Additive Manufacturing Applications in Pharmaceutical Sciences: osmotic delivery modular tablet and dry media grinding

PhD thesis
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1. Introduction

The interest in 3D printing has grown steadily in recent years due to its potential applications in personalized medicine. Additive manufacturing techniques have proven to be innovative and flexible, enabling their extensive applicability in industrial manufacturing and drug therapy. The cost-effectiveness and sustainability of this method represent significant advantages; thus, future developments may focus on the implementation of 3D printing into everyday practice. In this dissertation, the formulation of an osmotic drug delivery system, the properties of the elements of the complex systems, behaviour of the tablets created by the combination of microfabrication and conventional pharmaceutical technology methods were examined. The complex, modular tablets were assembled from Lego®-like elements. The potential applicability of the 3D printed milling balls in the dry medial ball milling operations was examined. The grinding efficiency of the grinding media fabricated with additive manufacturing and the warmup of the system caused by the friction during the operation were compared with traditional stainless steel grinding balls.

2. Objectives

The current research aimed to design and fabricate a push-pull type osmotic delivery system with controlled and tailored drug release by combining additive manufacturing with the methods of conventional pharmaceutical technology. By assembling the optimal pull and push layers, a semipermeable membrane and a 3D printed frame like Lego® pieces, our goal was to formulate a delivery system with zero-order drug release kinetics, which was independent of the gastrointestinal motility. The investigation of the potential applicability of additive manufacturing technologies in dry media ball milling as an alternative to grinding media made from traditional, widely used materials was also aimed. As a further objective, the efficiency of the milling operations performed with additively manufactured grinding media and the warmup of the system were compared with traditional stainless steel balls, thereby enabling the replacement of currently used materials with 3D printed balls

3. Methods

3.1. The formulation and examination of the osmotic drug delivery system and its elements.

The composition of the push and pull layers was mixed with V-blender (Xinxiang Chenwei Machinery Co., Ltd., Xinxiang, China) at 40 rpm for 20 minutes. The layers were compressed with Fette Exacta 1 (Fette Compacting GmbH, Schwarzenbek, Germany) single-punch machine. The cellulose acetate membranes were cast with Elcometer 3580 Casting Knife Applicator (Elcometer Limited, Manchester, UK). The films were dried at 25 °C and 40°C. The 3D printed frame was designed with Autodesk Fusion 360 (Autodesk Inc., San Rafael, USA). The obtained stl file was sliced in the Prusa Slicer (Prusa Research a.s., Prague, Czech Republic) software, and then the object was printed out with the Original Prusa SL1S Speed 3D Printer (Prusa Research a.s., Prague, Czech Republic) The fabricated frames were postcured with the Original Prusa Curing and Washing Machine (Prusa Research a.s., Prague, Czech Republic). The physical characterisation of the layers was conducted and evaluated in accordance with the Ph. Eur.11. For the weight distribution test, the Kern ANJ-NM/ABS-N analytical balance (Kern&Sohn GmbH, Balingen, Germany) was used, the height the diameter and hardness of the tablets

were measured with the Erweka TBH 200 TD (Erweka GmbH, Langen, Germany), and the friability tests were performed with the Erweka AR (Erweka GmbH, Langen, Germany) friabilator. The wetting characterisation of the cellulose acetate membranes with a thickness of 100 μm was performed with the Fifi Image J Software Contact Angle Plug-In (Image J NIH, USA) image analyser software. The pictures for the image analysis were captured with the Keyence VHX-980 Lens Z20 (Keyence International, Osaka, Japan) digital microscope. The mechanical characteristics of the films were analyzed with the Brookfield CT3-4500 Texture Analyser (Brookfield Eng.Lab.Inc., USA). The microstructure of the films was analyzed with a Positron Annihilation Lifetime Spectroscopy (PALS) with two BaF_2 crystalline detectors. The Doppler-broadening was measured with a germanium gamma detector. The water content of the membranes was measured with Karl-Fischer titration with the Metrohm 787KF Titrino Karl-Fischer Titrator. The membrane permeabilities were examined with the Franz Vertical Diffusion Cell (Hanson Research, Los Angeles, CA, USA). The osmolality of the obtained samples was measured with the Gonotech Osmomat 030 (Gonotec GmbH, Berlin, Germany), and the pH of the samples was measured with the Compact micro pH/Ion meter (Mettler-Toledo International Inc., Columbus, OH, USA).

