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Impact of drug load and polymer molecular weight on the 3D microstructure of printed tablets

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ABSTRACT

This study investigates the influence of drug load and polymer molecular weight on the structure of tablets three-dimensionally (3D) printed from the binary mixture of prednisolone and hydroxypropyl methylcellulose (HPMC). Three different HPMC grades, (AFFINISOL^{TM} HPMC HME 15LV, 90 Da (HPMC 15LV); 100LV, 180 Da (HPMC 100LV); 4M, 500 Da (HPMC 4M)), which are suitable for hot-melt extrusion (HME), were used in this study. HME was used to fabricate feedstock material, i.e., filaments, at the lowest possible extrusion temperature. Filaments of the three HPMC grades were prepared to contain 2.5, 5, 10 and 20 % (w/w) prednisolone. The thermal degradation of the filaments was studied with thermogravimetric analysis, while solid-state properties of the drug-loaded filaments were assessed with the use of X-ray powder diffraction. Prednisolone in the freshly extruded filaments was determined to be amorphous for drug loads up to 10%. It remained physically stable for at least 6 months of storage, except for the filament containing 10% drug with HPMC 15LV, where recrystallization of prednisolone was detected.

Fused deposition modeling was utilized to print honeycomb-shaped tablets from the HME filaments of HPMC 15LV and 100LV. The structural characteristics of the tablets were evaluated using X-ray microcomputed tomography, specifically porosity and size of structural elements were investigated. The tablets printed from HPMC 15LV possessed in general lower total porosity and pores of smaller size than tablets printed from the HPMC 100LV. The studied drug loads were shown to have minor effect on the total porosity of the tablets, though the lower the drug load was, the higher the variance of porosity along the height of the tablet was observed. It was found that tablets printed with HPMC 15LV showed higher structural similarity with the virtually designed model than tablets printed from HPMC 100LV. These findings highlight the relevance of the drug load and polymer molecular weight on the microstructure and structural properties of 3D printed tablets.

1. Introduction

Tailoring treatment to patients based on their genetic, physiological, and pathological needs has received significant attention in recent years. The concept of designing pharmaceuticals for a specific patient based upon their therapeutic needs is commonly known as personalized medicine (Vaz and Kumar, 2021).

In the pharmaceutical field, three-dimensional printing (3D printing) has emerged as a method to manufacture patient-specific medications with customized dosage strength and drug release profile (Oladeji et al., 2022; Solanki et al., 2018). One of the manufacturing methods most explored in the literature of pharmaceutical 3D printing is fused deposition modelling (FDM) with filaments prepared by hot-melt extrusion (HME) (Kissi et al., 2021; Oladeji et al., 2022). HME is a method that can be used to incorporate an active pharmaceutical ingredient (API) into a polymeric matrix, which is then used as a feedstock material, i.e., filament, in FDM. FDM works by advancing the API-loaded polymeric filament through the liquefier in the print head. The liquefier has a heating zone where the filament is melted at a specific temperature before being extruded through the nozzle and deposited layer by layer on the printer's build plate according to the customized digital design (Mora-Castaño et al., 2022; Oladeji et al., 2022; Solanki et al., 2018). It is important that the produced filaments show adequate printability to be used for preparation of solid dosage

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forms (Aho et al., 2019). Printability encompasses both the ability of the filament to be fed into the liquefier of the 3D printer without breaking before printing, as well as to ensure consistent and reproducible feeding and extrusion during printing (Tabriz et al., 2021; Xu et al., 2020).

Manufacturing of solid dosage forms with complex geometries, adjustable dimensions, and density can be achieved by manipulating the geometry in the digital file (Mora-Castaño et al., 2022). In other words, the benefits of 3D printing for the drug manufacturing purposes lie in the possibility of quickly adjusting the dose and drug release profile of the dosage forms. These can be tuned by simply changing the dimensions and geometry of the object digitally before printing, avoiding the need for making a new batch of formulation every time adjustments are needed. A challenging aspect of the pharmaceutical production with FDM is the preparation of suitable drug-loaded filaments, since polymers that are typically used as excipients in drug products are either not thermoplastic, too brittle or not stable at high temperatures. On the other hand, polymers that are commonly used for FDM, are often not suitable for printing oral dosage forms due to poor aqueous solubility or inadequate safety profile (Govender et al., 2021; Parulski et al., 2021). Recently, a grade of hydroxypropyl methylcellulose (HPMC) specifically designed for HME (AFFINISOL^{TM} HPMC HME, DuPont), has generated a lot of interest, as it shows both good printability, thermal properties, and aqueous solubility (Huang et al., 2016; Mora-Castaño et al., 2022; Patel and Serajuddin, 2021; Prasad et al., 2019; Skalická et al., 2021). This type of HPMC with its advantageous extrudability, has a low glass transition temperature (approximately 115°C) and a high thermal stability (up to 250°C) (Dow Pharma and Food Solutions, 2016). All three available grades of AFFINISOL^{TM} HPMC HME were used in this study: 15LV, 100LV and 4M with molecular weights (Mw) of 90 Da, 180 Da and 550 Da, respectively.

In the present work, prednisolone was selected as a therapeutically relevant model drug for fabrication of drug-loaded filaments and tablets due to the therapeutic need for varying doses of oral prednisolone for different groups of patients, e.g., children and elderly as well as for different indications and the level of progression of the disease; Prednisolone tablets were reported to be among frequently manipulated for use in children (Bjerknes et al., 2017; Zahn et al., 2020). Prednisolone is a corticosteroid used as an anti-inflammatory or immunosuppressive agent for numerous conditions. It has a narrow therapeutic window with the therapeutic oral doses ranging from 0.5-100 mg. The dosing regiments of prednisolone are often strict and varied for many patients. As an example, kidney transplant patients will often need low doses of prednisolone just after transplantation, then the doses will be increased due to the increase in the total hepatic clearance (Steiner and Awdishu, 2011). FDM could improve the management of these patients' therapy by enabling on-demand production of desired doses of prednisolone in an automated and controlled manner. This would reduce the need for manual dose manipulation of solid drug products available on the market, which is laborious and prone to errors (Brustugun et al., 2021; Meléndez et al., 2008). Since prednisolone is known to have a high melting point (reported between 218 and 258°C) (Corvis et al., 2016), it is potentially suitable to be used in FDM.

Besides thermoplastic polymer and thermostable API, plasticizers can be included in the filament formulation. Plasticizers can improve printability in FDM and reduce thermal degradation of the components by allowing the use of lower temperatures for the first extrusion during HME and the second extrusion during printing. For instance, Melocchi et al. (2016) have used polyethylene glycol 400 as a plasticizer for extrusion of HPMC-based filaments. However, many plasticizers are hygroscopic compounds that can negatively affect the chemical and microbiological stability of the API and the polymer during storage. In addition, plasticizers can compromise the physical stability of the API in the formulation by hastening its crystallization (Govender et al., 2021). Interestingly, the API itself can act as a plasticizer, circumventing the need for additional components to be included (Aho et al., 2019; Kissi et al., 2021; Samaro et al., 2020).

