Engineering 3D Printed Microfluidic Chips for the Fabrication of Nanomedicines

Aytug Kara[1], Athina Vassiliadou[2], Baris Ongoren[1], William Keeble[3], Richard Hing[4], Aikaterini Lalatsa[2,], Dolores R. Serrano[1]

[1] Pharmaceutics and Food Technology Department, School of Pharmacy, Universidad Complutense de Madrid, Plaza Ramón y Cajal s/n, 28040 Madrid, Spain.
[2] Biomaterials, Bio-engineering and Nanomedicine (BioN) Lab, Institute of Biomedical and Biomolecular Sciences, School of Pharmacy and Biomedical Sciences, University of Portsmouth, White Swan Road, Portsmouth PO1 2DT, UK.
[3] School of Mechanical and Design Engineering, University of Portsmouth, Portsmouth PO1 3DJ, UK.
[4] Electron Microscopy and Microanalysis Unit School of the Environment, Geography and Geoscience, University of Portsmouth, Portsmouth PO1 3QL, UK.

1. Purpose

Nanomedicine manufacture remains expensive and difficult to scale-up which limits the uptake of nano-enabled technologies by industry. Thus, there is an urgent unmet need for continuous and controlled manufacturing processes. Microfluidic manufacture has emerged as a novel and easily adaptable strategy to overcome these challenges, but majority of chips used are fabricated using polydimethulsiloxane (PDMS) and soft mask lithography that remains tedious, not easily customizable and requires specialized equipment and expertise for their production. 3D printed chips are a novel and easily adaptable cost-effective alternative able to provide microfluidic chips for enabling quick pilot studies towards the manufacture of nanomedicines under controlled conditions with optimal and controlled characteristics enabling easy scale-up and shorter development times. However, for 3D printed chips to be successful as an alternative, 3D printing channels with adequate resolution to produce the required geometry needs to be demonstrated. In this work, we utilized the most easily accessible 3D printing techniques (fused deposition modelling (FDM) and sterolithography (SLA)) and commercially available solvent resistant filaments and resin to produce designed microfluidic chips with appropriate geometry and channel characteristics to allow for the manufacture of polymeric nanoparticles based on polymethacrylate polymers encapsulating high concentration of a BCS class II drug (nifedipine, NFD).

2. Method

Chips were designed in Tinkercad® (Autodesk®) and measured 8.2 cm in length, 3.5 cm in width, and 0.7 cm in height. Channel length was 44 cm and the diameter was 1 mm. Chip designed was exported into a standard tessellation language (.stl) digital file. An Anycubic Mega Zero FDM printer printed 70 layers of the microfluidic chip at 245°C, with a 0.4 mm diameter nozzle, 0.1 mm layer height, and 10 mm/s printer and 30 mm/s travel speed with cyclic olefin copolymer filament. The Anycubic Photon Mono X (LCD-based SLA printer with 405 nm light source and 0.01 mm Z resolution) was used for stereolithography. Anycubic® UV sensitive resin (transparent yellow) was photopolymerized at 405 nm. The print settings were 0.05 mm layer height, 60 s bottom exposure, 3 s normal exposure, 1 s off-time, and 140 layers. Polymeric

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nifedipine loaded nanoparticles were prepared using solvent evaporation and microfluidically. For the latter, the aqueous phase (8 ml) consisting of Tween 80 in deionized water (0.25 % w/v) and the organic phase consisting of Eudragit L100-55 (30 mg) and NFD (10 mg) dissolved in ethanol (2 ml) were loaded into two 10 ml syringes. Using two syringe pumps (New Era Pump Systems, NY, USA), the organic phase was flown at a rate of 0.5 ml min^{-1} and the aqueous phase at 2 ml min^{-1}. The eluate was rota-evaporated for 10 minutes at 150 rpm and 60 °C to remove the ethanol and centrifuged at 5,000 rpm for 5 minutes to remove any free NFD. Part of the supernatant was lyophilized for 24 hours under 0.2 mbar pressure at -50^{o}C. Formulations were characterized in terms of drug loading, particle size, zeta potential and morphology and the channels were imaged with light microscopy, scanning electron microscopy while the surface roughness was measured with profilometry. Solid state characterisation of lyophilized particles were also undertaken. Release of NFD from nanoparticles was assessed using a type II dissolution apparatus (Ewerka DT 80, Heusenstamm, Germany) under simulated gastric and intestinal media (Ayyoubi S.).

