Characterisation of the Pore Structure of 3D Printed Solid Dosage Forms by XμCT

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Abstract
3D printing is a novel manufacturing technology which was recently employed to produce innovative pharmaceutical drug products. One of the important characteristics of printed solid dosage forms is its microstructure as it directly impacts the drug release in a patient. Therefore, a thoroughly understanding about the relationship between the microstructure and process parameters has to be developed and key characteristics (e.g., porosity) have to be assessed in a non-destructive manner. This study demonstrates how X-ray computed microtomography (XμCT) can be used to gain insight into the effect of changes in process settings of the 3D printer on the pore structure of the dosage form. It further highlights that 3D printed dosage forms can be reproduced consistently, although they may vary considerably from the designed model. The results from XμCT measurements were compared to terahertz pulsed imaging measurements enabling a contactless, non-destructive and fast quantification of the prints’ porosity.

Keywords: X-ray computed microtomography, 3D printing, pharmaceutical tablets, terahertz pulsed imaging

1 Introduction
Typical pharmaceutical tablets are complex powder compacts which can be formulated to release a drug immediately after oral administration or to systematically modify the release kinetics in order to improve therapeutic efficacy, reduce toxicity, and improve patient compliance and convenience. The complex structure of a pharmaceutical tablet makes the rational design of specific drug release profiles very difficult. However, innovative manufacturing principles are rapidly maturing into a commercially feasible platform for drug production, which enable a rational design of specific drug release profiles. One of the most promising technologies is additive manufacturing (i.e., 3D printing), which makes it possible to achieve tailor-made drug release behaviour from a range of design including multilayer devices [1] or compartmental devices [2] comprising a different API in each layer or compartment. However, there is a lack of understanding of the impact of the structural accuracy and integrity of printed structures for different materials in the pharmaceutical context as well as of material property variations and changes of the process configuration on the drug release kinetics. In particular, the microstructure of innovative pharmaceutical dosage forms produced by additive manufacturing plays a crucial role in the performance of the drug and has potential for designing totally new types of products. X-ray computed microtomography (XμCT) is highly suitable to characterise the microstructure, down to 1.5 µm [3], of such 3D printed dosage forms. Due to their high energy, X-rays have the advantage of being able to easily penetrate all pharmaceutically relevant excipients while undergoing negligible diffraction [4]. This work demonstrates the microstructural characterisation of 3D printed solid dosage forms using XμCT. A fused deposition modelling (FDM) based printer was used to realise simple discs and compartmental dosage forms enabling the containment of multiple API formulations. The samples were used to evaluate the impact of process settings on the pore structure of the prints. These discs were further characterized by terahertz time-domain spectroscopy enabling the measure of the effective refractive index, which is related to the porosity of the 3D print.

2 Materials and Methods
Two different geometries were printed using polylactic acid (PLA) and polyvinyl alcohol (PVA) as filament materials. A cylindrical dosage form with two compartments and simple discs were designed in Comsol Multiphysics (Comsol, Stockholm, Sweden, v5.1) and printed with a Makerbot Replicator 2 desktop 3D printer (New York, NY, US). The different structures were examined by a SkyScan 1172 high-resolution XμCT scanner (Bruker, Antwerp, Belgium). The changes in the porosity were quantified for the PLA discs by modifying the print temperature, the print resolution and the print setting of the filament diameter (see Table 1). The terahertz measurements were performed in a transmission setting by a TeraPulse 4000 (TeraView Ltd, Cambridge, UK) device.

2 Results
XμCT was utilised to analyse the microstructure of the prints in terms of porosity, pore volume and pore length. It was further used to examine the print resolution and quality on the basis of co-registered computer-aided design (CAD) models and XμCT data of the dosage form. Figure 1 illustrates the results of the 3D printed discs, which indicates the strong impact of slight
variations in process settings on the porosity of the prints. Therefore, the pore structure can be modified by altering the print temperature, the print resolution and the print setting of the filament diameter. These discs were further analysed by calculating the effective refractive index from terahertz measurements. The effective refractive index is directly related to the porosity and therefore, terahertz technology is an attractive potential tool to investigate the quality of a large number of samples.

<table>
<thead>
<tr>
<th>Print number</th>
<th>Nozzle temperature (Celsius)</th>
<th>Print resolution (mm)</th>
<th>Filament diameter (mm)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>220</td>
<td>0.1</td>
<td>1.67</td>
</tr>
<tr>
<td>2</td>
<td>230</td>
<td>0.1</td>
<td>1.67</td>
</tr>
<tr>
<td>3</td>
<td>230</td>
<td>0.3</td>
<td>1.87</td>
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<tr>
<td>4</td>
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<td>0.3</td>
<td>1.67</td>
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<td>0.1</td>
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<td>8</td>
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<td>0.3</td>
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</tbody>
</table>

Table 1: Experimental design of printed PLA discs.

![Figure 1: 3D renderings of subvolumes reconstructed from XμCT data of 3D printed PLA discs. The pore structure was extracted and illustrated separately below each 3D visualisation of the printed volume. The process settings used for the respective prints are listed in Table 1. The porosity, \( \varepsilon \), was calculated for each print.](image)

3 Conclusion

XμCT is highly suitable to characterise the architecture of the 3D print as well as to verify the print resolution and print quality. The results highlight that slight changes in the process setting strongly impact the pore structure of the 3D print. This understanding is essential in order to design microstructures which realise specific drug release profiles. Furthermore, the ease, speed and limited health care concern of terahertz technology renders it a feasible platform technology for invoking quality control of 3D printed medicines.

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References


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