One of the most common challenges with using FDM to produce tablets is the low structural reproducibility of the printed objects. This could be variations in micropores between the extruded layers and within the object (Markl et al., 2018). The reasons behind that could be (i) variation in the physical dimensions of the filament to be printed; (ii) inhomogeneity of the formulation that could be a result of partial solubility/miscibility of the API with the polymer and (iii) imprecise position of the nozzle during repetitive printing cycles. The difference in the structure, e.g., micro- and macropores in the tablet, could potentially influence weight variation, crystallization, and release characteristics of the API from the dosage form. For some polymeric matrices, the rate of drug release is substantially affected by the presence and nature of pores (Vasvári et al., 2018). However, HPMC-based polymeric matrices have been shown to be swelling in contact with water (Colombo et al., 1999). Swellable polymers can diminish the effect pores have on release rate. This is because the pores disappear in contact with an aqueous medium, and the API diffuses through the formed polymer gel layer (Viridén et al., 2009). Rate of release was not studied in this paper, but has been planned to be included in a future study involving comparable formulations of prednisolone and HPMC.

The structure of the tablets produced in this study was characterized, visualized, and quantified using X-ray micro computed tomography (XμCT). XμCT is a technique that has recently been applied in the field of pharmaceutical 3D printing. By measuring the 2D absorption of X-rays from multiple directions through the tablet and interpreting the results, it is possible to generate 3D images of the tablets. These images can then be analyzed to investigate microstructures like presence and size distribution of pores, as well as larger structures like walls or the fusion of layers in the printed tablets (Markl et al., 2017a,b).

In the current study, the binary mixture of the API prednisolone and the polymer HPMC was used to explore its printability in HME and FDM with the aim of achieving single-phase glass solutions for further characterization. This characterization included a thorough investigation of the structure of 3D printed tablets to establish a connection between the composition of the binary mixture, particularly the drug load and the polymer Mw, and the obtained porosity of the printed tablets.

2. Methods and materials

2.1. Materials

Prednisolone in the crystalline form was purchased from Fagron (Denmark). Hydroxypropyl methyl cellulose (HPMC, AFFINISOL^{TM} HPMC HME 15LV, 90 Da; 100LV, 180 Da; 4M, 500 Da) in the amorphous form were kindly donated by DuPont (Switzerland). These three polymer grades will be referred to as HPMC 15LV, 100LV and 4M. All other reagents and solvents were of analytical grade.

2.2. Hot-melt extrusion

Filaments for printing were prepared by hot-melt extrusion (HME) with an Xplore micro-compounder equipped with co-rotating twin screws. Filaments were made of binary mixtures of prednisolone and HPMC of all three grades, and had target drug loads of 2.5, 5, 10 and 20 % (w/w). 5 g physical mixtures of the API and the polymer was added to the hopper with a spoon. The powder mixture was melted and mixed under feedback recycling and extruded at a temperature of 150°C, 160°C or 180°C for HPMC 15LV, 100LV or 4M, respectively, with the screws rotating at 100 RPM. After 2 min, the molten mixture was extruded through an in-house made extruder die with an elongated hole with a diameter of 2.85 mm and a length of 12 mm (Fig. S1, Supplementary material). Filaments were kept in plastic bags and stored in a desiccator over a saturated magnesium chloride hexahydrate solution (~34 % relative humidity) until further use.

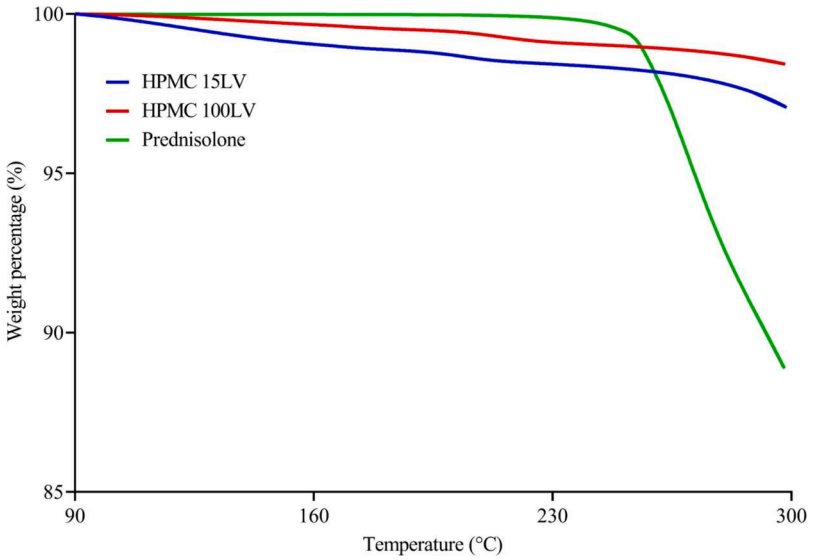

Fig. 1. Thermogravimetric analysis of prednisolone, HPMC 15LV and HPMC 100LV. Normalized to the absolute weight at 90°C.

2.3. Fused deposition modeling

Suitable filaments produced in section 2.2 were loaded in an Ultimaker 3 equipped with an Ultimaker Print Core AA with 0.4 mm nozzle (Ultimaker B.V., The Netherlands) to print tablets. G-code files for the 3D printer were generated using Ultimaker Cura software (version 4.7.1, Ultimaker B.V., The Netherlands) using the standard set-up settings for an Ultimaker 3 included in the software. Printing temperature for the tablets was 200°C with the first layer being printed at 220°C to improve adhesion to the build plate. The build plate temperature was set to 90°C. Layer height was 0.1 mm, wall thickness was 0.5 mm and print speed was 30 mm/s. The cooling fan was not used during printing. The remaining parameters were kept as the standard set from the software. Tablets had a honeycomb design with a circular outer diameter of 11 mm and height of 5 mm. The honeycomb structure was made with seven hexagon-shaped holes each with widths of 3 mm and wall thickness of 0.5 mm (Fig. S2, Supplementary material). 3D models of the honeycomb tablets were designed with Fusion 360 (Autodesk Inc., CA, USA).

2.4. Dynamic mechanical analysis

Samples of HPMC 15LV, 100LV or 4M were loaded into a stainless-steel powder holder and clamped into a 35 mm dual cantilever. Triplicate dynamic mechanical analysis (DMA) scans were measured on a DMA Q800 (TA Instruments, TX, USA) using the multi-frequency strain mode with an amplitude of 20 μm, a frequency of 1 Hz and a heating rate of 3°C/min from 25 to 200°C. Data was analyzed using TA universal analysis software (TA instruments, TX, USA). Glass transition temperatures (T_gs) are reported as the average tan(Δ) of the three scans.

2.5. Thermogravimetric analysis

Thermal degradation of prednisolone, HPMC 15LV, HPMC 100LV or cut HME filament samples were analyzed with a thermogravimetric analyzer (TGA) Discovery (TA instruments, TX, USA). Approximately 10 mg of the sample was heated from 90°C to 300°C with a heating rate of 20°C/min. Results were analyzed using TRIOS Software (TA instruments, TX, USA).

