distance of 5 cm. PDMS molds were filled by passing through the spray for approximately 3 s. The filled molds were dried for 2 h at room temperature and ambient humidity conditions. A polymer backing layer composed of 5% CMC w/v and 0.1% glycerol w/v was then applied and left to dry overnight. The backing layer was applied to increase the ease of handling.

2.4. Manufacture of layered dissolvable microneedle arrays

Layered trehalose microneedles were manufactured by a similar process to that described for the homogeneous microneedles arrays above. Instead of a single spraying step, microneedle arrays were manufactured by a series of five individual spraying steps of a 1% w/v trehalose solution with an intermittent drying time of 30 min at room temperature between each spraying step. The mold

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