Proceedings of the Canadian Society for Mechanical Engineering International Congress 2020
CSME Congress 2020
June 21-24, 2020, Charlottetown, PE, Canada

Investigation of the Effects of Infill Pattern and Percentage on Drug Release from 3D Printed Scaffolds

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Abstract—A recent understanding of the broad dose ranges of mass-produced drug delivery systems has increased the demand for patient-tailored matrices. The fabrication process with conventional techniques, however, is inefficient and needs to be restructured. The adjustment of 3D printing parameters can be investigated as an alternative method of controlling drug release. In this study, the combined effect of infill percentage and infill pattern on the release of 3D printed scaffolds were examined over a 50-hour period. The model drug, Rhodamine B, was combined with a highly degradable polymer, polycaprolactone (PCL). It was concluded that surface area played a key role in the release over time, thus indicating this study will aid in restructuring the production of personalized drug-delivery systems.

Keywords-3D printing; scaffold; infill percentage; infill pattern; release profile; drug delivery; customizable dosages; polycaprolactone

I. INTRODUCTION

The incorporation of Three-dimensional (3D) printing technologies into the pharmaceutical industry has created a multitude of advantages, including the mass production of drug delivery systems [1]. This process is highly efficient in manufacturing time as drug-matrix compositions stay consistent. However, standardizing dosages for patients with varying drug responses leads to unintentional and undesirable side effects [4,5]. The solution is to formulate patient-specific drug delivery systems. This approach can be made possible with conventional techniques, although this would drastically affect the supply chain [2,3,6,7]. The application of 3D printing technologies in this area could mitigate the above problem and simplify production [5]. An understanding of how 3D printing parameters affect the release profile will aid in future design and development of patient-tailored drug delivery systems.

Recently, scientists have explored alternative 3D printing methods to obtain the desired release while maintaining the same drug-matrix composition. Methods explored include altering surface area, ratio of surface area to volume, and infill percentage [2,3,7]. In one study, several scaffold geometries were tested to determine the most prevalent factors that influence drug release. It was concluded that drug release is directly proportional to the ratio of surface area to volume, thus indicating that geometrical design can affect the release profile [3]. The infill pattern is another important parameter in controlling the surface area to volume ratio of 3D printed drug delivery systems. Although previous studies have investigated the effects of infill patterns on the kinetics of the drug release from degradable 3D printed constructs, the combined effects of infill pattern and infill percentage on the drug release of matrices with longer degradation periods (as compared to the release time) must be further investigated [5].

In this paper, infill percentage (15%, 30%, 60%) and infill pattern (honeycomb, grid, linear) of 3D printed scaffolds were examined to explore their effect on drug release. The release of the model drug, Rhodamine B, within the polymer polycaprolactone (PCL) was measured over 50 hours. It was hypothesized that the manipulation of infill percentage and infill pattern will significantly alter the release profile. The results of this study could help identify the effect 3D printing parameters have on drug release, therefore increasing the feasibility of 3D printing in pharmaceutical applications.

II. MATERIALS AND METHODS

A. Scaffold Design and Fabrication

A 3D bio-printer (BioX, Cellink, Sweden) was used to print the scaffolds (Fig. 1). Polycaprolactone (PCL) powder (25090-100, Polysciences, USA) and Rhodamine B (R6626, Sigma Aldrich, USA) were used as the polymeric matrix and model drug, respectively. Rhodamine B and PCL were mixed (0.05% w/w), and a thermoplastic nozzle (NZ8020000102, Cellink, Sweden) was filled with the mixture. A square scaffold (15 × 15 mm) with 0.8 mm height was designed using computer-aided design (CAD) (Solidworks, Dassault Systems, USA), and the scaffold was sliced with the printer slicer software. The layer height was set at 0.4 mm. The printing temperature, pressure and the speed were set at 120 ℃, 1-2 kPa and 2.2 mm/s, respectively. The print settings were adjusted as necessary throughout the printing process.