2.6. Differential scanning calorimetry

Differential scanning calorimetry (DSC) were done to determine the melting point of prednisolone as received and in physical mixtures with HPMC 15LV and 100LV. DSC was performed on a DSC Discovery (TA instruments, Texas, USA) in Tzero aluminum pan with a perforated Tzero hermetic lid. Approximately 2 mg of sample were scanned from 25 to 260°C with a heating rate of 10°C/min.

2.7. X-ray powder diffraction

Solid-state form of the starting materials, physical mixtures and drug-loaded filaments (after extrusion and after storage) was assessed by X-ray powder diffraction (XRPD) using a X'Pert PRO X-ray diffractometer (PANalytical B.V., The Netherlands) operated in reflection mode with a Cu Kα radiation source (λ=1.54 Å) with a voltage of 45 kV and a current of 40 mA. All samples were scanned from 2 ° to 30 ° 2θ with a stepwise increase of 0.026 ° 2θ and a scanning speed of 0.067 s^{-1}. Starting material and physical mixtures were powders when measured. Slices of filaments were cut and measured freshly prepared and after approximately 6 months of storage. All samples were scanned on aluminum plates as the background.

2.8. Drug content in extruded filaments

The exact drug loads in the extruded filaments were determined in triplicate using high-performance liquid chromatography with an ultraviolet detector (HPLC-UV). The exact weight of approximately 20 mg cuts from different parts of the filaments were dissolved in mobile phase and analyzed on an Ultimate 3000 HPLC with a Diode Array UV-detector (Thermo Fisher Scientific Inc., MA, USA). A 3.9 × 150 mm - 4 μm Nova-Pak® C_{18} column (Waters Corporation, MA, USA) was used at 40°C. The mobile phase consisted of methanol/acetonitrile/purified water 2/2/6 v/v/v with an isocratic flow rate of 0.7 mL/min. Prednisolone was measured at 254 nm and had an approximate retention time of 5.0 min. Results were analyzed with Chromeleon v7 software (Thermo Fisher Scientific Inc., MA, USA).

2.9. X-ray micro computed tomography

The Skyscan 1172 microCT system from Bruker (Kontich, Belgium) was employed for the scanning of the samples. The acquisition parameters were set as follows: 1163 projections, an isotropic voxel size of 3.5 μm, a 2 × 2 binning of the CCD-camera (11 Mpixel CCD detector), a 50 kV accelerating voltage, a 190 μA current, and no physical filter. The sample was rotated by 360° about its vertical axis with a step size of 0.31°, and an exposure time of 460 ms per projection, taking an average

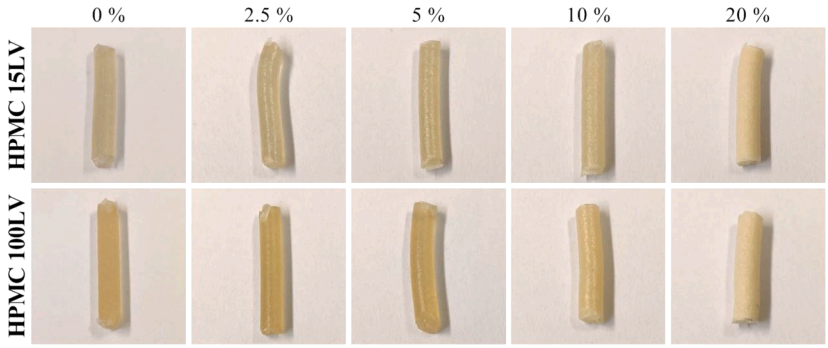

Fig. 2. Photographs of filaments containing HPMC 15LV and HPMC 100LV, as well as prednisolone at a target drug load of 0, 2.5, 5, 10 or 20 %.

of 3 frames to reduce noise. The tomograms were reconstructed with NRecon v.1.7.1.0 software (Bruker) using a filtered back-projection algorithm, which involved ring artefact correction of 8, beam hardening correction of 80 %, and no smoothing.

For the analysis, a virtual wrapping of the surface of the tablet was created, which entailed closing all openings greater than 70 μm, resulting in a Volume of Interest (VOI) for the analyses. The virtual object (tablet) was then segmented using the Otsu method (Otsu, 1979). CTAn (1.20.8+ Bruker) was utilized to calculate the following parameters: total volume (TV, which is the VOI used), object volume, percent object volume, object surface, structure thickness, pore diameter (within the structures), and open, close, and total porosity.

To compare the 3D printed tablets with the 3D model, the 3D surface model was converted into a volume using Avizo 3D Pro (ThermoFisher Scientific). Finally, colour-coded difference images were generated to provide a visual representation of the regions where the printing lacked material or where excessive printing occurred.

3. Results and discussion

3.1. Fabrication of filaments

T_g of HPMC 15LV, 100LV and 4M were determined with DMA to be 114.6 ± 0.6, 120.9 ± 2.7 and 122.5 ± 1.3°C, respectively, using the peak max in the tan(Δ) signal (Fig. S3, Supplementary material). This is in accordance with the reported T_g for these polymer grades to be approximately 115°C (Dow Pharma and Food Solutions, 2016). The increase of T_g with increasing Mw of the polymer, was not surprising as the molecular mobility is usually reduced when the Mw of the polymer increases. The start of the thermal degradation for HPMC and prednisolone was observed to be above 250 and 230°C, respectively (Fig. 1). Therefore, extrusion at lower temperatures than 230°C were investigated to identify the lowest possible temperature that would yield consistent filaments with acceptable visual appearance (i.e., least change in coloration) and diameter to avoid unnecessary thermal stress to the binary mixture. The lowest temperatures were found to be 150 and 160°C for pure HPMC 15LV and 100LV, respectively. These temperatures were around 40°C higher than the measured T_gs and were used to make filaments for all investigated drug loads. This is in line with the findings reported by Mora-Castano et al. (2022), who found that at extrusion temperatures below 130°C for HPMC 15LV the produced filaments had a rough surface, while filaments produced at temperatures above 160°C showed changes in coloration. Similarly, Prasad et al. (2019) showed that extrusion of HPMC 15LV filaments was only successful at 180°C, using a screw speed of 100 RPM. HME of HPMC 100LV 70 % and carbamazepine 30 % was feasible at temperatures of 140 and 160°C using screw speeds of 100 and 150 RPM, respectively (Huang et al., 2016). The authors noted that, although both temperatures were suitable, using the lower temperature enabled extrusion of more transparent and less yellow filaments. The lowest temperature that could be used to extrude HPMC 4M was 180°C, however, these filaments showed an inconsistent shape and brownish discoloration. This grade of HPMC was therefore excluded from the study.

It was documented that HPMC designed for HME swells upon exiting the die during extrusion (Prasad et al., 2019; Samaro et al., 2020). To minimize die swelling and give more time for the polymer chains to align, the extruder was equipped with an in-house made die with an elongated cylindrical section at the exit (Fig. S1, Supplementary material). This die design was inspired by Melocchi et al. (2016), who showed that this design can lead to more reproducible dimensions of the filament. The diameter of the extruded filaments was consistently 2.80 ± 0.10 mm for all included grades of HPMC and drug loads. This was considered as the best outcome that could be achieved with the available lab-scale extruder, having a heated barrel of a 5 ml in volume. It is expected that deviation of the filament dimensions would influence the deposition rate of the material during FDM and, therefore, would have an effect on the microstructure of the printed tablets.

