Characterisation of Cylindrical Drug Delivery Devices Using Rapid Prototyping

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Abstract: With the improvement in the technology, Rapid Prototyping techniques have begun to be applied in the field of biomedical devices in medicine. The controlled release of drugs is an important area in which rapid prototyping techniques can be successfully used in developing models of release matrix for drug delivery devices. This paper deals with the characterisation of cylindrical Drug Delivery Device (DDD) models with one such RP technique, the Fused Deposition Modeling (FDM). The main aim is to see if the matrix model fabricated using this technique is feasible to be used as a successful drug delivery device. Using various parameters involved with FDM, polymeric DDD matrices with different macrofeatures are fabricated. Experiments are conducted to study the release characteristics of the fabricated models with a model drug and to see how they are affected by FDM build parameters.

Keywords: Rapid prototyping, Fused Deposition Modeling, Drug delivery devices, Diffusion

1. Introduction

Rapid Prototyping (RP) started out as a process for creating prototypes quickly for verifying the design and also to check if the manufacturing and assembly of parts was possible as desired. With the improvement in technology and the use of various materials, it became possible to use rapid prototyping in new field such as biomedical engineering. Rapid Prototyping techniques such as Selective Laser Sintering, Three-Dimensional Printing and Fused Deposition Modeling have been used in this field initially to build models of human anatomical structures, which were used for education, surgery planning and medical diagnosis [1]. Later, some of these Rapid Prototyping techniques were used to build 3D scaffolds, which would help in developing body tissue substitutes in Tissue Engineering [2, 3]. Now, by controlling the various process parameters involved in the Rapid Prototyping techniques and also by using biocompatible and biodegradable materials, a new application of RP is emerging in developing medical devices to allow control release of drugs. These devices are generally known as drug delivery devices (DDD). These devices are placed inside the body either surgically or by taking it as an oral dosage. These devices can also be designed to be placed on the surface of the skin, or can be used as an external device to deliver drugs into the body. The main purpose of these devices is to release drugs by diffusion at a required rate over a required duration of time. Rapid Prototyping technology offers a great potential to develop effective drug delivery devices rapidly and at low cost.

Rapid prototyping techniques are highly
suitable for fabrication of non-biodegradable reservoir-matrix type drug delivery devices. This type of DDD is found to be capable of providing zero-order release of drugs through diffusion [4]. Traditional methods of fabrication of matrix type DDD include compression moulding, solvent casting, lost mould method and vacuum foaming method. However, these methods have inherent problems due to the nature of processes involved and the lack of control in pore size, connectivity and distribution of pores. Poor pore connectivity and non-uniformity in some of these conventional methods make the device non-permeable and inefficient. These limitations are overcome greatly by rapid prototyping processes, which provide better manufacturing flexibility and high level of control on the macro and micro-features and porosity. Researchers at MIT, Massachusetts, were the first to investigate the application of Three-dimensional Printing (3DP) RP process to fabricate model DDDs [5, 6] and to study the controlled, targeted and cyclic release profiles. More recently, researchers at Nanyang Technological University, Singapore have investigated the use of Selective Laser Sintering (SLS) RP process to fabricate porous polymeric DDDs and studied the effects of various SLS parameters on drug release profiles [7, 8].

This paper presents an investigation on building drug delivery device matrix models using Fused Deposition Modeling RP process. The focus of the study is on the effect of FDM fabricated micro-features of reservoir-matrix DDD models on the drug release rates through the diffusion process. By varying the key FDM parameters of raster gap and raster angle to control the porosity, a number of cylindrical shaped porous matrix models of DDD are created on the FDM machine using the standard ABS grade material. The porous matrix models are then inspected for their drug release characteristics and pore morphology. A drug model is used to infiltrate the porous matrices in vitro to study the release rates.

2. Fused Deposition Modeling Process

Fused Deposition Modeling (FDM) is a leading rapid prototyping process based on layer by layer manufacturing technology [9]. The FDM machine builds the part by extruding the model material in filament form through a heated nozzle in a prescribed pattern building layers onto a platform to create any shape as defined by the CAD model. This process is continued until the desired three-dimensional model is obtained. The part is easily removed from the platform, supports are removed, and the part is ready for use. Figure 1 shows the schematic diagram of the FDM process.