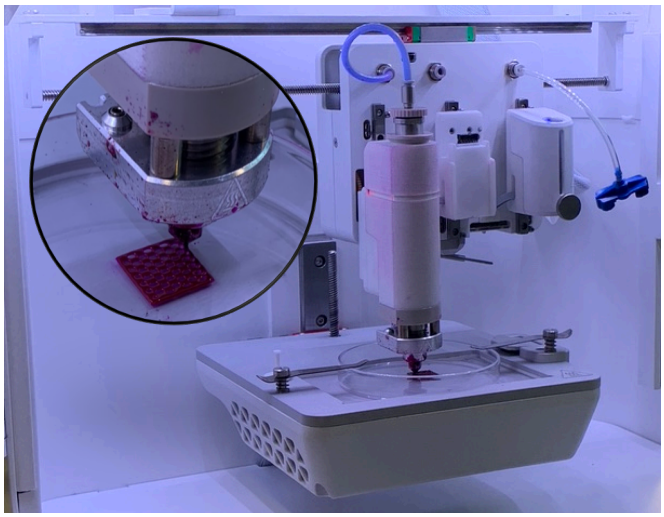

Fig. 1 3D bio-printer printing honeycomb pattern with 30% infill

B. *Infill Percentage and Infill Pattern*

To investigate the effect of infill pattern on the drug release, three infill patterns were explored: honeycomb, linear, and grid. The infill percentage was fixed at 15%. To study the effect of infill percentage, a honeycomb structure was printed in different infill percentages: 15%, 30% and 60%.

C. *UV Analysis and Sampling*

Each scaffold was placed in a beaker with 20 mL of phosphate buffer saline (PBS). The beakers were placed on a magnetic hot plate stirrer at 37 °C. 1 mL samples were taken at different time points: 1 hour, 2 hours, 6 hours, 1 day, and 2 days, and the same amount of sample was replaced with fresh PBS. The samples were analyzed by a UV-Vis spectrophotometer at 510 nm wavelength. All the tests were implemented in triplicates.

D. *Statistical Analysis*

A two-sample Student's t-test was performed to determine the significance between the releases over time of the 3D printed scaffold [8]. *p*-values less than 0.05 were considered to be significantly different.

III. Results and Discussion

3D printed scaffolds are shown in Fig. 2. Discrepancies between the CAD designs and printed scaffolds were observed. The highest discrepancy is observed in the honeycomb scaffold with the highest infill percentage (60%) (Fig. 2a) and the linear pattern scaffold (Fig. 2e) due to merging of the filaments. Additionally, the sharp corners of the honeycomb, grid and linear scaffolds were not successfully printed. This is due to the high interfacial tension of molten PCL and the relatively high solidification time of the printed scaffolds (~ 1 minute).

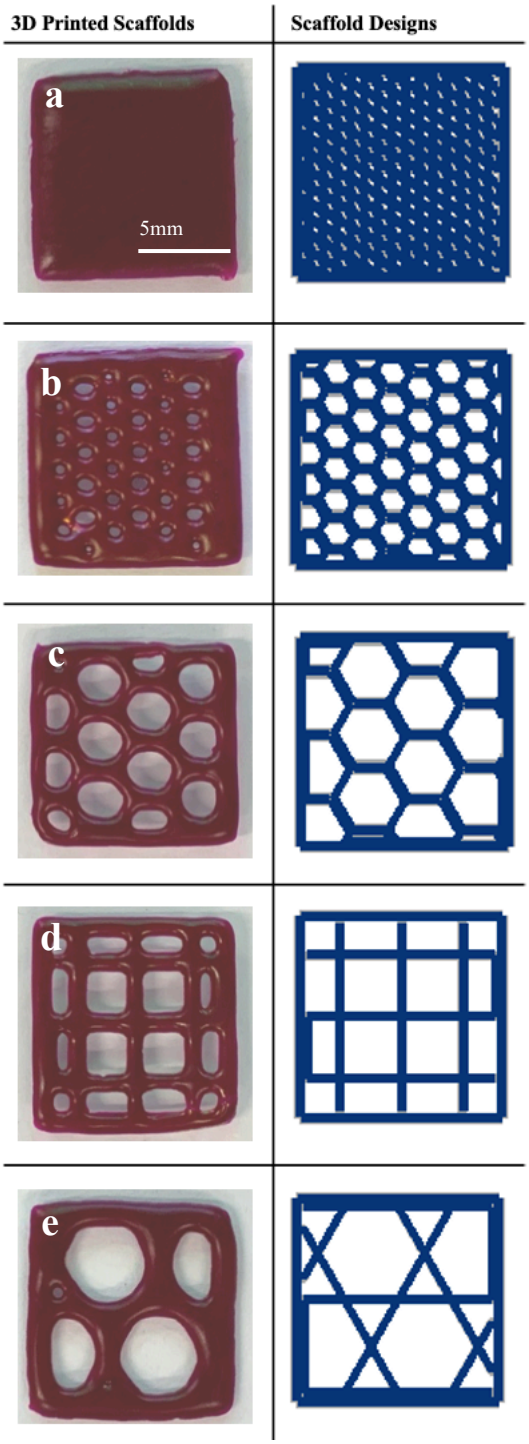

Fig. 2 A comparison of 3D-printed scaffolds and their design. (a) Honeycomb 60%, (b) Honeycomb 30%, (c) Honeycomb 15%, (d) Grid 15%, (e) Linear 15%