The produced filaments with the target drug loads of 2.5, 5 and 10 % had a consistent yellow to beige color (Fig. 2) and were slightly transparent when looking at them against a light source. It has been stated by the manufacturer of these grades of HPMC that this change in color is to be expected and should not impact the quality of the material (Dow Pharma and Food Solutions, 2016). Prednisolone was not expected to degrade at these extrusion temperatures (150°C and 160°C) due to its higher thermal degradation temperature (>230°C) as stated above, therefore the change in color was concluded not to be related to the drug. The transparency of the prepared filaments appeared to be reduced with the increase in the drug load, which is in line with previously reported findings on filaments made from indomethacin and polycaprolactone (Holländer et al., 2016). This could be both due to the lesser transparency of the API from a single-phase glass solution of the two components, as well as diffraction from undissolved particles of the API, when the drug load increases. The filaments prepared with a target drug load of 20 % were whiter in color than the rest of drug-loaded filaments for both polymer grades. Particles of the API were observed within the filament, when looking against light. These particles were not observed for filaments with a target drug load below 20 % (Fig. 2). Therefore, it was concluded that prednisolone in the filaments with 20 % drug load did not completely melt and mix with the polymer under the applied conditions during extrusion.

It is expected that visible heterogeneous distribution of crystalline and/or amorphous API within the filament has an impact on the printability of the filaments and the reproducibility of the prints, and consequently, will affect the microstructure of the printed tablets. It is possible that the addition of plasticizers would reduce the viscosity of the melt and enable the formation of filaments with 20 % or higher drug loads, however, it would be expected that the addition of plasticizers would change the composition of the mixture and this, in turn, would impact the microstructure of the printed tablets. The aim of this work was, however, to study the effect of drug load and polymer molecular

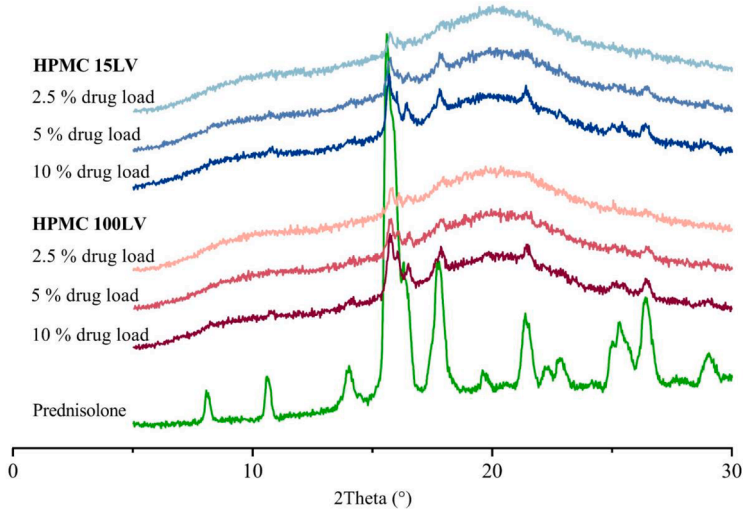

Fig. 3. X-ray powder diffractograms of physical mixtures of either HPMC 15LV or HPMC 100LV with prednisolone at a drug load of 2.5, 5 or 10 %, as well as prednisolone measured as received. Y-axis represents arbitrary intensity.

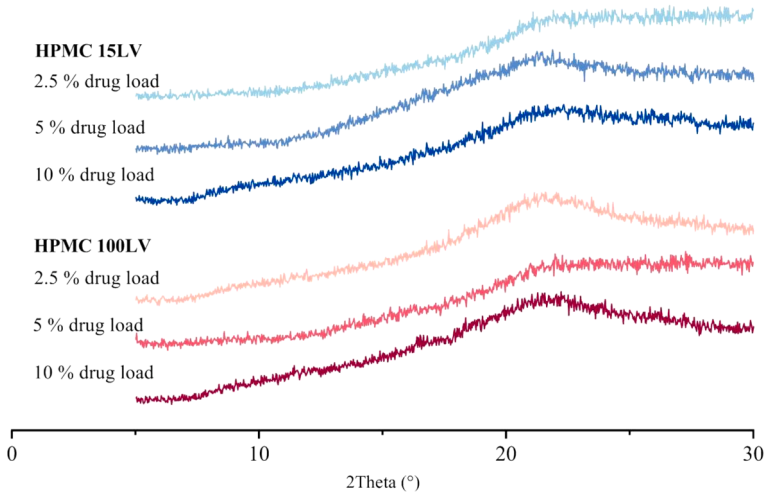

Fig. 4. X-ray powder diffractograms of freshly prepared filaments of either HPMC 15LV or HPMC 100LV with prednisolone at a drug load of 2.5, 5 or 10 %. Y-axis represents arbitrary intensity.

weight on the printability of the binary mixture, and not of the tertiary mixture. Taken into account the observed phenomena, the filaments with 20 % drug load with or without a plasticizer were not used further in this study.

The onset of melting for pure prednisolone was measured to be 249°C by DSC. This was in line with published findings for prednisolone (Corvis et al., 2016). Although HME was performed at temperatures below the melting point of the pure crystalline API, it is well known that the presence of polymer can lead to depression of the melting point and at least partial dissolution of the drug in the polymer (Aho et al., 2019; Holländer et al., 2016; Marsac et al., 2009). Therefore, it is not excluded that a single-phase homogenous filament (glass solution type solid dispersion), could be obtained as the result of HME. The exact miscibility of prednisolone with HPMC at different temperatures was not investigated in the current study, though it can be assumed that a higher temperature would be able to dissolve a larger portion of prednisolone in the polymer to form a glass solution during the mixing stage of HME (Knopp et al., 2015; Marsac et al., 2009). Printability of filaments made from HPMC 15LV and 100LV has been previously studied in the literature regarding their mechanical properties and were found to be printable (Tabriz et al., 2021; Xu et al., 2020). The mechanical properties of the produced filaments were, therefore, not investigated in this study prior to printing. Our studies confirmed that both drug-free and prednisolone-containing filaments of 2.5, 5 and 10% target load were printable for both polymer grades.

