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Hot Melt Extrusion and 3D-Printing of different PVA-Qualities

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Abstract: 3D printing of oral dosage forms offers a possibility to individualize the dose. This paper examines the suitability of different PVA qualities for 3D printing. By using Hot Melt Extrusion it was possible to produce filaments containing the active substances which could be printed into tablets. The drug release profile can be influenced depending on the PVA quality used and the infill of the tablets.

I. Introduction

With the U.S. Food & Drug Administration (FDA) approval of the first 3D printed dosage form, additive manufacturing has finally found its way into the medical and pharmaceutical sciences [1]. Advantages such as the simple handling of modern devices, the possibility of dose individualisation and the freedom of printing nearly any shape according to patient-specific requirements were responsible for the latest developments. Besides stereolithography and powder bed printing, the fused deposition modelling (FDM) is the most important method in pharmaceutical research. In FDM, a filament made of thermoplastic polymer is melted and applied in several layers via a nozzle onto the print bed. This process is comparable with the hot melt extrusion of thermoplastics, a process that is already established in pharmaceutical industry. In fact, hot melt extrusion also plays an early role for 3D printing, in the production of the plastic wire that is used as the raw material. With the aid of suitable excipients, such wires can also be made from pharmaceutical polymers, which are considered safe and intended for human application. Moreover, these polymer wires could be drug loaded during the production. However, the number of pharmaceutical polymers whose applicability for 3D printing has already been demonstrated is relatively low (e.g. methacrylates or cellulose derivatives). Another promising polymer is polyvinyl alcohol (PVA). PVA is a widely used, water soluble and swellable thermoplastic polymer which suitability for 3D printing was already examinated by Goyanes et al [2, 3]. Furthermore, PVA`s suitability for human use is demonstrated by his GRAS designation [4, 5]. However, there has been no systematic investigation of the influence of PVA quality on the melt extrusion process and 3D printing quality of dosage forms so far. Therefore, the aim of this work was to investigate the suitability of different PVA qualities for Hot Melt Extrusion and 3D printing. In addition to three pharmaceutical qualities, a technical grade of PVA, which was especially developed for 3D printing, was investigated.

II. Material and methods

Materials:
Parteck MXP and EMPROVE PVA 18-88 were purchased from Merck (Germany); PVA 5-88 was kindly gifted from Shin-Etsu (Japan). These qualities were pharmaceutical grade PVA, intended for human use. Furthermore, one technical quality, Mowiflex C 17 was kindly gifted from Kuraray (Japan). Caffeine was used as model drug (Fagron, Germany). Additives were Sorbitol (Merck, Germany), fumed silica (Fagron, Germany) and magnesium stearate (Sigma-Aldrich, Germany). Where necessary, granules were milled using a batch mill (IKA tube mill 100, Germany).

Filament production:
The powder mixtures were produced using a Turbula mixer (Turbula T2F, System Schatz, Germany, 49 rpm at 5 min). The composition of the batches is shown in table 1. Hot melt extrusion of the filament was done with a twin-screw-extruder (Three-Tec ZE 12, Switzerland). The CAD-file (cylindric tablet, diameter 10 mm, 5 mm height) was sliced using Cura (version 3.3.1).

3D printing:
The 3D printing was done using an Ultimaker 3 (Ultimaker, Netherlands, 0.4 mm die, printing speed 20-70 mm/s, layer height 0.1 mm, printing temperature 170-200 °C) and the infill rate of the tablets were varied (20%, 50% and 100%).

Characterization of the filaments and printed objects:
Images of the extruded filaments and printed tablets were taken using a reflected-light microscope (Zeiss Stemi 2000-C with Zeiss CL 1500 ECO, AxioCam and AxioVision software, all Carl Zeiss Microscopy GmbH, Germany). Drug release studies of printed tablets were carried out in 900 mL PBS pH 7.4 using a paddle apparatus (USP apparatus 2, 37 °C, 75 rpm, Pharmatest DT 17, Pharma Test Apparatebau AG, Germany). Drug release was measured via UV/VIS-spectrometry with a fiber-optics based system for on-line measurement (Cary® 60, Agilent Technologies, USA, slit width 1 mm, measuring interval 60 s, wavelength 273 nm).

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Table 1: Composition of the tested batches (each batch contains 10 % Caffeine and 35 % Sorbitol).