There are a number of process parameters involved with fused deposition modeling. By controlling the process parameters like the Road Width, Raster Gap, Raster Angle and Slice Thickness, the internal structure of the models fabricated can be manipulated intelligently [10]. Road width is the width of the material that is laid by the nozzle. This can be increased by increasing the material flow through the nozzle. Slice thickness is the thickness of the individual layers and it depends on the thickness of the material being laid. Raster Gap is the gap between two adjacent roads. Traditionally there will not be any gap between the roads in order to fabricate a solid model. But in the case of applications like tissue engineering or fabrication of Drug Delivery Devices, gaps are provided between two roads to obtain a porous matrix. Raster Angle is the angle by the laying pattern between the two successive layers during the building process measured from the X-axis in the building envelope. Thus a raster angle of 0-90 means the first layer is build at 0 degrees, the next layer up at 90 degrees, and so on alternately with respect to the X-axis. This also controls the porosity and pore distribution within the part. The parameters can be changed using the INSIGHT software of the FDM process.
3. Fabrication of DDD Matrix on FDM

Since the introduction of FDM technology in the field of Tissue engineering, it was possible to study the various macro-features that could be created using FDM [3]. The creation of uniformly spaced pores, which are interconnected, has been used to create scaffolds in the Tissue Engineering field. These FDM features could also be exploited and used for creating DDDs that require pores to hold drugs and require interconnected porous matrices for releasing the drug from the inner core of the device to the outer surface. Another reason that can be mentioned for using FDM for fabricating these devices is its ability to control the size of these pores using a variety of process parameters such as Raster Gap, Road Width, Raster Angle and Slice Thickness. The models can be easily fabricated from the CAD model and the fabricated models are very robust.

During the fabrication process using FDM, the nozzle injecting the material out initially lays down the outer boundary of that particular sliced layer. After the outer boundary is laid down the inner area is filled. The inner area is filled based on the parameters set for these layers namely raster gap, raster angle, road width and slice thickness. In this research, only the raster gap and the raster angle are changed to obtain unique matrices keeping the slice thickness and road width constant. The raster gaps are set in such a way that there is gap between adjacent roads. Once all the layers are laid down and due to the varying laying pattern (i.e. raster angle) a highly uniform and interconnected porous structure is formed. This matrix helps to retain the drug and is also involved in the diffusion process. Figure 2 shows a close up scanning electron microscope (SEM) view of the formation of porous matrices due to the specified raster gap and raster angle.

In order to control the drug release, controlling the porosity of the matrix is an important factor. The porosity is usually controlled by controlling the gap between the adjacent roads. By increasing or decreasing the raster gap the porosity is increased or decreased. Road width has not been varied in this study since varying the road width basically varies the raster gap and this function is taken care of by varying the raster gap itself. Raster angle, which is basically the pattern in which the nozzle lays down the inner layer, is also varied in this study. It was used as one of the varying parameters because by varying the raster angle, the weight of the drug model loaded into the DDD samples is also varied.
6. Results and Discussion

All the ten FDM model samples were filled with the dye, the drug release pattern were observed and noted. Table 1 also shows the time taken for the dye to diffuse fully through the matrix. The last column of Table 1 also shows the average drug release rate, calculated by dividing the volume of the initial dye in the reservoir by the time taken to fully penetrate through the diffusion matrix of the DDD. As shown in Table 1, it was observed that the dye penetrated through the sample number S2, S4, S8 and S9 very quickly (ten minutes) and so these DDD models were not deemed suitable to act as DDD. Hence release rate were not calculated for these models. The dye penetrated samples S2, S4 and S8 quickly because the raster gap is large enough to allow the dye to flow through it easily. Although the sample S9 had a smaller raster gap the dye penetrated easily due to the raster angles 45° and 90°. These angles provided a greater opening providing a bigger pore size than a sample with the same raster gap but a different raster angle.

Since the raster gap was 0.0762 mm it took the dye 64 hours to penetrate the sample S1, which was the longest among all the samples. The dye took 28 hours to penetrate sample S7 that was the second longest duration among the samples. Both the raster gap and the raster angle of sample S7 were responsible for the slow penetration rate. Sample S6 took the shortest time for the dye to penetrate. Although the raster gap was the same as in sample S2, S4 and S8 the penetration took three hours because of the raster angles 45° and 30°, which makes the pore size smaller than samples S2, S4 and S8.

Figure 5 Drug Release versus time taken for the DDDs
4. Fabrication of Cylindrical DDD Models

A cylindrical DDD matrix model was designed using the Pro/Engineer CAD software, as shown in Figure 3. The device had an outer diameter of 30 mm and height of 30 mm. The cylindrical DDD had a reservoir embedded into the cylinder whose inner diameter was 25 mm and the depth of the reservoir was 10 mm. The remaining 20 mm of the cylindrical DDD model was used as the solid matrix. By using the INSIGHT software of the FDM3000 system, the solid section of the model is sliced into layers and each layer is provided with the assigned process parameters. As mentioned earlier, a uniformly interconnected porous matrix is created within the solid matrix of the cylindrical DDD. When the reservoir is filled with a model drug, the drug is supposed to diffuse through the porous matrix. The rate at which the drug penetrates through the porous matrix entirely depends on the porosity of each cylindrical DDD sample. By varying the raster gaps and raster angles ten different DDD samples were fabricated. Table 1 shows the FDM parameters (raster angle and raster gaps) used in fabricating the ten DDD models fabricated on FDM. The slice thickness and road width were each set at a constant value of 0.254 mm.

