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Density Mediated Drug Release From Dapivirine Vaginal Rings Produced by Additive Manufacturing

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Background: Droplet deposition modelling (DDM) is a form of 3D printing that fuses droplets of molten polymer to create each layer, providing exquisite levels of control over an object’s design and morphology. Such manipulation allows properties including density, geometry and surface area to be manipulated in ways that have been unthinkable using conventional thermoplastic processing techniques. Here we utilise the DDM process and compare this to injection moulding to produce dapivirine (DPV) loaded vaginal rings using a pharmaceutically relevant, life science grade thermoplastic polyurethane.

Methods: Vaginal rings (54.0 mm outer diameter, 4.0 mm cross sectional diameter) were fabricated by injection moulding or Arburg Plastic Freeforming - a proprietary DDM process, using a hydrophobic TPU loaded with 10% w/w dapivirine. Using the DDM process, rings of 100, 50 and 10% matrix density were produced. Rings were evaluated for in vitro drug release over 29 days in an aqueous release media and assessed for thermal characteristics.

Results: Daily DPV release from all ring designs ranged between 387 - 8666 µg (Day 1) and 193 - 992 µg on Day 29. DDM printed VRs with 10% infill density (68 mg DPV load) exhibited a seven fold increase in DPV release rate as a percentage of total drug loading. Thermal analysis showed that the DPV melt endotherm was absent from TPU + 10% w/w DPV, suggesting that DPV was fully solubilised within the TPU at the experimental conditions.

Conclusions: DDM printing on an Arburg Freeformer has been shown to create vaginal rings with a range of densities and has provided a new potential to either increase the release rate of poorly water soluble compounds or reduce the loading required to maintain a desired release rate.

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Vaginal Ring for Sustained Release of DL-lactide as a Lactic Acid Pro-drug

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Background: There is interest in developing vaginal ring (VR) products for long-acting administration of lactic acid (LA). However, LA is generally not compatible with silicone elastomers, the most common material for fabrication of VRs. Here, we investigate the potential for controlled release of the LA-prodrug DL-lactide (LT) from a silicone elastomer VR. LT is a cyclic dimer of lactic acid which hydrolyses to form LA.

Methods: The kinetics of LT hydrolysis were studied. Matrix-type silicone elastomer (DDU-4320) rods containing LT (11% w/w) were prepared by reaction injection molding (80°C, 3 min.). In vitro release testing of individual rods (n=8) placed in a 0.2% v/v solution of Tween 80 was performed over 10 days, with half the replicates having their release medium changed daily and the other replicates having drug release accumulated. The amounts of LT and LA released were quantified by HPLC. pH of the release medium was also monitored over the release period.

Results: Unlike LA, LT was compatible with silicone elastomer and did not inhibit cure. The rate constant for hydrolysis of LT at 37°C was 0.05658 days⁻¹. LT was released the matrix-type silicone elastomer rods continuously over the 10-day period. Day 1 daily release was between 15-25 mg, while Day 10 values ranged from 0.2 - 0.5 mg. Hydrolysis of LT also occurred in the release medium, as evidenced by the detection of LA by HPLC. pH of the medium was significantly lowered due to release of LT, with values dropping as low as 2.75 on Day 1. On Day 10, a mean pH of 3.5 was achieved with daily release medium change. When medium was not replaced daily, a mean pH of 2.5 was recorded.

Conclusions: Matrix-type silicone elastomer rods containing 11% w/w LT provided in vitro release of LT and rapid conversion via hydrolysis to the monomeric LA. The LA thus produced led to reduced pH in the release medium.