Batch #	PVA quality	PVA (%)	Fumed Silica (%)	Magnesium stearate (%)
1_1	Parteck MXP	52	0.5	2.5
1_2	Parteck MXP	54.5	0.5	0
2_1	5-88	52	0.5	2.5
2_2	5-88	54.5	0.5	0
3_1	Emprove 18-88	52	0.5	2.5
3_2	Emprove 18-88	54.5	0.5	0
4_1	Mowiflex C 17	52	0.5	2.5
4_2	Mowiflex C 17	54.5	0.5	0

III. Results and discussion

Hot melt extrusion of drug loaded filaments was successfully done at temperatures of 150-170 °C. The use of magnesium stearate led to a decrease of the extrusion torque. Figure 1 exemplarily shows microscopic images of the manufactured filaments from batch 2_1, 2_2, 3_1 and 3_2.

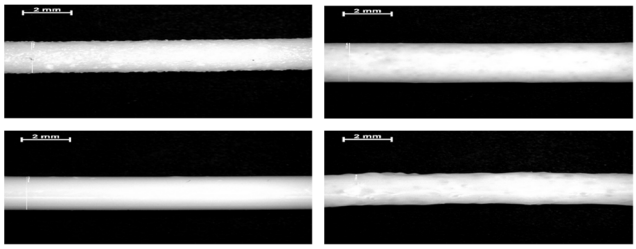

Figure 1: Influence of the magnesium stearate on surface quality (top row: batches 2_1 and 3_1; bottom row: batches 2_2 and 3_2).

In case of batch 2_2, the addition of magnesium stearate improved the surface quality. This was in contrast to the results from batch 3_2. For 3D printing, filament batches 1_2, 2_2, 3_1 and 4_2 were used. With the exception of batch 3_1, tablets could be successfully printed. Figure 2 shows microscopic images of the printed tablets.

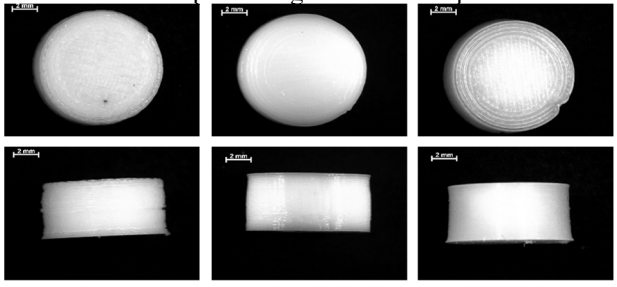

Figure 2: Reflected light images of the printed tablets (from left to right: batch 1_2, 2_2 and 4_2).

All printed tablets had a white-opaque appearance and an even surface. Printing of batch 3_1 was not possible due to the high flexibility of the filament and poor layer adhesion.

Figure 3 shows the dissolution profiles of the tablets with 100% infill. Depending on the PVA quality, the tablets showed different drug release profiles. Batch 1_2, containing the PVA quality with the lowest viscosity, showed the fastest release with 80% of caffeine released within about 50 min. Batch 2_2 and batch 4_2 released 80% of the drug within 93 and 107 min, respectively. The tablets printed with 20% infill and 50% infill showed clearly faster drug release (data not shown).

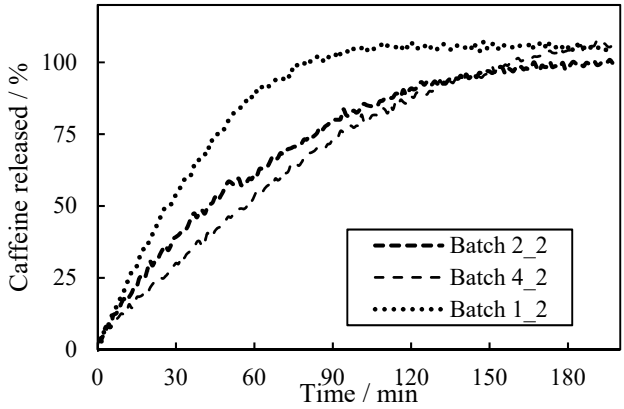

Figure 3: Dissolution profiles from the printed tablets with 100 % infill (mean of n=3).

IV. Conclusions

Within the scope of this work, three of four PVA qualities were successfully processed into filaments which could then be 3D printed. Depending on the PVA quality, it was possible to generate different release profiles. Further optimization of the formulation will provide an insight into the extent to which the release can be modified.

AUTHOR'S STATEMENT

The Authors state no conflict of interest.

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