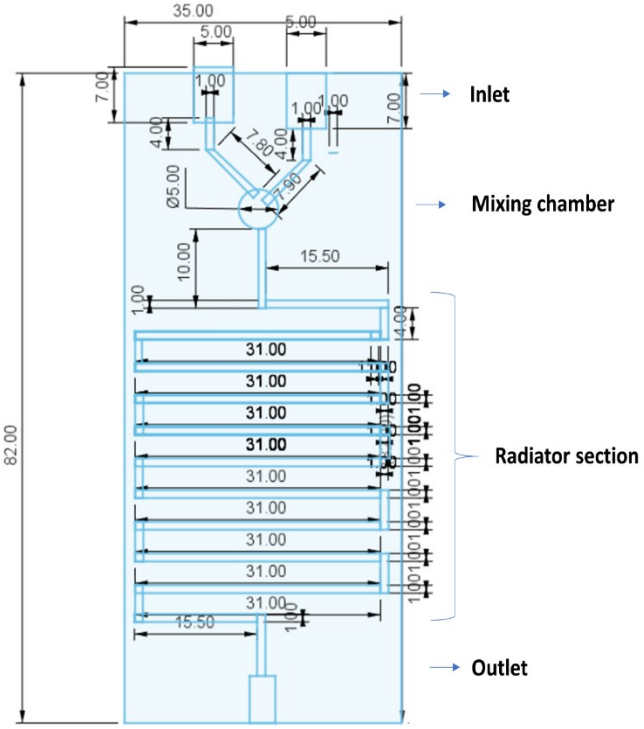
3. Results

The chip geometry produced was in close accordance to the .stl file sent for printing (Fig. 1a). The channel diameter ranged from 985 – 1015 µm. SLA-printed chips exhibited channels with a smoother surface (10.5-fold) than FDM chips. NFD nanoparticles showed a 7% greater drug encapsulation when manufactured by SLA than with FDM chips (one-way ANOVA, $p < 0.05$) which was closer to the loading reported by solvent evaporation. NFD nanoparticles manufactured using SLA chips were significantly smaller than those particles obtained from FDM chips, 68 ± 1 nm versus 75 ± 1 nm, respectively (one-way ANOVA, $p < 0.05$), which was closer to the particle size obtained by solvent evaporation (Fig. 2). Lyophilised nanoparticles showed similar FTIR, pXRD, and DSC patterns obtained from both SLA and FDM chips.

NFD release was hampered in acidic media (<20% at 1 hour), but near complete released was achieved when the pH was raised to 6.8 within 6 hours, which was similar to that obtained for particles prepared with solvent evaluation (Fig. 3). However, NFD particles produced with FDM showed a burst release in acidic media (~40%) followed by controlled release in simulated intestinal media ($p<0.05$, One-way Anova). NFD localization within the particles produced with different 3D printed chips due differences in surface roughness and drug–polymer interactions are contributing to these findings. The smoother channels of SLA chips lead to a more homogenous loading process, where NFD is located within the core of the polymeric nanoparticles, which is further supported by the smaller particle size and controlled release profile in acidic media where NFD is more likely to be soluble.