The dissolution tests of the different assembled delivery systems were performed with the Hanson SR-8 Plus (Hanson Research, Los Angeles, CA, USA) dissolution tester with paddle apparatus (USP dissolution apparatus II). The volume of the dissolution medium was 900 ml, and the temperature was 37°C±0.5°C, and the pH was 1.2 in the first hour of the dissolution test and 6.8 for the rest of the 24-hour dissolution studies. The collected samples were analyzed with the Agilent 8453 (Agilent Technologies Inc., Santa Monica, CA, USA) spectrophotometer. The wavelength of the measurement was 346 nm in the case of the samples collected in the first hour and 318 nm for the rest of the samples.

3.2. The applicability of the 3D printing in dry media ball milling.

The milling balls with diameters of 25 mm, 20 mm and 10 mm were designed in the Autodesk Fusion 360 (Autodesk Inc., San Rafael, CA, USA) software, sliced with the Prusa Slicer (Prusa Research a.s., Prague, Czech Republic) software. The milling balls were printed with the Original Prusa SL1S Speed 3d printer (Prusa Research a.s., Prague, Czech Republic), and postcured with the Original Prusa Curing and Wasing Machine (Prusa Research a.s., Prague, Czech Republic).

The digital microscopic pictures of the milling balls were taken with Keyence VHX 970 Digital Light Microscope (Keyence International, Osaka, Japan). The densities of the different grinding balls were calculated from the diameter and the mass of the balls, which were measured with the Kern ABJ-NM/ABS-N (Kern&Sohn GmbH, Balingen, Germany) analytical balance. The weight loss tests were performed in the Retsch PM 100 (Retsch GmbH, Haan, Germany) planetary ball mill, and the weight losses were measured with the Kern ABJ-NM/ABS-N (Kern&Sohn GmbH, Balingen, Germany) analytical balance. The saccharose model material was ground with the Retsch PM100 (Retsch GmbH, Haan, Germany) planetary ball mill with 3D printed and conventional stainless steel balls at 200 rpm. The process time was 15 minutes with 5 minutes intervals and 5 minutes break. The particle sizes were analyzed with the Retsch AS 200 (Retsch GmbH, Haan, Germany) vibrational sieve. The lactose monohydrate was ground in a planetary ball mill for 45 minutes at 400 rpm. The structural alteration of the lactose was examined with the Seiko Exstar 6000/6200 (Seiko Instrument Inc., Chiba, Japan) Differential Scanning Calorimeter (DSC). The heating rate was 10°C/minute between 0°C and 200 °C.

4. Results

After the optimization of the settings, 3D printed frames with internal reservoirs and drug delivery orifices and grinding balls of various diameters were printed with good reproducibility, taking into account the required dimensions.

After the compression of the push and pull layers, the physical characteristics of the tablets were examined, and all parameters fulfilled the pharmacopeial requirements.

The macro and microstructural characterization of the films was executed. The compositions of the different membranes are shown in Table 1

Table 1: *The compositions of the membranes*

The label of the films	**Plasticizers**	**The ratio of CA and softeners (w:w)**	**Preparation temperature (°C)**
A-25	PG	CA:PG= 1:1	25 ± 2
A-40	PG	CA:PG= 1:1	40 ± 2
B-25	PG, GLY	CA:PG:GLY= 1:1:1	25 ± 2
B-40	PG, GLY	CA:PG:GLY= 1:1:1	40 ± 2

Among the membranes containing glycerol softener and those with the same composition and dried at 40°C had better wettability (shown in Figure 1).

