Biomaterials 128 (2017) 1–7

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials

Tolerability, usability and acceptability of dissolving microneedle patch administration in human subjects

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ARTICLE INFO

Article history:
Received 23 January 2017
Received in revised form
27 February 2017
Accepted 28 February 2017
Available online 2 March 2017

Keywords:
Dissolvable microneedle patch
Human study
Skin vaccination
Acceptability
Usability
Tolerability
Drug delivery

ABSTRACT

To support translation of microneedle patches from pre-clinical development into clinical trials, this study examined the effect of microneedle patch application on local skin reactions, reliability of use and acceptability to patients. Placebo patches containing dissolving microneedles were administered to fifteen human participants. Microneedle patches were well tolerated in the skin with no pain or swelling and only mild erythema localized to the site of patch administration that resolved fully within seven days. Microneedle patches could be administered by hand without the need of an applicator and delivery efficiencies were similar for investigator-administration and self-administration. Microneedle patch administration was not considered painful and the large majority of subjects were somewhat or fully confident that they self-administered patches correctly. Microneedle patches were overwhelmingly preferred over conventional needle and syringe injection. Altogether, these results demonstrate that dissolving microneedle patches were well tolerated, easily usable and strongly accepted by human subjects, which will facilitate further clinical translation of this technology.

1. Introduction

Microneedle patches contain hundreds of microneedles less than 1 mm long to deliver drugs and vaccines into skin. The patch contains an array of microneedles attached to an adhesive backing to facilitate application to the skin. In a dissolving microneedle patch, the microneedles dissolve in the skin within minutes, thereby delivering the drug contained in them and not generating sharps waste. Microneedle patches are being developed as an alternative to conventional needle-and-syringe injections due to the expectation of ease of administration, good tolerability in the skin and strong patient acceptance. This study is designed to assess these expectations.

Microneedle patches have previously been studied for delivery of a number of drugs and vaccines in pre-clinical studies, but limited information is available about the use of dissolving microneedle patches in human subjects [1–7]. Microneedle patches are typically designed either as coated microneedle patches made of solid metal, silicon or polymer microneedles coated with drug that is released upon dissolution of the coating in the skin or as dissolving microneedle patches containing solid, dissolving microneedles made of water-soluble materials that encapsulate the drug and release it when the microneedles dissolve in the skin.

Coated microneedle patches are being evaluated in clinical trials for delivery of parathyroid hormone to treat osteoporosis [8], glucagon to treat hypoglycemia [9] and zolmitriptan to treat migraine [10]. Dissolving microneedle patches are being evaluated in clinical trials for delivery of parathyroid hormone as well as for influenza vaccination [11].

Previous clinical trials involving microneedle patches have used high velocity insertion devices, which can improve reliability of microneedle penetration into skin, but add additional bulk and cost to the microneedle device. In this study, we are examining the usability of dissolving microneedle patches without the use of an applicator in human subjects; the microneedle patches are applied with thumb pressure only. To our knowledge, no other study has evaluated the puncture and delivery efficiencies of dissolving microneedle patches in humans or the acceptability preferences regarding vaccination using dissolving microneedle patches. As dissolving microneedle patches continue being developed for clinical translation in the coming years, it is important to fully characterize the insertion and dissolution of microneedles in humans.

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http://dx.doi.org/10.1016/j.biomaterials.2017.02.040
0142-9612/

The goal of this study is to evaluate skin tolerability, usability and acceptability of dissolving microneedle patches in human subjects to further clinical translation of microneedle patches for delivery of drugs and vaccines. This work was specifically designed to prepare for a phase 1 clinical trial of influenza vaccination using microneedle patches of a similar design [12]. We therefore developed placebo dissolving microneedle patches (i.e., not containing vaccine) and conducted a human study to assess reactions in the skin after microneedle patch application, determine microneedle patch delivery efficiency in investigator-administration and self-administration, and carry out a survey about participants' preferences concerning microneedle patch administration.

2. Materials and methods

2.1. Fabrication of dissolving microneedle patch

The microneedle fabrication process has been described previously [13]. In this study, microneedle patches contained 100 conical microneedles measuring 650 μm in height and 200 μm in base diameter positioned in a ~1 cm^2 area that were adhered to a medical-grade tape (3 M, St. Paul, MN) that incorporated a force-feedback indicator that made a clicking sound when a force greater than 10 lbf is applied. The microneedles were composed of 50% (w/w) polyvinyl alcohol (molecular weight 31 kDa) and 50% (w/w) sucrose. Microneedle patches were stored for 2–4 weeks in a sealed foil pouch with silica gel desiccant (5 g of desiccant) at room temperature (20–25 °C) and humidity (30–60% rh) until used at the time of study. Each patch was visually inspected under a microscope before and after storage to verify the integrity of the patch and the microneedles.