4. Conclusion

3D printed microfluidic chips with 1 mm diameter channels have been successfully designed and manufactured and are capable to engineer polymeric nanoparticles with good encapsulation efficiencies and particle sizes of ~100 nm, like nanoparticles obtained by solvent evaporation. 3D printed microfluidic chips control the process and convert discontinuous methods into a continuous nanomedicine manufacturing process that are easily industrialized.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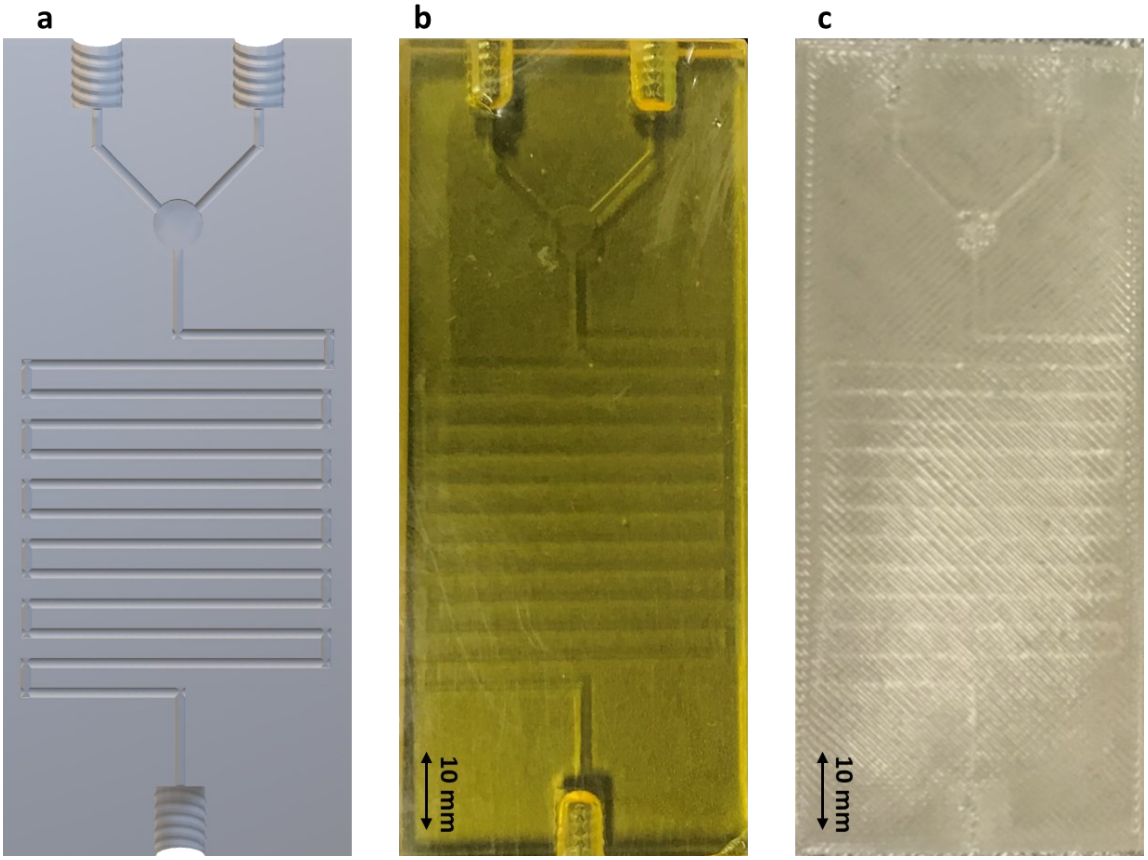
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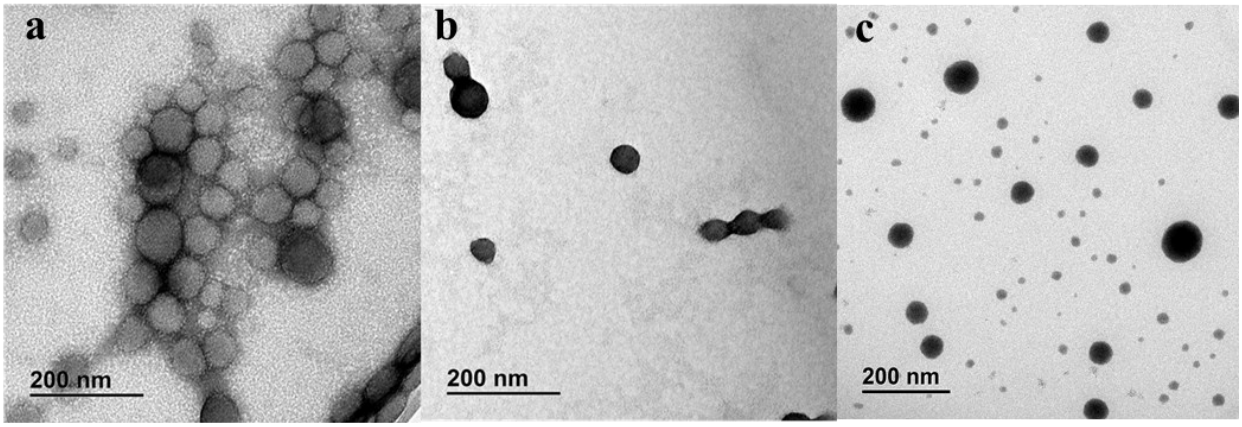
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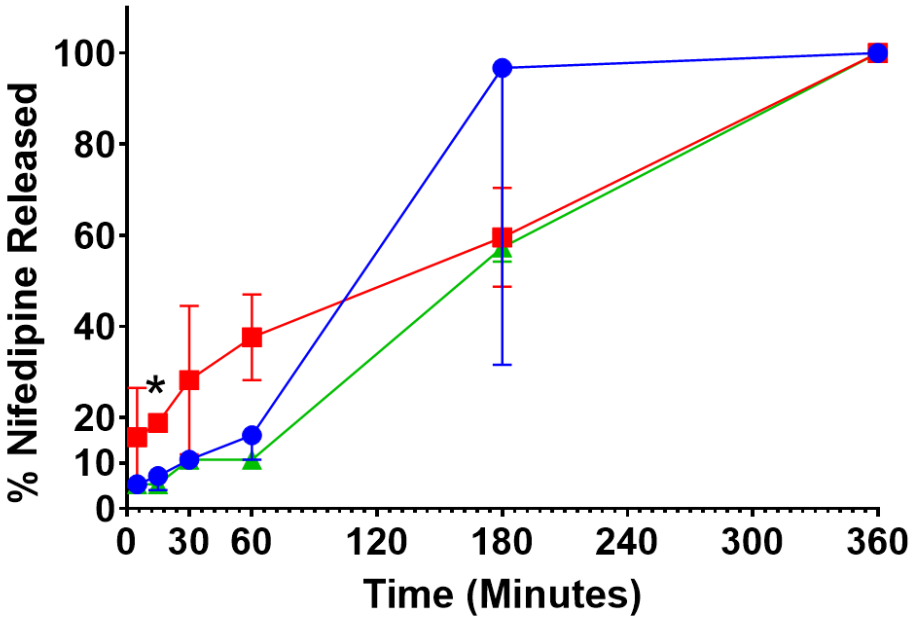
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