It was aimed to create filaments of a single-phase glass solution as it would give more reproducibility to the results upon FDM. XRPD was used to investigate the potential crystallinity of the studied API in the prepared filaments. Results in Fig. 3 show the presence of the crystalline API in the physical mixtures as low as 2.5 % drug load as characteristic peaks of prednisolone were observed. A halo with no distinct peaks were observed for freshly prepared filaments (Fig. 4), showing that it was possible to prepare a glass solution with HME under the conditions used for these formulations. To support the XRPD finding, DSC experiments with physical mixture and freshly prepared filaments were conducted. However, DSC findings were inconclusive. Melting of prednisolone could be well detected only in the physical mixtures with 10 % drug load. Due to a large peak widening and melting point depression, it was difficult to detect melting point of the API in the physical mixtures with 5 % drug load, and it was not visible at all in the physical mixtures with 2.5 % drug load (Fig. S4 and S5, Supplementary material). Because of this the solid-state form of prednisolone in the prepared filaments was

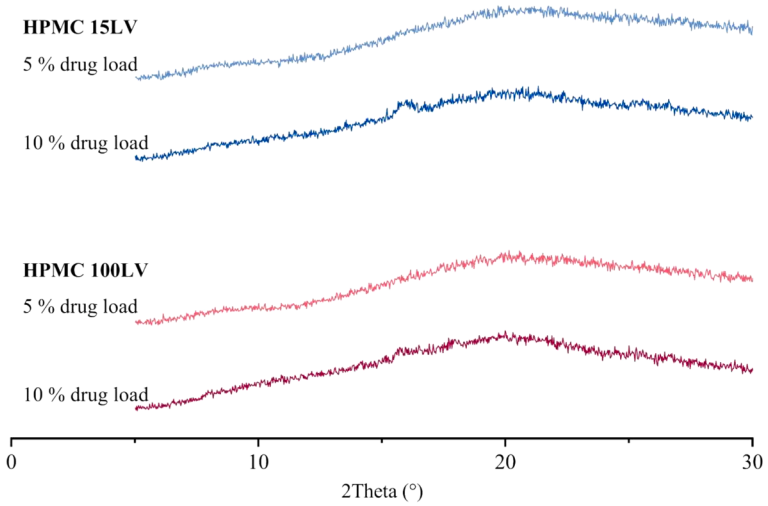

Fig. 5. X-ray powder diffractograms of hot-melt extruded filaments after 6 months of storage at 25°C and approximately 34 % relative humidity of either HPMC 15LV or HPMC 100LV with prednisolone at a drug load of 5 or 10 %. Y-axis represents arbitrary intensity.

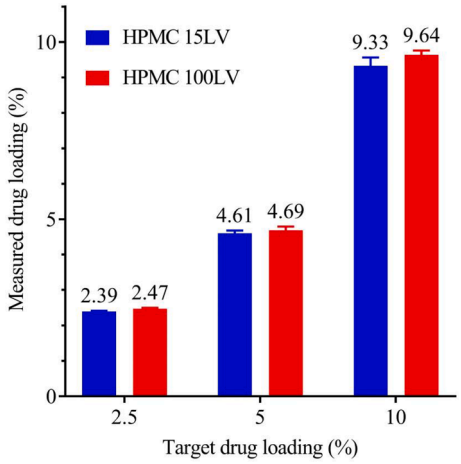

Fig. 6. Measured mean drug loads of hot-melt extruded filaments of either HPMC 15LV or HPMC 100LV with prednisolone at a target drug load of 2.5, 5 or 10 %. Data are present as mean plus/minus standard deviation (n=3).

solely assessed based on the XRPD data. It is worth noting that depression of the melting point of prednisolone does indicate a significant miscibility between the drug and the polymer. This increases the likelihood of obtaining a single amorphous phase in the drug-loaded filaments. More experiments are required to confidently define the miscibility of prednisolone and HPMC over the range of temperatures relevant for HME and FDM (Marsac et al., 2006). This would allow predictions of (i) whether both grades would be equally miscible with prednisolone at the printing/extrusion temperature and (ii) the highest drug load that would still form a one-phase glass solution with the polymer under the printing conditions. It would be expected that whether the API was crystalline or in a glass solution could have an impact on the microstructure of the printed tablets. Although under some conditions, small crystalline domains could melt during FDM and potentially have a limited impact on the microstructure of the printed tablets.

It is well-known that the API in the drug-loaded filaments and 3D printed geometries can recrystallize upon storage (Holländer et al., 2016). Therefore, physical stability of prednisolone in the filaments was assessed after six months of storage (room temperature, approximately 34 % relative humidity) (Fig. 5). There was a lack of distinct peaks in the diffractograms for all filaments except for the one with a drug load of 10 % in HPMC 15LV, which showed a distinct peak at around 16° 2θ. Since only this one broad peak is visible, it indicates that a small amount of crystalline prednisolone formed in this filament during storage. This could mean that the upper drug load limit for physically stable prednisolone-HPMC 15LV glass solutions are between 5 and 10 %. Since no peaks were observed from the diffractograms of stored filaments with 10 % drug load in HPMC 100LV, it is expected that this grade either has higher miscibility with prednisolone or produces glass solutions with higher physical stability. Higher physical stability is expected, since this grade has a higher Mw, higher viscosity, and therefore lower chain mobility at the storage conditions (Shi et al., 2022).

3.2. Determination of drug content in filaments

To confirm that the target drug contents in the filaments were obtained, an HPLC-UV study was performed. As shown in Fig. 6, there was a slightly lower measured drug load than the target for all filaments. A small loss of the API, less than 10 %, during HME is common due to losses in the hopper due to poor flowability or adhesion of the API or by dead zones in the feedback loop of the extruder (Genina et al., 2017). Losses like these should be limited or adjusted to obtain a good content uniformity of the resulting tablets. Variation between sample cuts from different sites of the same filament was less than 3 % for all filaments, showing homogenous mixing of the API and the polymer during extrusion. The drug loads of extruded filaments were consistently measured to be higher with HPMC 100LV for all targeted drug loads. However, only the targeted drug load of 2.5 % showed a statistically significant difference between the two polymers using unpaired student t-test with a significance level of 0.05.

3.3. 3D Printed tablets

Tablets were printed using a honeycomb design inspired by Kyobula et al. (2017). This design is made with the intention of increasing the surface to volume ratio of the resulting tablets with high enough physical strength to be handled (Fig. S2, Supplementary material). In a similar fashion to find the suitable HME temperature, the lowest printing temperature that would consistently deposit the material was investigated by trial-and-error method. It was found that for both filaments containing HPMC 15LV and 100LV, the lowest suitable printing temperature was 200°C. It is common that printing temperature should be higher than HME temperature, due to the smaller die size of the printing nozzle, the lower forces exerted for extrusion and short exposure to heating (Pietrzak et al., 2015). This is in line with the findings of Castano

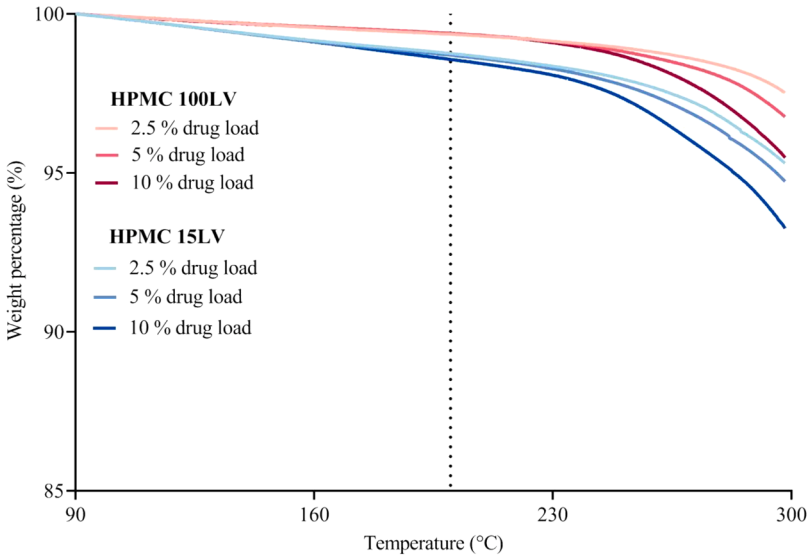

Fig. 7. Thermogravimetric analysis of filaments containing prednisolone and either HPMC 15LV or HPMC 100LV. Normalized to the absolute weight at 90°C. Dotted line indicates the used printing temperature for fused deposition modelling (200°C).

