SAFC®
Pharma & Biopharma Raw Material Solutions

White Paper

Shaping the Future of Formulation Development with Melt-based 3D Printing Technologies

Three-dimensional (3D) printing is a powerful technology that has wide-ranging applications, including many in the pharmaceutical industry. Among the approaches that are being explored in the production of pharmaceutical dosage forms powder-based systems which utilize either drop-on-powder or selective laser sintering and liquid-based systems which use drop-on-drop deposition or stereolithography are frequently applied. With liquid-based technology, either UV, laser energy or high temperature is used to induce polymerization and build the 3D structure.[1] The process of 3D printing offers the potential to produce medications tailored to the needs of patients and dosage forms in various shapes, sizes and textures with different release profiles that can be difficult to produce using conventional techniques.[2]

In this white paper, the use of 3D printing to overcome challenges during formulation development is explored, with a focus on enhancement of bioavailability of active pharmaceutical ingredients (APIs) in solid dispersions. It is estimated that 60–70% of drug substances currently in clinical pipelines are categorized as Class II in the Biopharmaceuticals Classification System (BCS) which indicates low solubility.[3] For an oral formulation, the proper API solubility is critical for absorption in the gastrointestinal tract. If solubility issues cannot be overcome during formulation development, an otherwise promising therapeutic candidate may have to be abandoned.

Hot Melt Extrusion using Polyvinyl Alcohol

The creation of amorphous solid dispersions processes, a well-established strategy for formulating APIs by embedding them in some type of excipient, has evolved over the years from the use of crystalline carriers such as urea, to polymers for hot melt extrusion (HME) and polyvinyl alcohol (PVA) to enhance and prolong the supersaturated state of low soluble compounds. To form a solid dispersion using HME, the API is molecularly dispersed in a polymer matrix using elevated thermal energy and mechanical forces applied by extruder screws (Figure 1). This process is capable of producing drug-loaded polymer filaments which can be used for various downstream applications.

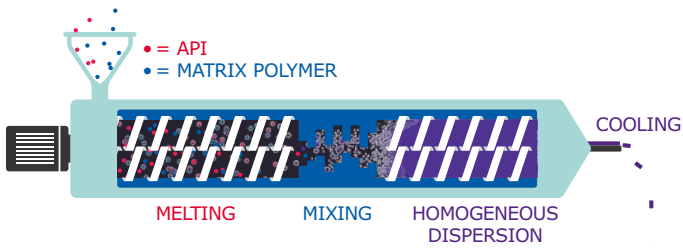


Figure 1.

In hot melt extrusion, the API is mixed with a matrix polymer in the extruder to enable homogeneous dispersion of the API within the polymer.

Various polymers can be used in HME processes including cellulose derivatives, polyacrylates, polymethacrylates, polyethylene glycols and polyvinyl pyrrolidone (PVP). Recently, polyvinyl alcohol (PVA) has been highlighted as a polymer particularly well-suited for HME.[4,5,6] It is a synthetic polymer produced by the polymerization of vinyl acetate and partial hydrolysis of the resulting esterified polymer. Novel polymer screening tools are now available that overcome the disadvantage of conventional HME screening by using a minimum quantity of API.[7]

MERCK

PVA-based Parteck® MXP excipient is specifically developed for use in HME; the optimized particle properties provide a constant and precise dosing of material resulting in a stable process (Figure 2). The flowability of Parteck® MXP excipient is optimized to ensure homogenous feeding of the polymer in the hot-melt extruder. Particle size and the angle of repose are also important criteria; both are optimized to ensure good flowability. The melting temperature is approximately 170 °C due to the strong alignment of polymer chains while the high degradation temperature means that the polymer can withstand temperatures of more than 250 °C.