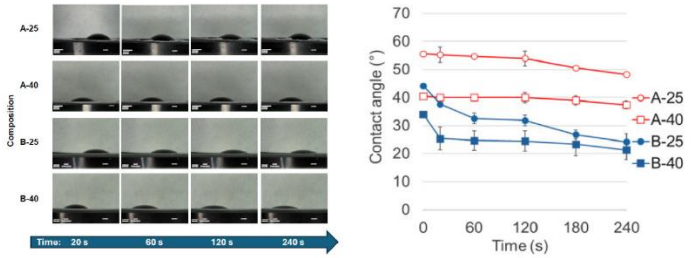

Figure 1: *Wettability of the different membranes*

The results of the wettability measurements were supported by the PALS experiments. Membranes containing glycerol as a plasticizer have more pores, but these pores are smaller than those in membranes containing only propylene glycol. Membrane composition B-40 exhibits high o-PS values, which correspond to free volume pores. By increasing the membrane formulation temperature, the structures of the films became more relaxed and mobile. The glycerol containing membrane compositions have H-bridges in their structures according to the S and W parameters of these membranes. The glycerol within the membrane serves to separate polymer chains, weakening the intermolecular forces between adjacent chains and lowering

brittleness, which improves the films' flexibility and stretchability. The results of the PALS measurements are shown in Figure 2.

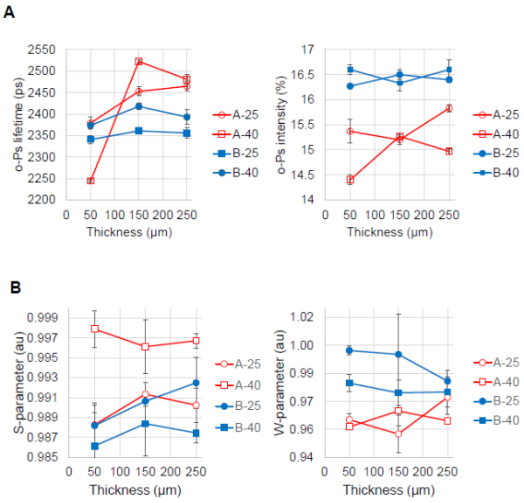

Figure 2: *PALS examinations of the membranes (A: PALS measurements, B: Doppler-broadening measurements)*

Based on the Karl-Fischer titration results (shown in Table 2), the glycerol containing membranes, and from the same membrane compositions, the films prepared at a lower temperature (25°C) had higher moisture content.

Table 2: *The moisture content of the membranes*

Membrane compositions	Moisture content (%)
Comp. A-25	8.12 ± 0.46
Comp. A-40	6.33 ± 1.17
Comp. B-25	11.15 ± 0.55
Comp. B-40	10.04 ± 0.25

The incorporation of glycerol into the membranes improved the mechanical properties of the films, especially in the case of higher thicknesses (shown in Figure 3).

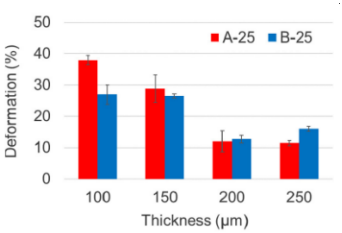

Figure 3: *Elongation of cellulose acetate membranes*

The membrane permeability studies showed that the membranes plasticized with glycerol had higher permeability in the salt and pH buffer permeability tests as well (shown in Figure 4 and 5).