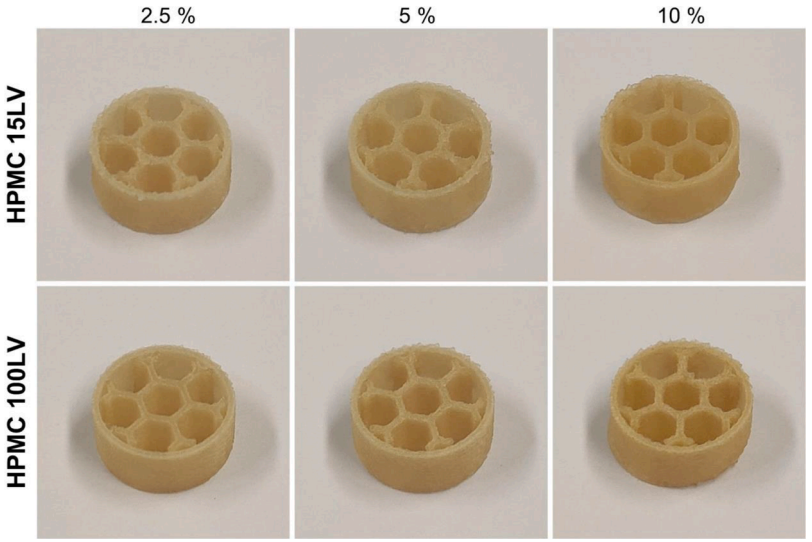

Fig. 8. Photographs of tablets containing HPMC 15LV and HPMC 100LV, as well as prednisolone at a target drug load of 2.5, 5 and 10 %.

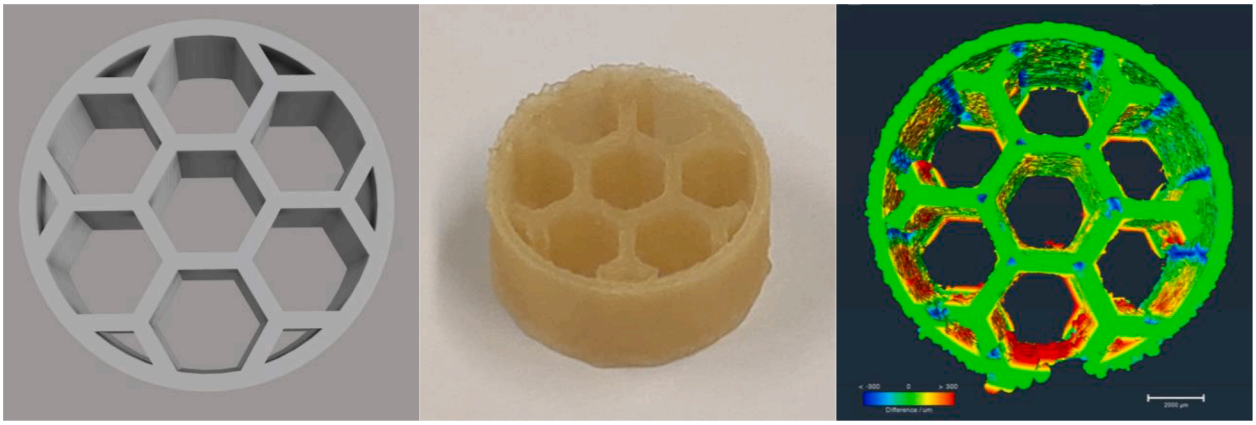

Fig. 9. Honeycomb design model (left). Example photograph of printed tablet (middle). 3D image made with XμCT (right) showing an example of the difference between the 3D printed tablet and the design model used for printing. Hot spots where there was excess material shown in yellow-reddish colours (deviation + 300 μm) and lack of material shown in blueish colours (deviation -300 μm). Green colour show print according to the model (0 deviation).

Table 1
Total porosity of FDM printed tablets of HPMC 15LV and HPMC 100LV with 2.5, 5 and 10 % drug loads of prednisolone. Determined from 3D images made with XμCT, n=1.

Polymer grade	Target drug load [%]	Total Porosity [%]
HPMC 15LV	2.5	9.30
	5	7.53
	10	8.65
HPMC 100LV	2.5	12.88
	5	14.04
	10	15.46

et al. (2022), who reported that the optimal printing temperature was 200°C using filaments containing 50 % HPMC 15LV and 50 % metformin hydrochloride. This study also confirmed that the temperature needed for printing (200°C) was higher than that used for the extrusion (150°C). Similarly, Prasad et al. (2019) used a temperature of 190°C for extrusion of a filament composed of HPMC 15LV and 10% or 50 % paracetamol. It is worth mentioning that the chosen printing temperature (200°C) was lower than the thermal degradation temperature observed for the filaments (above 230°C) (Fig. 7). It appears that there is a faster loss of weight for filaments containing HPMC 15LV compared to HPMC 100LV. However, the same weight loss was also observed for the pure polymers (Fig. 1) and should therefore not be interpreted as degradation of prednisolone.

It was found that it was difficult to achieve sufficient adhesion of the deposited material on the build plate to print the complete tablet. This could be due to a lower sticking of the extruded material compared to the conventional FDM material, such as polylactic acid, and the small surface area of the honeycomb tablet touching the build plate. In order to improve adhesion, the build plate temperature was set to the highest achievable, 90°C, and the first layer of material was deposited at 220°C. The printing temperature of the first layer was closer to, but still lower, than the measured thermal degradation temperature. In addition, since exposure to this temperature was short and the layer count was as high as 50, this was expected to have a minor impact on the overall chemical stability of the components in the printed tablets. Though, degradation of prednisolone in 3D printed tablet is worth investigating in the future. Tablets containing HPMC 15LV weighed on average 189.9 mg with a standard deviation of 6.5 mg, while tablets containing HPMC 100LV weighed on average 174.2 mg with a standard deviation of 5.9 mg. From visual inspection, the printed tablets showed a consistent appearance and shape, with yellow to beige color similar to the ones observed for the HME filaments (Fig. 8). These tablets were used for XμCT.

3.4. X-ray micro computed tomography

3.4.1. Deviations in print from the design model

Tablets were investigated using XμCT to identify structural differences between printed tablets and the design model it was printed from (Fig. 9). The figure shows areas of high and low density of material. Images like these highlights the intra-variation observed for the printed tablets and the strength of XμCT as a tool to investigate these structures. In the following paragraphs, data analysis done on these computed 3D images will be used to quantify the microstructural difference between the printed tablets.

3.4.2. Total porosity and pore size distribution

Tablets were also investigated using XμCT to identify structural differences between tablets made from different grades of HPMC and with different drug loads. In Table 1, the total porosities of these samples are shown.