Product Properties	
Bulk density [g/mL]	0.53 ± 0.02
Tapped density [g/mL]	0.74 ± 0.02
Particle size (D50) [µm]	60–80
Loss on drying [%]	<3.0
Angle of repose [°]	35
Hydrolysis grade [%]	85–89
Solubility [%] (max. in water)	33
Mass average molar mass	approx. 32,000
pH-value (4%/water)	5.0–6.5

T_g (by DSC)	T_m (by DSC)	T_d (by TGA)
40–45 °C	170 °C	>250 °C

Temperature	Melt Viscosity D=200 (s^{-1})	Melt Viscosity D=1,200 (s^{-1})
210 °C	702 Pa*s	283 Pa*s
230 °C	345 Pa*s	174 Pa*s

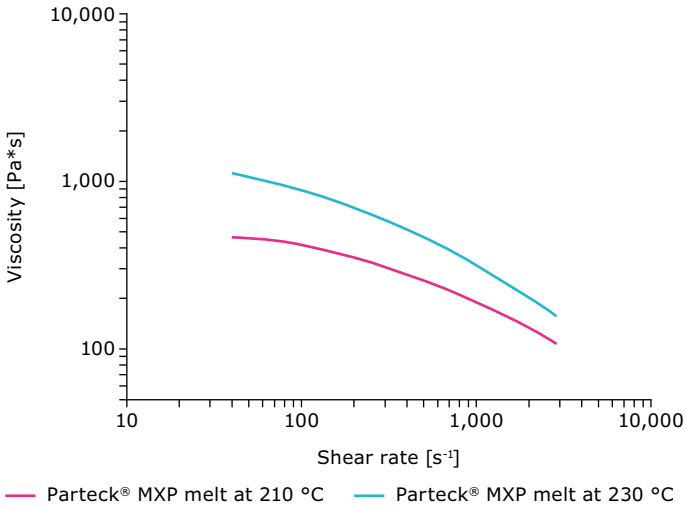


Figure 2.

Characteristics of Parteck® MXP make it well-suited for use in HME.

Figure 2 shows the viscosity plotted against the shear rate with viscosity decreasing with an increasing shear rate. This is essential when it comes to processing of the material through very small nozzles; the viscosity will decrease with higher shear impact which will enable an efficient downstream process.

Filament creation via HME

A typical HME process is shown in Figure 3. The speed of the conveyer belt is used to determine the diameter of the filament which can be wound or used as individual strands; commercial diameters are typically 1.75 or 2.85 millimeters.

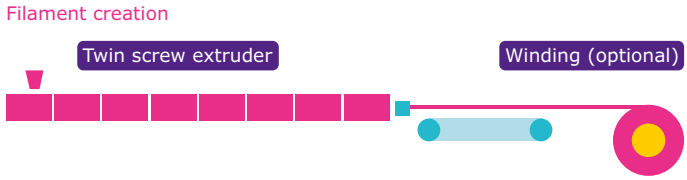
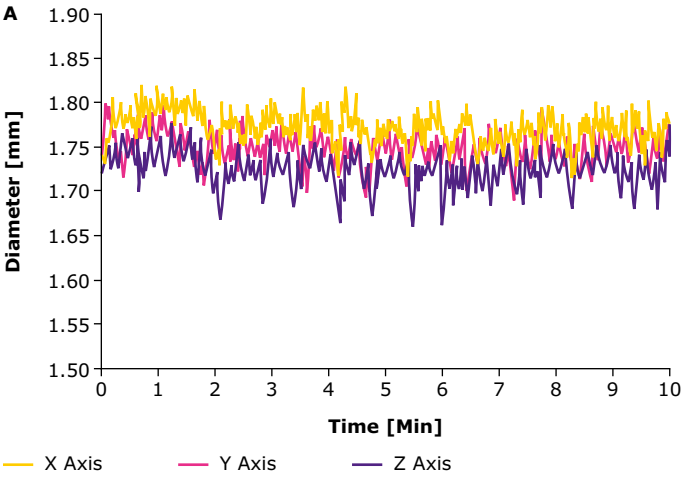


Figure 3.

Schematic view of the melt extrusion process for filament production.

To evaluate and optimize the process of filament production, optical laser scanning technology was added as an online in-process control to continuously monitor the filament geometry and improve homogeneity of the filaments which is essential to assure an exact dosing of the final medicine. This process analytical technology (PAT) allowed three axes to be measured simultaneously and can be integrated into the manufacturing process.

Figure 4A shows the in-process control of placebo filaments, plotted as diameter versus time, containing only with Parteck® MXP excipient with a melt pump accessory that manages uniformity of filament diameter; 4B shows the fluctuations when the melt pump was not used. Fluctuations in diameter were drastically reduced with use of the melt pump indicating that the homogeneity of the process could increase.