Table 1 FDM Parameters for DDD models

<table>
<thead>
<tr>
<th>DDD models</th>
<th>FDM Raster Angle</th>
<th>FDM Raster Gap (mm)</th>
<th>Time for full dye release (hours)</th>
<th>Avg. Drug Release Rate mm/hr</th>
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</thead>
<tbody>
<tr>
<td>S1</td>
<td>0-90</td>
<td>0.0762</td>
<td>64</td>
<td>306</td>
</tr>
<tr>
<td>S2</td>
<td>15-30</td>
<td>0.254</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S3</td>
<td>15-30</td>
<td>0.127</td>
<td>19</td>
<td>1033</td>
</tr>
<tr>
<td>S4</td>
<td>30-60</td>
<td>0.254</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S5</td>
<td>30-60</td>
<td>0.127</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S6</td>
<td>45-30</td>
<td>0.254</td>
<td>4</td>
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<tr>
<td>S7</td>
<td>45-30</td>
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<td>701</td>
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<tr>
<td>S8</td>
<td>45-90</td>
<td>0.254</td>
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<td>-</td>
</tr>
<tr>
<td>S9</td>
<td>45-90</td>
<td>0.127</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>S10</td>
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<td>0.0889</td>
<td>9</td>
<td>2181</td>
</tr>
</tbody>
</table>

5. Drug Release Test

Once the FDM models were fabricated, drug release experiments were conducted to find out the effect of FDM parameters on the penetration of dye through the DDD matrix. Each of the DDD samples has unique FDM parameters.

For mimicking the use of drug flow in the DDD models, methylene blue dye was used as the drug model. The basic reason for using this dye was its bright colour. This blue dye helped to check the loading of DDD samples visually. A 10,000 ppm (parts per million) solution of dye was prepared. The dye was little viscous. A 10,000 ppm solution was prepared by taking 1 gram of the dye powder and making it into a 100ml solution. This concentration was selected in order to load the maximum amount of dye possible into the DDD models and also for simpler calculation during the dilution of dyes for the purpose of creating the calibration chart.

Once all the samples are fabricated the samples are taken out and cooled for sometime. Each sample is then filled with the dye in the hollow section. The start time is noted and the time taken for the decrease in the level of the dye in each samples is noted at periodic intervals. Figure 4 shows the schematic diagram of the working of the cylindrical DDD.
The dye penetration through sample S10 was the second quickest. Although the raster gap was small the dye penetration was second quickest because of the pore opening created due to the raster angles 45° and 90°. The dye in sample S3 initially took more time to penetrate than in sample S5 but later it quickened. At the end, dye in sample S3 took 20 hours and the dye in sample S5 took 18 hours for penetration.

The actual rate of diffusion of drug through each DDD model was also observed at hourly intervals over a long period of time. As shown in Figure 4, as the drug is partially released into the matrix, the depth of drug level in the reservoir reduces until at time T, the drug is fully released when a depth level of 10 mm is reached in the reservoir. The amount of depth will represent the volume of drug penetrated into the reservoir. This depth measured at each hour for drug release test for each DDD model. Figure 5 shows the graph of depth (proportional to the volume of drug released) versus time for each of the six DDD samples S1, S3, S5, S6, S7 and S10. The trends in the graphs show that a variety of release profiles can be obtained for the same device design with the same material and the same input drug volume but with changing FDM process parameters. An ideal DDD is expected to release drug at a constant rate throughout its period of operation, but the time of operation of the device and the amount of drug released by the device can be controlled by varying the porosity and pore structure of the release matrix of the DDD. The graphs give useful information on how different FDM process parameters can be used to obtain different drug release devices with different release patterns.

7. Conclusions

The work presented has demonstrated that computer aided design (CAD) and the fused deposition modeling (FDM) rapid prototyping technique can be used successfully to characterise drug delivery devices (DDDs). Compared to other RP techniques, FDM process offers several advantages in such application such as minimum waste of material, non-toxic and safe process, and possibility of new materials. The work focused on controlling the macrostructure of the DDD samples by manipulating the FDM process parameters. Cylindrical DDD matrices were fabricated on FDM and the time taken for the dye to penetrate the devices was noted.

It was observed that the FDM parameters, raster gap and raster angle, play significant roles in controlling the structure and drug release characteristics of the FDM fabricated DDDs. For example, an FDM made cylindrical DDD sample, whose raster angle was 0°-90° and raster gap was 0.0762 mm, was found to release the drug over a period of 64 hours through diffusion. The experimental observations reveal that appropriate FDM parameters can be selected to fabricate DDD device with desired release rate of drug and the desired period of operation of the device.

8. References