No overall conclusion could be made for the effect of drug loads on the total porosity since only one sample was analyzed per formulation. Replication might have revealed an increasing trend with increasing drug loads, as suggested for HPMC 100LV. As a matter of fact, only one sample deviated from an increasing trend of total porosity for higher drug loads also for HPMC 15LV; the tablet with 2.5 % drug load showed slightly higher porosity than the 5 and 10 % drug loads. Nevertheless, the differences in porosity related to varying drug loads appeared to be minor and the increased scanning time associated with replications was not considered worthwhile. From XRPD results, it was concluded that it was possible to form amorphous solid dispersion and that some miscibility of prednisolone with both grades of HPMC exists, at least at elevated temperatures. Higher drug loads led to a trend of larger porosity for HPMC 100LV, with nonconclusive findings observed for tablets made with HPMC 15LV. One could hypothesize a lower total porosity in tablets made with more plasticized material, as in a larger concentration of the API in a single-phase glass solution (Kissi et al., 2021). Though such an effect was not observed here, with the opposite trend being seen for tablets made with HPMC 100LV. A more thorough study into the API-polymer miscibility could provide insight into the reasons for the differences observed between different drug loads with

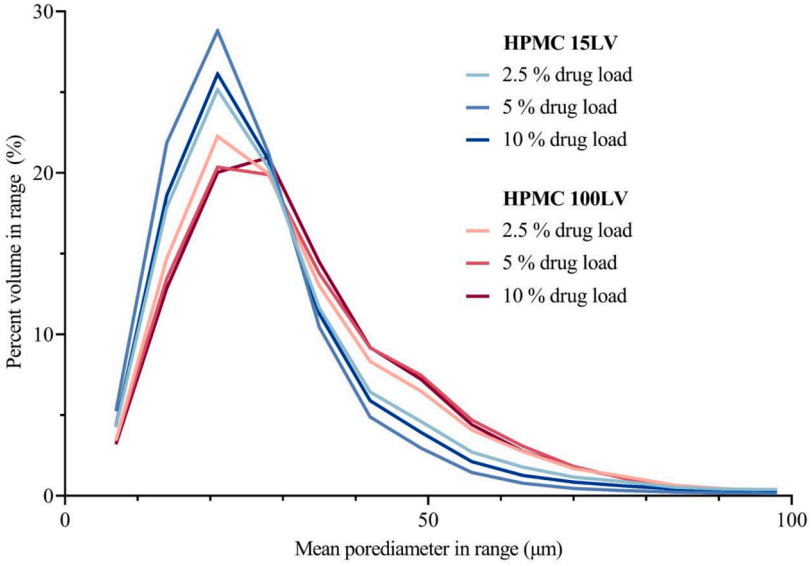

Fig. 10. Pore size distribution of printed honeycomb tablets with either HPMC 15LV or 100LV, as well as drug loads of 2.5, 5 or 10 % prednisolone measured using X-ray micro computed tomography (n = 1).

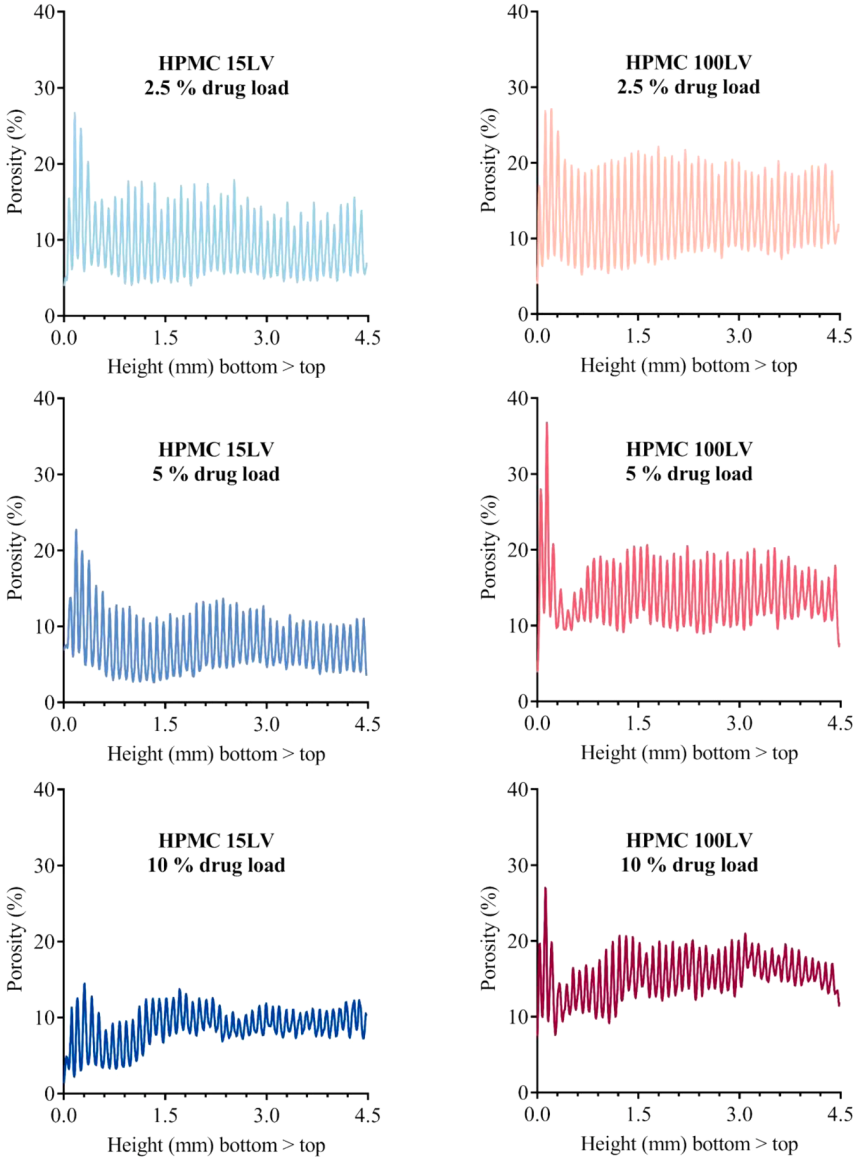

Fig. 11. Total porosity of each tomography slice against the height of printed honeycomb tablets with either HPMC 15LV or 100LV, as well as drug loads of 2.5, 5 or 10 % prednisolone measured using X-ray micro computed tomography (n = 1). Porosity distribution is evaluated in the range from 0 – 4.48 mm. Left side of x-axis being the bottom of the tablet as printed.

the same grade of HPMC.

A clear difference in porosity was observed between the two grades of HPMC, with the porosity being consistently lower for tablets containing HPMC 15LV compared to HPMC 100LV. This is likely due to a difference in viscosity between the two polymers during printing. The lower Mw HPMC (HPMC 15LV) might fuse 3D printed layers more consistently and therefore form fewer pores. It would also be expected that HPMC 15LV would flow more freely when heated up. The flow of molten binary API-polymer mixture would likely be able to fill voids formed between strands of extruded filaments more readily for the lower Mw polymer before cooling stops the flow of material.

