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Safety, acceptability and tolerability of uncoated and excipient-coated high density silicon micro-projection array patches in human subjects

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ABSTRACT

Most vaccinations are performed by intramuscular injection with a needle and syringe. However, this method is not ideal due to limitations, such as the risk of needle-stick injury, the requirement for trained personnel to give injections and the need to reconstitute lyophilized vaccines. Therefore, we tested an alternative delivery technology that overcomes the problems with needle and syringe. The Nanopatch™ is an array of 10,000 silicon micro-projections per cm^2 that can be dry-coated with vaccine for skin delivery. The high number and density of micro-projections means that high velocity application is required to achieve consistent skin penetration. Before clinically testing a vaccine Nanopatch, this study tests the safety, tolerability and acceptability/utility of uncoated and excipient-coated Nanopatches in healthy adults.

Nanopatches were applied to skin of the upper arm and volar forearm and left in contact with the skin for two minutes before removal. The application sites were assessed for local skin response over 28 days. Acceptability interviews were also performed.

No unexpected adverse events directly related to the Nanopatch application were reported. All applications of the Nanopatch resulted in an expected erythema response which faded between days 3 and 7. In some subjects, some skin discolouration was visible for several days or up to 3 weeks after application. The majority (83%) of subjects reported a preference for the Nanopatch compared to the needle and syringe and found the application process to be simple and acceptable. On a pain scale from 0 to 10, 78% of applications were scored "0" (no pain) with the average scores for less than 1.

The results from this study demonstrate the feasibility of the Nanopatch to improve vaccination by showing that application of the product without vaccine to human skin is safe, tolerable and preferred to needle and syringe administration.

Clinical trial registry ID: ACTRN1261500083549.

1. Introduction

The potential benefits of micro-projection array patches (MAPs) for skin delivery of vaccines have been well-described, including: ease and safety of use, potential for using reduced doses, improved patient acceptability and thermostability [1–6]. At the time this study was conducted, only one human study with a MAP delivering a vaccine (influenza) had been published [7]. In this study erythema, purpura and pigmentation were observed in more than half the subjects. More recent studies have assessed the tolerability and acceptability of dissolving MN patches without a vaccine [8] and delivering trivalent inactivated influenza vaccine [9]; both studies observed that the MAPs were well tolerated, with mild-erythema

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being seen at the application site. Several studies have assessed the pain experienced following MAP application [9–14]. In each study, MAP application was found to be less painful than IM injection. Of these, only one [12] evaluated application site redness, which peaked at 15 min post application. There is also a body of safety data from the clinical use of MAPs to deliver human teriparatide. In these studies, daily, self-administration of the patch was well tolerated and the resulting erythema was mild to moderate and transient [15,16].

Vaxxas Pty Ltd is developing the Nanopatch™ (NP), a solid high density micro-projection array onto which the vaccine formulation is dispensed and dried. In preclinical studies, the dry coated micro-projections of the NP deliver vaccine to the viable epidermis and dermis. The potential advantages from using the Nanopatch in terms of the immune response generated and dose sparing compared to the needle and syringe have been demonstrated in preclinical studies in mice [17–22] and in rats [23].

To achieve sufficient force to overcome the 'bed of nails' effect associated with a high-density of micro-projections, and to achieve consistent and reproducible application, the NP is applied to the skin using a spring powered applicator which accelerates the NP up to a velocity of 20 m/s. In the current configuration, the applicator is a separate component; in the final commercial form of the NP system the applicator and NP will be integrated into a single device.

Prior to conducting a first-time-in-human study with a vaccine antigen, a pilot clinical study was done to ensure that application of the NP to skin is safe, tolerable and acceptable to adults. Subjects in the study had sterile uncoated and/or excipient-coated NPs applied to the skin at two anatomical sites; the upper arm (deltoid) and the volar forearm. The deltoid site was selected as it is conventionally used for intramuscular injection of adults. The volar forearm was selected because it is easily accessible, allows for easy observation of local reactions, and is a common site for intradermal skin reactivity testing. Subjects were monitored over 28 or 35 days following administration and application site reactions were recorded. Interviews were performed to gather views on the acceptability of NP application in comparison to needle and syringe; attitudes to the overall process of NP administration; preference for site of administration and perception of the effectiveness of the NP as a vaccine delivery system.