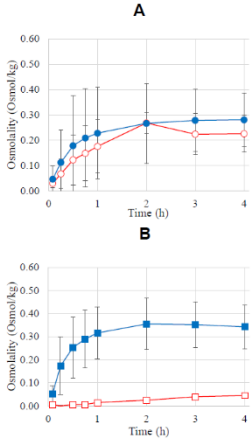

Figure 4: *Salt permeability of the membranes (A: red: A-25, blue: B-25, thickness: 150 µm; B: red: A-40, blue: B-40, thickness: 150 µm)*

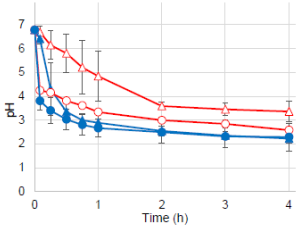

Figure 5: *pH permeability of the different films (red triangle: A-25, 100 µm; red circle: A-25, 150 µm thickness; blue triangle: B-25, 100 µm thickness; blue circle: B-25, 150 µm thickness)*

It was shown by in vitro dissolution studies that in the case of formulation I, which contained a pull layer, a gel barrier layer is formed by HPMC after the rapid wetting and swelling of the tablet, resulting in the slowed release of the active agent. The dissolution was described by the first-order kinetics. In the instance of formulation II, the pull layer was inserted into the 3D printed frame, the drug release was extended compared with formulation I because the medium must enter the frame through the bottom part of the frame or through the drug delivery orifices on the top to reach the central reservoir. If a semipermeable membrane was inserted into the 3D printed frame, the ingress of the water into the frame was slowed down. The dissolution of the active substance showed an initial burst phase, but after that, the zero-order release kinetics may provide a prolonged and more predictable API release from the drug delivery systems. In the case of formulation IV and V, the push layer was used in the assemble of the drug delivery systems, the swelling of the pull layer was inhibited by the push tablet, and the release of the API was initiated through the drug delivery orifices due to the swelling of the push layer. Zero-order drug release kinetics were developed from the second hour of the dissolution study.

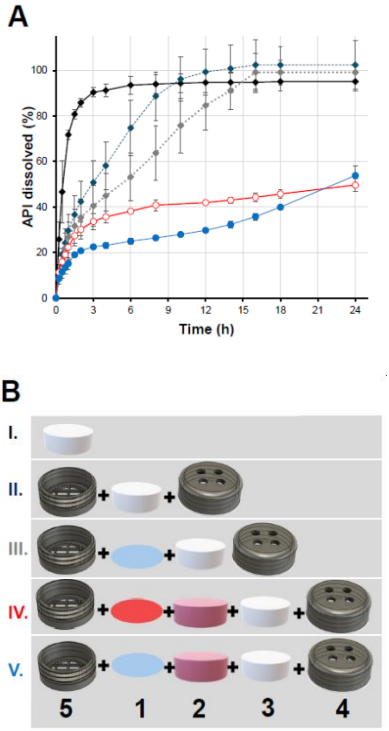

Figure 6: *Dissolution profiles of the delivery systems assembled from different elements*

The membrane compositions can affect the release of the API from the various drug delivery systems. According to the analysis of the different dissolution curves, the presence of glycerol in the membrane compositions resulted in a slower burst phase, but a faster drug release in the zero-order kinetics phase in the instance of membranes formulated at 25°C. The

membranes prepared at 40°C had approximately the same zero-order release rate. The drug release of the delivery systems prepared with different membranes is shown in Figure 7.

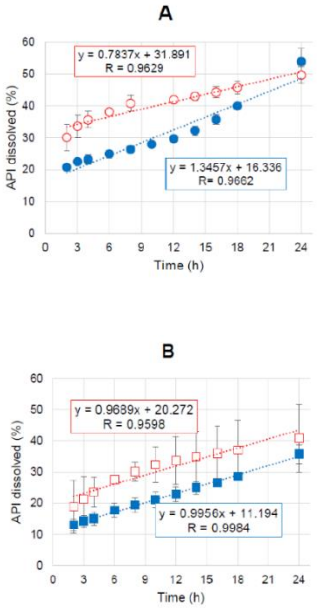

Figure 7: *Dissolution profile of the different drug delivery systems prepared with different membranes (A: red: A-25, blue: B-25; B: red: A-40, blue: B-40)*

The dissolution profiles of the API in different revolution speeds are shown in Figure 8. It was experienced that the zero-order release of the delivery system is independent of the agitation intensity.

