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Dissolvable microneedle fabrication using piezoelectric dispensing technology

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ABSTRACT

Dissolvable microneedle (DMN) patches are novel dosage forms for the percutaneous delivery of vaccines. DMN are routinely fabricated by dispensing liquid formulations into microneedle-shaped moulds. The liquid formulation within the mould is then dried to create dissolvable vaccine-loaded microneedles. The precision of the dispensing process is critical to the control of formulation volume loaded into each dissolvable microneedle structure. The dispensing process employed must maintain vaccine integrity. Wetting of mould surfaces by the dispensed formulation is also an important consideration for the fabrication of sharp-tipped DMN. Sharp-tipped DMN are essential for ease of percutaneous administration.

In this paper, we demonstrate the ability of a piezoelectric dispensing system to dispense picolitre formulation volumes into PDMS moulds enabling the fabrication of bilayer DMN. The influence of formulation components (trehalose and polyvinyl alcohol (PVA) content) and piezoelectric actuation parameters (voltage, frequency and back pressure) on drop formation is described. The biological integrity of a seasonal influenza vaccine following dispensing was investigated and maintained voltage settings of 30 V but undermined at higher settings, 50 and 80 V. The results demonstrate the capability of piezoelectric dispensing technology to precisely fabricate bilayer DMN. They also highlight the importance of identifying formulation and actuation parameters to ensure controlled droplet formulation and vaccine stabilisation.

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1. Introduction

Skin is an immunological rich tissue that contains an abundance of antigen presenting cells (Wang et al., 2015) and is also the body's largest organ. In theory, this makes skin a highly desirable target for the delivery of vaccines and drug molecules. However, due to the tough, lipid rich outer layer of the skin, the stratum corneum, the skin is impermeable to most biopharmaceuticals and small molecules (Wiedersberg and Guy, 2014; Vučen et al., 2013). Percutaneous delivery is commonly limited to lipophilic, low molecular weight, chemical entities formulated as creams, ointments, gels and non-invasive transdermal patch systems. Parenteral delivery via subcutaneous, intradermal, intramuscular or intravenous routes using a needle and syringe or automated injection system is required for the majority biopharmaceutical molecules and vaccines.

Dissolvable microneedles (DMN) are a novel delivery system whereby the vaccine is incorporated into the microneedle structure. Upon application to the skin, these needles penetrate the stratum corneum, dissolve via the uptake of moisture within the skin and deliver the vaccine to the body exerting an immune response (Bonificio et al., 2015). This percutaneous vaccine delivery system eliminates biohazardous sharps waste and the risk of needle stick injury. The thermostability of the vaccine is enhanced due to formulation as a solid dosage form, potentially circumventing the need for a refrigerated distribution system (Vassilieva et al., 2015). In comparison to coated microneedle devices, dissolvable microneedles can potentially incorporate a higher drug load and they eliminate all sharps waste as the needles dissolve following application.

DMN are routinely manufactured by firstly dispensing liquid formulations into polydimethylsiloxane (PDMS) moulds and then

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drying before removal of DMN from moulds (Martin et al., 2012; Moore and Vrdoljak, 2013). Moulds are produced by casting a PDMS solution over a microneedle master to create pores with the inverse shape of the microneedle master. PDMS has a long history of use in the micro-electro-mechanical systems (MEMS) field due to its flexibility, simplicity of fabrication and relatively low cost. In addition, PDMS has an extensive track record of use in biomedical applications due to its physiological inertness, biocompatibility and low toxicity (Abbasi et al., 2001). Conversely, the inherent hydrophobicity of PDMS limits the range of applications of this material (Tan et al., 2010).

Wetting of the mould's microneedle shaped pores with aqueous or polar formulations can be limited by a high interfacial tension between the liquid formulation and the PDMS surface. The addition of surfactants can decrease the contact angle and improve wetting. However the structural integrity of proteins and vaccines can be undermined by levels of surfactant lead to unfolding and loss of activity (Otzen, 2002; Vrdoljak et al., 2012). Poor mould wetting can lead to air entrapment within its pores, resulting in poor microneedle tip formation (Mcgrath et al., 2014; Martin et al., 2012).

Poor mould wetting has prompted the use of additional processing steps such as vacuuming or centrifugation following dispensing to ensure complete wetting of mould pores (Kim et al., 2012). These processing steps, while effective at laboratory scale, may not be amenable to efficient, high-throughput, continuous fabrication. An alternative method of formulation dispensing, using an atomised spray process to overcome interfacial tension issues, offers the potential for continuous, high-throughput fabrication (Mcgrath et al., 2014). The atomised spray process coats the entire mould surface but does not permit targeted formulation dispensing into the mould's microneedle shaped pores. Such targeted dispensing is desirable when fabricating DMN containing high value cargos such as vaccines, and bilayer DMN.