2.2. Study approval and study subjects

This study was approved by the Georgia Institute of Technology Institutional Review Board and informed consent was obtained from all participants. To be eligible, participants had to be healthy non-pregnant adults with normal skin, no known problems with pain perception and no known allergies to the materials used in the study. Participants could not have previously seen or worked with microneedle patches to be eligible for the study. Fifteen subjects (seven females and eight males), ages 18–57 were recruited from the Georgia Institute of Technology and other sites in Atlanta, GA.

2.3. Experimental design

Participants received three microneedle patches – one self-administered and two investigator-administered. Participants were provided a brief overview of the study and watched a short instructional audiovisual presentation on self-administration of microneedle patches. An outline of the microneedle patch administration process is shown in Fig. 1.

Each participant first self-administered a microneedle patch to his or her forearm without assistance from the investigator. After the patch removal, the investigator stained this skin site (see below). The investigator then applied two microneedle patches to the participant, one on each forearm. Only one of these skin sites was stained by the investigator. The site not stained was used to make measurements of skin tolerability (see below). The two stained sites were used for usability measurements (see below).

Participants then answered a survey about microneedle patch administration to assess acceptability of the microneedle patches. Participants returned to the study site 1, 2, 3, 4 and 7 days after microneedle patch administration for skin tolerability measurements.

2.4. Skin tolerability measurements

Skin tolerability was measured using the skin scoring scale listed in Table S.1 (see Supplementary Material). The scale was adapted for microneedle patches using established guidelines for vaccine clinical trials and clinical testing of transdermal patches [14,15]. The skin site was scored for pain, tenderness, erythema (size and intensity) and swelling on a grading scale of 0–4. Pain and tenderness were scored based on the participant's response whereas erythema and swelling were measured by the investigator.

Participants were asked if they felt any pain at the skin site after microneedle patch administration was complete. This pain was assessed separately from the pain during microneedle patch application, which is addressed in usability measurements. Tenderness was defined as any pain felt at the skin site when the investigator gently touched the skin site. Erythema size was measured using a ruler scale and intensity by visual observation of the skin site. Since there was no erythema scale for microneedle patches already in place, the investigator was trained on erythema measurements using guidelines and training available for Psoriasis Area Severity Index (PASI) scores [16]. Swelling was measured by the investigator by gently moving the thumb over the skin site to notice any raised surfaces on the skin. The investigator recorded a numerical score for each of these criteria and photographically imaged the skin at each time point.

2.5. Skin staining and microscopy to measure usability

Usability was measured in terms of microneedle puncture efficiency by skin staining (percentage of microneedles that penetrated the skin surface) and delivery efficiency by microscopy (percentage volume of microneedles that dissolved after administration).

To measure puncture efficiency, skin was stained using gentian violet 1% solution (Humco, Texarkana, TX). Immediately after microneedle patch administration, gentian violet was pooled on the skin site, dabbed dry with gauze after 1 min and cleaned with alcohol after 10 min. The stained skin site was imaged and microneedle puncture efficiency was measured by counting the number of stained skin punctures, which appeared as blue dots. It has been previously shown that the number of stained skin punctures visible after microneedle patch insertion is correlated with skin puncture by measuring trans-epidermal water loss [17].

To measure delivery efficiency, microneedle patches were imaged using brightfield microscopy (SZX12 Olympus, Center Valley, PA) before and after administration, and the microneedle dimensions were measured to calculate the volume dissolved after microneedle patch administration. Since placebo microneedle patches (i.e., containing no drug or other active substance) were used in this study, it was not possible to assay the microneedle patches for delivery efficiency of a drug or other active, and therefore this method of usability from staining and microscopy was used.

2.6. Survey about microneedle patch administration to measure acceptability

Participants answered a short questionnaire to solicit information about the acceptability of microneedle patches for delivery of drugs or vaccines. We surveyed the subjects about pain during microneedle patch application, confidence during self-administration and subject preferences regarding microneedle patches, conventional intramuscular injection and conventional oral delivery using pills.

Pain during microneedle patch administration was reported by