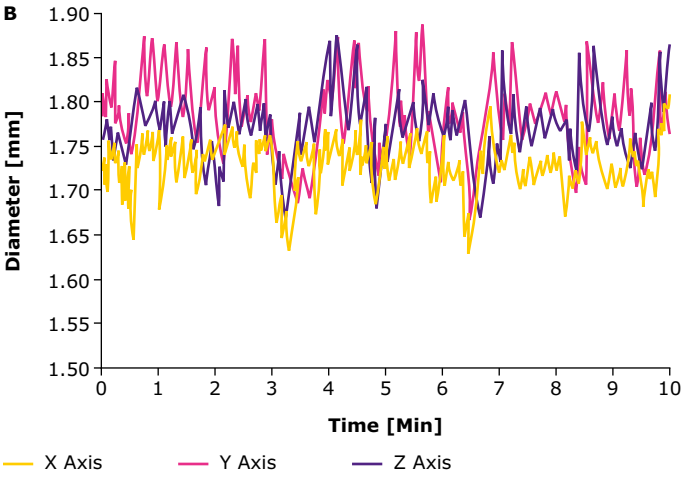
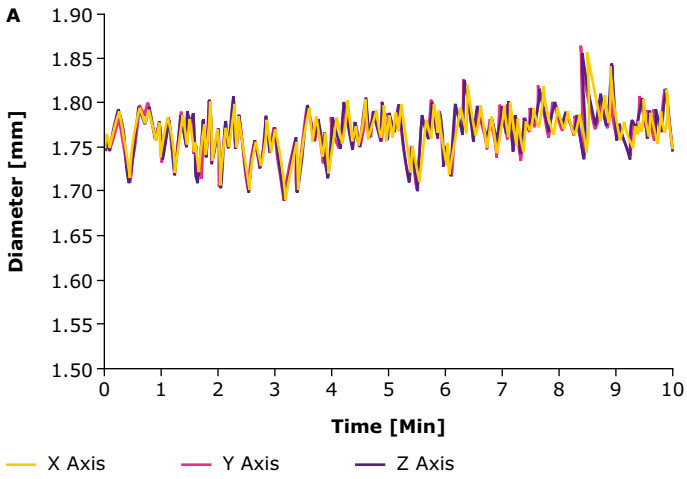


Figure 4.

In-process control of placebo filaments containing only with Parteck® MXP excipient produced with (A) and without (B) the melt pump.



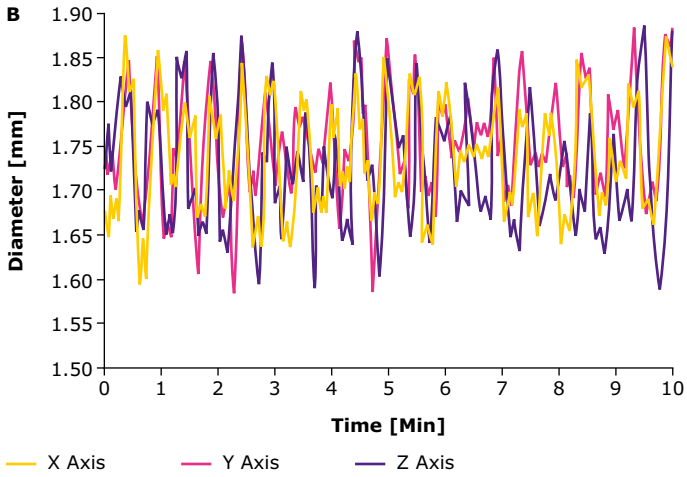


Figure 5.

In-process control of drug-loaded filaments produced with (A) and without (B) the melt pump.

The same study was conducted using filament loaded with 20 percent ketoconazole (Figure 5). Similarly, there was a high deviation of diameter without the melt pump (B) compared to that with the melt pump. The increased homogeneity of the final filament is important for the quality of the resulting Intermediate.

Melt Drop Deposition

Advanced melt drop deposition is an interesting technology under evaluation for production of solid dosage forms (Figure 6). In this process, the polymer is melted in a heated plasticizer barrel in which a screw transports the material to the nozzle tip. When the polymer melt reaches the polymer reservoir, pressure is applied via translational movement of the screw and droplets are discharged via a piezo actuator which can operate at a very high frequency of up to 250 hertz.