Piezo dispensing technology is a 'drop-on-demand' inkjet printing technology that allows the production of drop sizes in the low picolitre range (1–70 pl). High density drop patterns can be dispensed accurately and precisely using robotic systems (Daly et al., 2015). Piezoelectric dispensing relies on the application of voltage pulses to a piezoelectric material surrounding a liquid reservoir. The resulting electric fields cause the piezoelectric material to deform setting up a pressure wave within the reservoir and resulting in a drop being dispensed from a jet orifice or nozzle located at one end of the reservoir. The number of drops that can be dispensed per second is controlled by the frequency setting, with the potential to dispense tens of thousands of drops per second using this technology. A comprehensive review of the fundamental physical phenomena underlying the piezoelectric dispensing operation is provided by Wijshoff (2010). Piezoelectric dispensing technologies have been used commercially across a diverse range of applications and underpins modern micro array fabrication and bio-assay miniaturisation (Ihalainen et al., 2015). Piezoelectric dispensing technology has been previously employed to coat formulation onto microneedle patches (Boehm et al., 2015; Boehm et al., 2014; Uddin et al., 2015; Douroumis, 2013). However, to date there are no publications citing the use of piezoelectric technology to dispense formulation into microneedle moulds and produce DMN.

A prerequisite for precise and targeted dispensing of formulation into microneedle moulds is uniform and reproducible drop formation. Satellite drops are a feature of non-uniform drop formation. They are secondary drops distinct from the primary (mother) drop ejected from an orifice upon actuation of the piezoelectric material (Hoath et al., 2012). Satellite drops can be slower or faster than the primary drop. Satellite drops that are slower than the main drop are often uncontrollable and deviate laterally from the main drop stream. This results in a spray of drops around the primary drop. These drops are highly undesirable and difficult to control as their movement cannot be easily accounted for.

The drop formation behaviour of dispensed formulations is dependent on the formulation's rheology and surface tension (Woo et al., 2013). The ability to modify and optimise drop formation via adjustment of the fluid properties has been previously reported (Kagerer et al., 2014). Piezoelectric dispensing units generally have an operating viscosity range of 0–20 cP with an optimal range of 4–8 cP. Highly viscous solutions (>20 cP) can occlude the nozzle orifice (de Gans et al., 2004). Surface tension plays a critical role in drop formation with an operating range of 20–70 mN/m, with optimal drop formation observed at 30–50 mN/m (Di Risio and Yan, 2007). The behaviour of drop formation during piezo dispensing can be described theoretically by the Reynolds (Re), Weber (We) and Ohnesorge numbers (Oh) (Eqs. (1)–(3)).

$$Re = \frac{v.p.a}{\eta} \tag{1}$$

$$We = \frac{v^2.p.a}{y} \tag{2}$$

$$Oh = \frac{\sqrt{\mathrm{We}}}{\mathrm{Re}} = \frac{\eta}{\sqrt{y.\rho.a}} \tag{3}$$

where ρ, η and γ are the density, dynamic viscosity and surface tension of the fluid respectively, v is the velocity and a is a characteristic length i.e. orifice diameter (Derby, 2011). The reciprocal of the Oh number is defined as Z and has been used to determine the suitability of formulations for piezoelectric dispensing. Liquids with Z values of $1 < Z < 10$ were described as suitable for the formation of stable, well defined drops (Fromm, 1984). Z values less than 1 have been deemed too viscous to be jetted while drops with values in excess of 10 can form undesirable satellite drops (Reis and Derby, 2000).

To prevent the formation of satellite drops, one approach is to design a formulation with a Z value between 1 and 10 by adjusting its viscosity and surface tension. Conventional printing inks can be easily formulated using a wide range of inorganic and organic excipients and solvents to minimise satellite drops (Basaran et al., 2013). In contrast, vaccine formulations are mainly aqueous-based and the range of excipients that may be included is limited by their regulatory acceptability, bio compatibility and impact on vaccine integrity. A second approach to minimising the formation of satellite drops and alter drop formation is through the adjustment of actuation parameters such as voltage (Daly et al., 2015). Drop formation can also be manipulated by control of back pressure placed upon the liquid in the jet reservoir (Chen and Basaran, 2002).

Based on the advantages of piezoelectric dispensing over other more conventional dispensing technologies, it was our hypothesis that the fine drop formation and control achievable via piezoelectric dispensing would enable complete wetting of the PDMS mould microneedle-shaped pores. Complete wetting of pores would remove the requirement for a centrifugation or vacuuming step following dispensing during DMN fabrication. In addition, piezoelectric dispensing would precisely target the liquid formulation into the pores and facilitate the formation of bilayer DMN. Therefore the primary aim of this study was to fabricate bilayer DMNs using piezoelectric dispensing technology. In addition to fabricating microneedle structures, it was important to demonstrate that the integrity of the candidate vaccine to be incorporated

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