When analyzing the distribution of the pore diameters in the tablets, it was found that there was not just a difference in total porosity, but also in pore structure between the two grades. Fig. 10 below shows that the tablets printed with the low Mw polymer (HPMC 15LV) have a narrower distribution of the pores. The median pore diameter for these tablets is around 20 μm. Tablets printed with HPMC 100LV, instead, have a median pore diameter of around 30 μm and twice as many pores around 50 μm. This shows that smaller pores were formed with HPMC 15LV compared to HPMC 100LV. No clear difference in pore size distribution was observed between tablets with different drug loads and the same grade of HPMC.

3.4.3. Pore dependency on 3D printed layers

In Fig. 11, the distribution of pores from slices along the vertical dimension of the tablets can be seen. In these graphs, there is a clear repeating pattern of pore distribution vertically through the tablets. This is due to the way the tablets are printed. The 3D printer makes individual layers that stack on top of each other to make the full tablets. When a new layer is deposited on top, it is expected to fuse slightly with the layer beneath. However, as it can be interpreted from the clear pattern in pore distributed in all the tablets, this printing technique affects pore formation in the printed tablet. It is expected that a larger amount of pores forms between deposited layers. This is confirmed by the observed distance between repeating segments in the graph (~100 μm), which coincides with the layer height parameter used for the 3D printing.

Despite not being observed in the total porosity, it does appear the

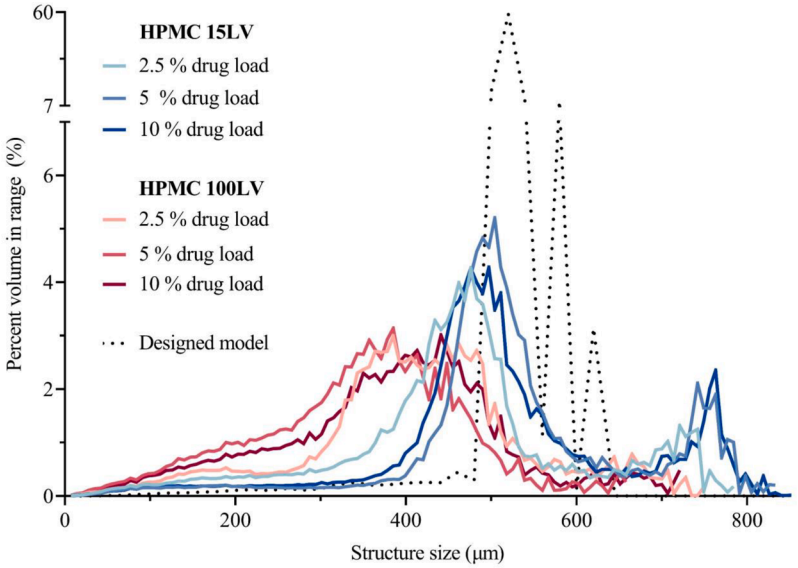

Fig. 12. Relative volume of possible computer-generated spherical structures observed in 3D images of printed tablets containing either HPMC 15LV or HPMC 100LV, as well as 2.5, 5 or 10 % drug load of prednisolone. Structure size is the diameter of the hypothetical largest possible sphere. Percent volume in range is the relative distribution of the total volumes of spheres with a certain diameter and center points in ranges of 7 µm. Y-axis in two segments to allow all values of designed model. Measured with X-ray microcomputed tomography (n=1).

drug load has an impact on the microporosity of the tablets. Higher drug loads showed lower variation in pore distribution between vertical slices, indicating that higher drug loads improve the fusion of the deposited layers. This is likely caused by the API molecules acting as plasticizers during printing as shown by Kissi et al. (2021). However, in this specific setup, it did not alter the total porosity, which might be related to the chosen honeycomb structure. This is a relatively open structure with less deposited material compared to the filled cylindrical tablets studied earlier (Kissi et al., 2021).

It can also be seen in Fig. 11, that the porosity of the first ten deposited layers, in general, did not follow the consistent pattern observed for the subsequent deposited layers. This is likely due to the close proximity to the heated build plate accentuated by a relatively high build plate temperature (90 °C). This inconsistency disappears as layers are deposited with more distance from the build plate during FDM. For all tablets, except 10 % drug load with HPMC 15LV, this led to large spikes in porosity. This underlines the effect that a heated printing plate can have on the microstructure of the resulting tablets. This could have an impact on the overall structural consistency of especially thin tablet designs. The sequential difference in porosity was generally around 16 percentage points (pp) for the 2.5 % drug loads, 11 pp for 5 % drug loads and 7 pp for 10 % drug loads for both investigated grades of HPMC.

3.4.4. Structural elements in printed tablets

The structural sizes, seen as the relative size of the largest spheres that could be computer-generated in the 3D structure without overlapping with walls or pores, shows that the largest difference was between using higher (100LV) and lower Mw (15LV) of HPMC for the printing (Fig. 12). No significant impact of drug loads was observed here. This indicates that the overall deposited structure of the printed object was different when using different grades of HPMC, but showed relative repeatability when using the same grade. As can be seen on Fig. 12, the structure size within the designed model showed the large volume of possible spheres with diameters around 520 µm, as well as smaller distribution around 580 and 620 µm. This would be the expected structure size distribution of a tablet printed with no flaws, neither on a macro and micro level. This distribution corresponded best with the structure size distribution seen for tablets printed with HPMC 15LV. These tablets had the largest distribution of possible spheres varying around 470 µm, while tablets printed with HPMC 100LV varied wider around 390 µm. It would have been unexpected that any of the tablets had appeared without any flaws from the printing, however, it can be seen that tablets made from HPMC 15LV was closer to the intended structure and had less variance in microstructure.

In addition to the structures in the expected size range, tablets printed with HPMC 15LV also showed a distribution of possible spheres with diameters around 740 µm. This is probably due to walls or corners fusing together during printing and creating larger structures. In large amounts, these unintended larger structures would be expected to impact the performance of the tablet and could be a source for poor reproducibility of the printed structure.

4. Conclusion

It was shown that HME filaments and 3D printed tablets could be prepared from binary mixtures of prednisolone and HPMC. Filaments were shown to consist of single-phase glass solutions for all drug loads, with six months physical stability for drug loads up to 5 % drug load. Printed honeycomb tablets had acceptable visual characteristics. The findings of this study also demonstrated that the drug load and polymer Mw had an impact on the 3D structure on a microscopic level of the printed tablets. Specifically, 3D printed tablets made from HPMC 100LV showed an increase in the total porosity and an increase in the average pore size. Drug load had a minor effect on the total porosity, but lower drug load showed a consistent increase in variability in porosity through the height of the axis. Careful selection of drug load and polymer Mw are relevant factors to be considered when designing 3D printed tablets for pharmaceutical applications.

Data availability

Data will be made available on request.

CRediT authorship contribution statement

Bjarke Strøm Larsen: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. **Eric Kissi:** Conceptualization, Methodology, Writing – review & editing, Supervision. **Liebert Parreiras**

Nogueira: Methodology, Investigation, Data curation, Formal analysis, Writing – review & editing. **Natalja Genina:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Resources. **Ingunn Tho:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Resources.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2023.106619.

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