2. Methods

2.1. Manufacture of the silicon NP

The NP is a 10 × 10 mm piece of monocrystalline silicon with a micro-projection area of 9 × 9 mm and a micro-projection density of 10,000 cm^{-2}. The conical micro-projections have length of 250 μm, a 40 μm base width and taper to sharp point of less than 2 μm (Fig. 1). A polished silicon wafer (WRS, CA, US) was processed by photolithography (Griffith University, Australia) and etched with deep-reactive ion etching to produce the micro-projection array (Bosch etcher, DSI, Singapore). Wafers were cut into 10 × 10 mm^2 before mounting onto polycarbonate backing (Romar Engineering, NSW) with A-100 medical silicone adhesive (Factor II, US). An embedded magnet interfaces with a magnet in the applicator. The full NP assembly is shown in Fig. 1.

The excipient-coating applied to the NP consisted of a solution of 1% w/v hypromellose (Shin-Etsu Chemical Company Ltd, Japan), 0.72% w/v trehalose (as dihydrate) (Pfanstiehl, Germany) and dPBS (Sigma Aldrich, USA). Excipient solution (41 μl) was applied to the NP and dried using sterile filtered nitrogen gas [24]. Following coating, NPs were placed into aluminium medicans (Amcor, UK) which were then foil sealed (Medipak, Switzerland) and gamma-sterilised (≥25 kGy, Steritech, QLD, Australia).

2.2. Manufacture of the NP applicator

The applicator is a hand-held spring powered device; a simple loading jig is used to compress the spring. This first version of the clinical applicator was reusable with the skin contact part of the applicator being sterile and disposable. Each applicator was checked for performance using an in-house high speed camera (FASTCAM SA4, Photron, Japan).

The excipient-coating resulted in a slight rounding of the silicon micro-projection tips, so a slightly higher velocity of application was used based on data from *in vivo* pig skin studies (unpublished internal report). The uncoated NPs were delivered to the skin at 17.5 m/s, whereas the excipient-coated NPs were delivered at 20 m/s.

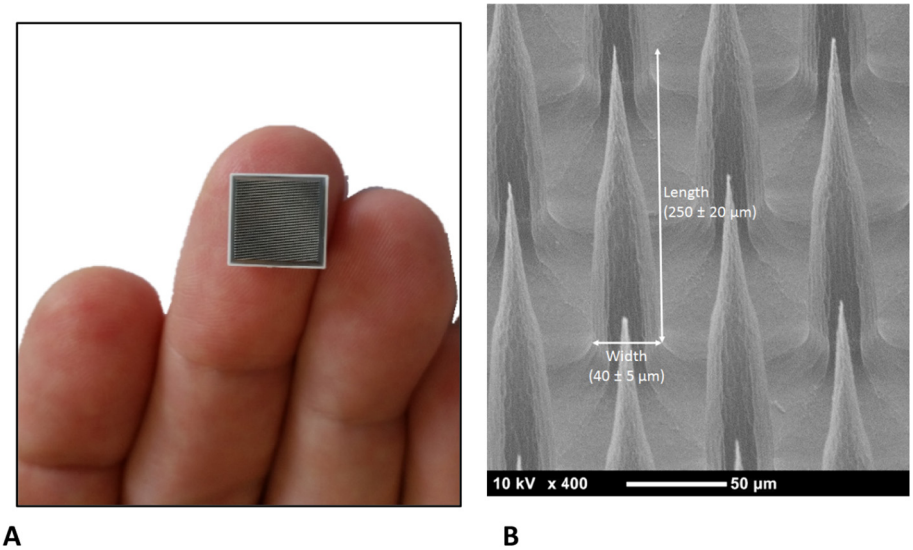

Fig. 1. Uncoated silicon NP and micro-projections. (A) Photograph of a NP (10 × 10 mm) on a white polycarbonate backing. (B) Scanning electron microscope (SEM) image of NP micro-projections including specific measured dimensions.

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