In the second part of my research, the 3D printed grinding balls were compared with the conventional stainless steel balls. Based on the particle size analysis of the milling processes, a more effective comminution can be achieved by the application of 3D printed balls in the same total weight.

The warmup of the system in case of the application of different material milling balls was investigated. The additively manufactured milling bodies were heated up less than the comparator metal balls under the same conditions (shown in Figure 9).

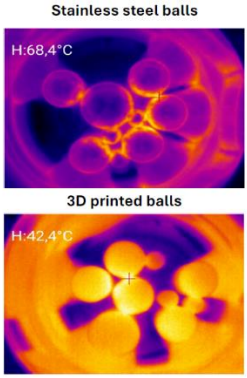

Figure 9: *Thermal camera investigation of the system*

Due to the heating that occurs during the process, changes may take place in the structure of heat-sensitive substances. From the DSC analyses performed after the grinding of the lactose model

substance, it can be seen that no change was made in the structure of lactose monohydrate during the milling carried out with additively manufactured milling balls, while in the instance of grinding with stainless steel balls, the crystal water was removed from the structure of the model substance

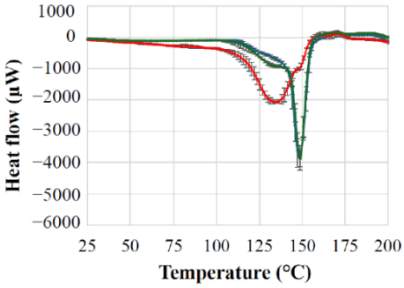

Figure 10: *The DSC analyses of the lactose samples (blue: initial, green: sample milled with 3D printed balls, red: sample milled with stainless steel balls)*

5. Conclusion

The formulation of complex, modular osmotic drug delivery systems were successful. The drug release was influenced by the assembled elements. By assembling the appropriate subunits, an extended, zero-order drug release kinetic was successfully achieved, with the drug release being independent of the motility of the gastrointestinal tract. This drug release profile provides more consistent blood levels in patients and enables the development of a dosing regimen that is more convenient for patients, resulting in better patient compliance with the therapy. The obtained results provide a good basis for the adoption of additive manufacturing technology in the field of hospital pharmacies.

The fabrication of different sized grinding bodies was successfully printed with an SLA printer. The comparison of the additively manufactured milling balls with the conventional stainless steel grinding bodies showed that the milling was more effective and the warmup was less in the case of 3D printed milling bodies. The reduction in the warmup can result in a safer process in the instance of the heat-sensitive substances, and the process time can be reduced. The application of 3D printing may also be promising for the pharmaceutical industry.

6. Bibliography of the candidate's publications

The publications on the subject of the thesis

1. Borbás B, Kállai-Szabó N, Lengyel M, Balogh E, Basa B, Süvegh K, Zelkó R, Antal I. Microfabrication of controlled release osmotic drug delivery systems assembled from designed elements. Expert Opinion On Drug Delivery. 2024; 21 (11)
IF: 5.4

2. Borbás B, Kohod Z, Kállai-Szabó N, Basa B, Lengyel M, Zelkó R, Antal I. Evaluation of 3D-Printed Balls with Photopolymer Resin as Grinding Medium Used to Alternatively Reduce Warmup During Dry Milling. Polymers. 2025; 17 (13)

IF: 4.9

Further publications

Basa B, Jakab G, Kállai-Szabó N, Borbás B, Fülöp V, Balogh E, Antal I. Evaluation of biodegradable PVA-based 3D printed carriers during dissolution. Materials. 2021; 14(6).

IF: 3,748