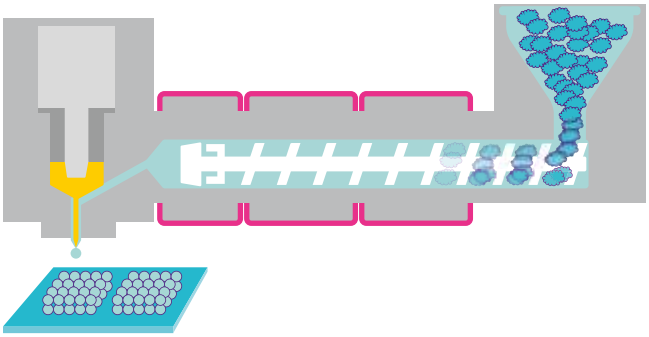


Figure 6.

The principle of advanced melt drop extrusion.

SME images of the top and side surfaces of 3D printed tablets and strands show high homogeneity of this deposition process; detailed view of the strands shows the individual drops that were deposited (Figure 7).

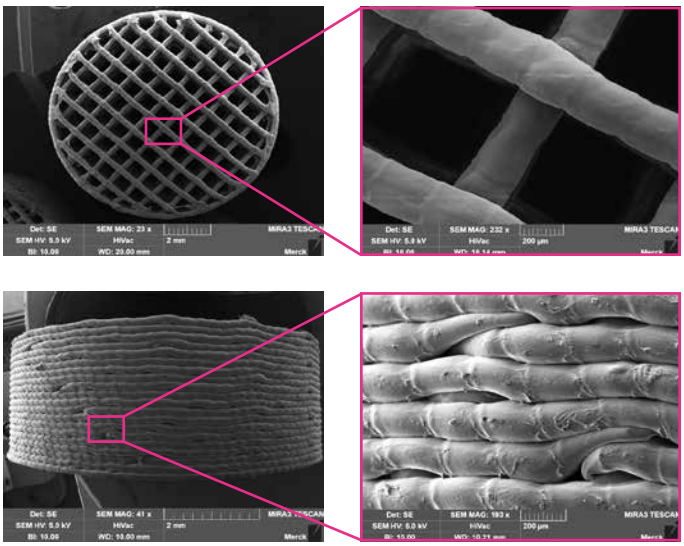


Figure 7.

SEM images of tablets and strands produced using melt drop deposition.

Variation of infill volume can be used to individually adjust the porosity of the tablets which allows to modify and match the targeted release kinetic (Figure 8).

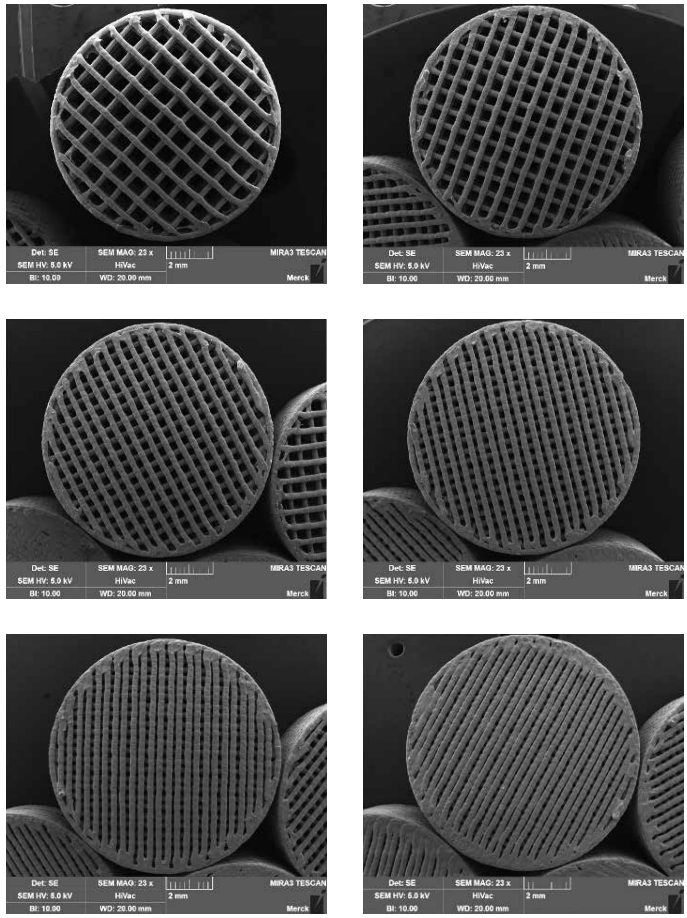


Figure 8.