Fig. 3 shows the cumulative release for various 3D printing patterns over 50 hours. The results of the infill pattern study showed an increase in the cumulative release over time. It has been determined that the grid pattern displayed the highest release with time followed by the linear and honeycomb patterns. Surface area is a factor to justify these release profiles. The grid scaffold has a higher surface area, followed by the linear, and the honeycomb scaffold.

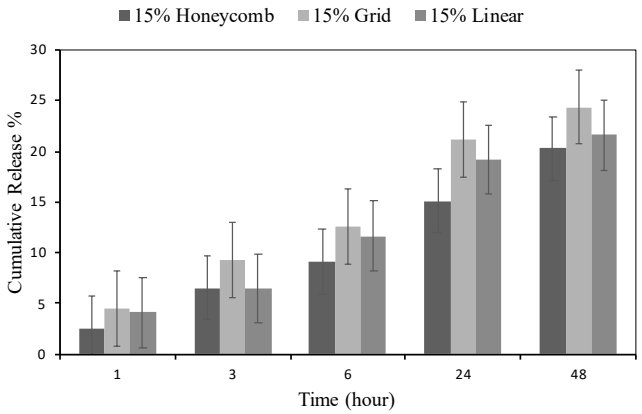

Fig. 3 Cumulative release for infill pattern study

Fig. 4 shows the cumulative release for various 3D printing infill percentages over 50 hours. The overall tendency for the infill percentage study was an increase in the cumulative release over time. Another observable trend for infill percentage was a correlation between a higher release and a smaller infill percentage: the 15% infill scaffold had the highest release over time, followed by 30%, and then 60%. The surface area of scaffolds with a small infill percentage is responsible for the higher cumulative release.

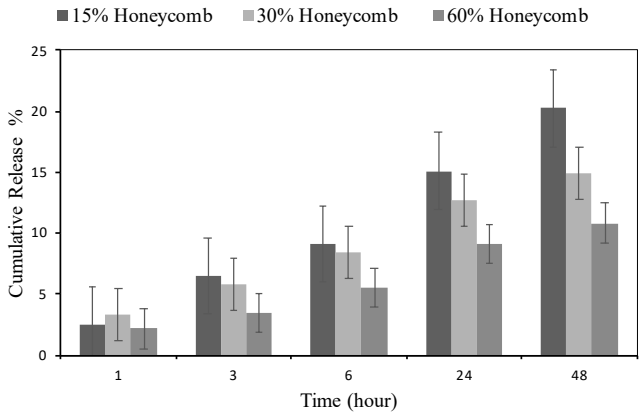

Fig. 4 Cumulative release for infill percentage study

TABLE I. T-TEST RESULTS – INFILL PATTERN

Values	*Honeycomb:Linear*	*Honeycomb:Grid*	*Linear:Grid*
t-value	0.407	0.759	0.356
p-value	0.695	0.470	0.731

TABLE II. T-TEST RESULTS – INFILL PERCENTAGE

Values	*15%:30%*	*15%:60%*	*30%:60%*
t-value	0.435	1.26	1.05
p-value	0.675	0.2419	0.324

As shown in Fig. 3 and Fig. 4, there was a difference in cumulative release between scaffolds. Therefore, a statistical analysis was completed to identify the significance of these differences. All *p*-values were greater than 0.05 ($p > 0.05$), concluding that the results were not statistically significant.

IV. CONCLUSION

These results indicate that the release over time of 3D printed scaffolds can be altered by changing parameters such as infill percentage and infill pattern. Although the differences in release profiles in this study were not statistically significant, the surface area is a critical factor in controlling drug release. Moving forward, understanding the relation of surface area and the release of drug delivery matrices will increase the feasibility of 3D printing technologies. Therefore, future experiments building on this study will aid in restructuring the production of personalized drug-delivery systems to accommodate the pharmaceutical industry.

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