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3D Printing of Progesterone-Loaded Intrauterine System Using Vat Photopolymerisation

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SUMMARY

Three-dimensional printing (3DP) provides the opportunity to personalise different dosage forms and therapeutic regimen where conventional manufacturing processes might not be applicable. Limited work has been done to investigate using 3DP for personalising hormonal intrauterine systems (IUSs). The aim of this work was to prepare 3DP IUS containing progesterone using vat photopolymerisation (VPP) technique. The device was successfully printed and showed a slow release in phosphate buffer (pH 7.4). VPP has the advantages of better printing resolution producing smoother surfaces, and the elimination of the pre-printing process of hot melt extrusion (HME) needed for fused deposition modelling (FDM) method. To the author's knowledge, this is the first report of using VPP for printing hormone-loaded IUSs.

INTRODUCTION

Utilising three-dimensional (3D) printing for pharmaceutical applications has gained a significant interest from oral dosage forms to medical devices (Willemen et al., 2022). Yet, 3D printing drug loaded implants has not enjoyed the popularity of printing oral tablets. Research is gaining momentum with applications varying from cancer therapies to tissue engineering. Nonetheless, limited research has been done to 3D print drug loaded implants for women's health applications, and almost exclusively using fused deposition modelling (FDM). Therefore, the aim of this work was to use vat photopolymerisation (VPP) to print progesterone-loaded IUS.

MATERIALS AND METHODS

Progesterone (≥ 98%) and phosphate buffered saline (Sigma Aldrich, Merck, UK), Anycubic 3D Printing UV Sensitive Resins Grey and Transparent (clear) and PrimaCreator Value UV/DLP Resin Flex Skin (amazon, UK), isopropyl alcohol (analytical grade), absolute ethanol and distilled water. An opensource design from Cults 3D (.stl file format) for the device was selected. 3D printing was performed with Anycubic Photon S Printer and Anycubic WorkShop (V2.1.24) (Anycubic, China).

Progesterone-loaded device was prepared by adding the required amount to load 10%w/w (4.6 mg) into the resin before printing. Rectangles (30x5x1.4 mm) were printed for thermal analysis tests. Differential scanning calorimetry (DSC) and Thermogravimetric Analysis (TGA) were performed using Q2000 DSC and Discovery TGA, respectively (TA Instruments, Waters, LLC). Samples were heated at 10°C/min. Squares containing 150ug of progesterone were printed for drug release test. Phosphate buffer pH 7.4 (20 mL) was used and kept at 37+-0.5°C and under

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magnetic stirring at 60 rpm. Samples were taken up to 24 hours by completely replacing the medium at each time point. Absorbance was measured at 248 nm.

RESULTS AND DISCUSSION

There are different shapes of IUSs and a T-shaped design was selected for the study. Three different types of resin were used for printing using settings in Table 1. Fig. 1 shows the view of the design in the slicer software with the support structure setting selected. Varying printing settings resulted in varying printing time and the quality of the resulted printouts. Printing with grey and clear resin resulted in rigid objects, with the clear resin gave more flexible object but it lost its flexibility upon post-printing curing for a few minutes. The dimensions of the device were adjusted to be within the range of existing IUSs.

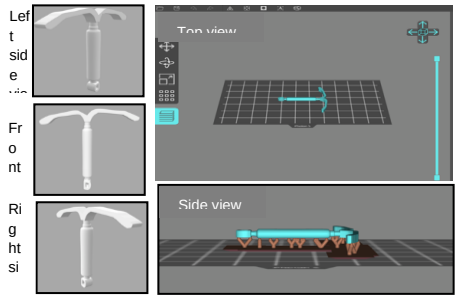

Fig. 1. *Left: Different views of the IUS in .stl File format, and Right: view of the object in the slicer software.*

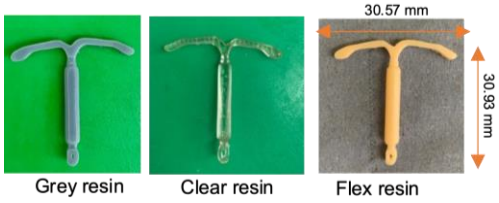

Fig. 2. *Images of printed IUSs.*

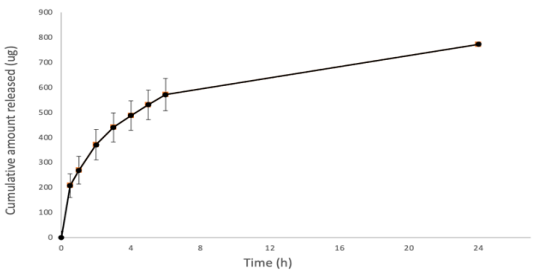

Fig. 3. *Drug release profile from 3D printed polymer.*

The resin used for the final printout was the flex resin which was of good flexibility. Fig. 2 shows images of printed devices. No melting endotherm was observed for drug-loaded printed polymer in the DSC. TGA shows thermal stability of the printout to be up to 260°C. Drug release shows a slow release over 24 hours.

Unlike FDM, VPP method eliminates the need of the pre-printing process of HME needed for FEM method. In addition, VPP gives better printing resolution resulting in smoother printouts which is key for implants and avoids using high temperatures.

Table 1. *Summary of printing settings used (bottom layers were 8 mm for clear and grey resin and 5 mm for flex resin).*

Resin type	Layer thickness (mm)	Normal time exposure (s)	Off time (s)	Bottom exposure time (s)
Grey	0.2	18	6.5	115
Clear	0.1	15	1	60
Clear	0.025	8	1	100
Flex	0.02	6	2	50
Flex[a]	0.02	6	2	50

[a] maintained adequate flexibility with addition of progesterone

CONCLUSIONS

Successful printing of IUSs containing progesterone was achieved using VPP method with better resolution than FDM. Further work is ongoing to customise resin formulation and tailor drug release.

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