Variation of infill can be used to adjust tablet porosity and surface area.

This system was highly reproducible for tablet production. Figure 9 shows the mass distribution for the Parteck® MXP excipient placebo tablets and those containing 10 percent caffeine. A comparison of the mass versus the inflow volume showed relatively lower homogeneity for the formulation with caffeine, but it remained within the required limits.

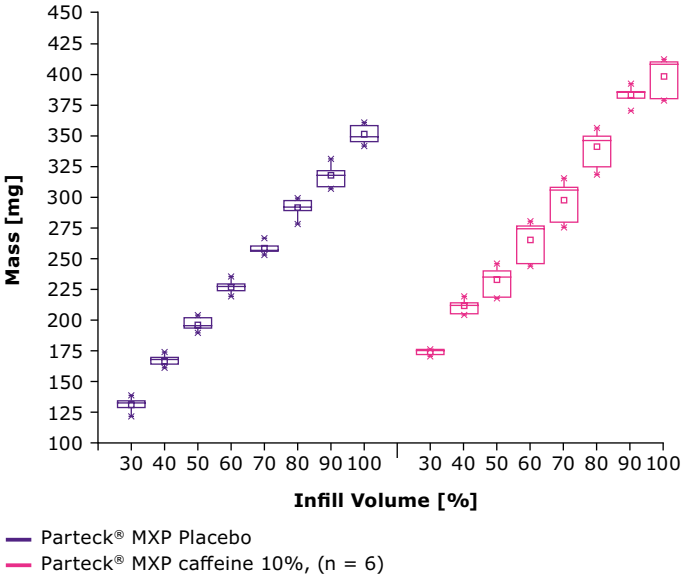


Figure 9.

Variation of infill can be used to adjust tablet porosity and surface area.

Mechanical stability of the tablets was also a key consideration. Diametral compression was assessed with a texture analyzer and showed that 3D printed tablets based on Parteck® MXP excipient provided high mechanical strength even at low infill volumes (Figure 10).

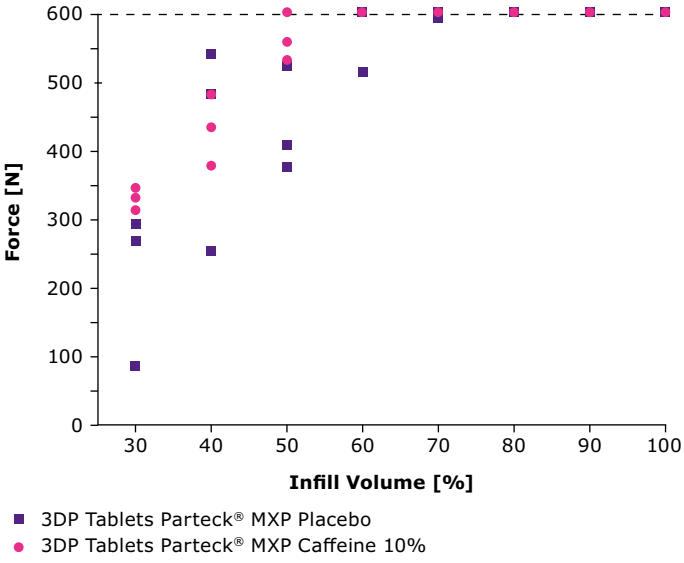


Figure 10.

Diametrical compression of placebo tablets (blue) and those containing 10 percent caffeine (pink); at 600 N the maximum force of the system is already exceeded.

A final consideration was whether this technology could be used to modify drug release. Figure 11 shows the release profiles of the caffeine-loaded tablets at different infill percentages compared to pure caffeine drug substance, a soluble compound which allows the effect of the polymer on the release rates to be determined. The results indicated that it was possible to modify drug release rates via the infill volume. Low standard deviations indicate a high reproducibility of the results which is an important step for a further industrial application of this technology.

