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Short communication

Fabrication of 3D-printed PLA microneedles as physical permeation enhancers in transdermal delivery

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Introduction

Many different and innovative approaches have been investigated to reduce the barrier effects of the *stratum corneum* (SC) and one of those are microneedles. Microneedles (MNs) are micron-sized needles which assist drug delivery through skin by creating microchannels (micron-scale pores) in SC that are large enough to enable drugs, including macromolecules, to enter the skin while being small enough to avoid pain, irritation and needle phobia. They have the capacity to play a role in modern healthcare as they reduce pain, tissue damage and transmission of infection and have potential for self-administration in comparison to traditional needles. MNs have been fabricated by a variety of methods, from a range of materials (including silicon, glass, metal, carbohydrates and polymers) and in varying geometries (Quinn et al., 2014).

Additive manufacturing (AM), more commonly known as three-dimensional (3D) printing represents a new, cutting-edge technology of 3D objects fabricated from a digital model generated using computer-aided design (CAD) software by fusing or depositing proper material (e.g., ceramics, liquids, metal, plastic, powders or even living cells) in layers. Suitable thermoplastic material in the form of a filament is fed into the printer by rollers, where it is heated to just above its softening point (glass transition temperature, Tg) by heating elements into a molten state. The melted or softened material guided by gears is moved towards heat end where it is extruded from the printer's head, through a nozzle and subsequently deposited layer-by-layer on a build plate, cooling and solidifying in under a second. The printer's head moves within the x- and y-axes, whereas the platform can move within the z-axis, thus creating 3D structures (Alhnan et al., 2016; Goole and Amighi, 2016; Jamróz, 2018; Prased and Smyth, 2016).

The aim of this work was to fabricate biodegradable PLA microneedles using innovative FDM 3D-printing technology on two different 3D printers and then chemically etch their arrays to obtain ideally sized and shaped needles.

Materials and methods

Materials

PLA filaments were purchased from 3D Republika, Serbia. KOH and NaOH were ordered from Sigma Aldrich, Germany.

Fabrication of 3D-printed PLA microneedles

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Microneedles with different heights (0,6 mm, 1,2 mm and 1,8 mm) and different number and orientation of single arrays on the base (5x5, 3x3, 1x5) were designed using Ultimaker Cura software and printed using two printers with different technical specifications (Ultimaker S3 and Ultimaker 5S 3D printer, Ultimaker, Netherlands).

The following print parameters were set up: print speed 15 mm/s at 190 °C, infill density was 100%, built plate temperature was 60 °C, microneedle diameter 0,5 mm, and microneedle base diameter 1 cm. PLA filament (2.85 mm) was used as the printing material.

Chemical etching and physical stability

Microneedles were etched using the wet etching process in a NaOH or KOH solution (Sigma Aldrich) with different concentrations (1, 3, 5, 9 M). Microneedles were divided in two groups. First group was placed in prepared KOH solutions for 4 h, such that only the peaks were sunk and then were washed several times with distilled water. After 4 h, microneedles were completely submerged in solutions for additional 5 h (Luzuriaga et al., 2018).

On the other hand, in second group microneedles were completely submerged in NaOH solutions for 6h. After etching, microneedles were finallay washed and observed by optical microscope (MejiML2000).

Physical stability was tested using hardness apparatus TB24 (Erweka, Germany).

Results and discussion

The physical stability of the microneedles was significantly higher when printing with the Ultimaker S5, compared to the Ultimaker S3. Also, a resolution of printing sizes below 0.5 mm (0.25 mm), and printing different shapes of microneedles, is not possible with the Ultimaker S3 printer. Nevertheless, Ultimaker S3 was able to print multiple models of microneedles at once (6 copies of microneedles at a time) without compromising the precision of single-needle while Ultimaker S5 shows significantly less precision when printing multiple copies at a time. Due to the printer resolution, the best results are achieved by printing microneedles with higher height (1,8 mm). 5x5 orientation of single arrays on the base resulted in more accurately printed microneedles without a lot of waste material between the needles.

The etching process, in both groups reduces the thickness of the microneedles, and the best results were achieved with 5 M and 9 M NaOH or KOH over a time of 9 hours. 1 M and 3 M solutions of NaOH and KOH did not show satisfactory removal of the waste material between the needles.

All microneedles printed on Ultimaker 5S have withstood a pressure of over 150 N without breaking.

Conclusion

Best results were obtained with Ultimaker 5S. Printing parameters can easily be adjusted to develop microneedles of optimal height and orientation of single arrays on the base. We envision using solid microneedles in combination with current transdermal patch technology. Integrated into a patch, microneedles may provide a minimally invasive method to increase skin permeability for diffusion-based transport that could make transdermal delivery of many drugs possible, including large molecules such as proteins.

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