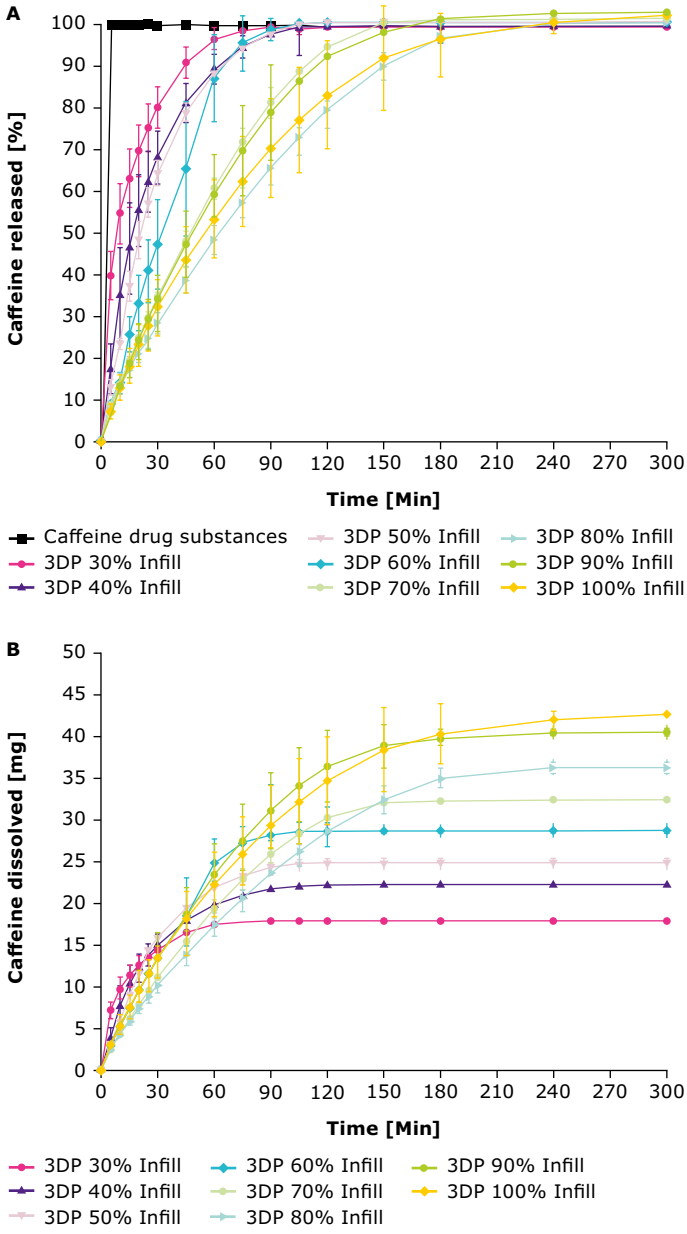


Figure 11.

Comparison of drug release kinetics using different infill volumes.

Conclusion

Due to its simplicity, HME can serve as an enabling technology for early formulation development. Various systems derived from plastics industry are already on the market and can be integrated in early research activities.

Direct melting technologies like the advance melt drop deposition, however, provides very high accuracy for melt-based printing systems as the droplet geometry can be precisely defined. A key differentiator from existing FDM technologies is that the process itself is based on a single melting step and as such, powder or granules can be used to start the process and a second melting step is not necessary. In addition, there is a very broad processing range linked to direct extrusion and complex forms can be realized due to highly defined material deposition. Independent of the 3D printing technology selected, polymer requirements are a critical success factor. High thermal stability of the polymer is a key requirement as well as its mechanical properties.

Opportunities for further development of melt-based 3D printing are numerous. The technology can be used to create tablets in a wide variety of shapes and sizes and regulate the number of active substances in the composition of the tablet. This approach also enables controlled release of the API which can increase the effectiveness of the medication and provides the ability to overcome solubility challenges. 3D printing also has the potential to accelerate pharmaceutical development timelines by rapidly supplying prototypes for clinical trials and at the same time, provides the ability to print small batches of drugs, saving time and money on the establishment of large scale manufacturing lines.

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