Solubility and Bioavailability Enhancement of Poorly Soluble Drugs Using Melt Extrusion Deposition (MED®) 3D Printing Technology

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INTRODUCTION

An increasing number of drugs from contemporary pharmaceutical pipelines have poor solubility and low bioavailability. It's of paramount importance to introduce new techniques and technologies that can help to address these challenges. Triastek and Boehringer Ingelheim (BI) collaborated as part of an opnMe project aiming to use MED® 3D Printing Technology to enhance the solubility and bioavailability of a BCS class II compound (BI02) provided by BI through opnMe. opnMe.com serves as the open innovation portal of Boehringer Ingelheim's R&D activities to crowdsource innovative scientific projects beyond its existing collaboration network of experts. Here, using Triastek's proprietary MED® 3D Printing Technology, a two compartment tablet and a grid tablet were designed and developed. In-vitro results demonstrated the prolonged in-vitro supersaturation of both MED tablets compared to amorphous solid dispersion (ASD) powders made from spray drying technology. Grid tablets were selected for in-vivo dog PK study due to better in-vitro performance. In-vivo dog PK results proved that bioavailability of the grid tablets was twice as the bioavailability of ASD powders.

METHODS

An ASD drug core intermediate was prepared by mixing BI02 with HPMCAS MG using a MC5 micro-conical twin screw compounder. Dissolution behavior of ASD powders and filaments with different diameters (0.4, 1, and 4mm) were studied by dissolving the materials in FaSSIF(pH 6.5) to evaluate the solubility, dissolution rate and crystalline rate of the API. Two prototypes (Tablet C and Tablet G) were printed using Triastek 3D printer with printing modules capable of handling 3 materials. Tablet C (Figure 1. a, b, c) was a two compartments core-shell structure and the pulse release of APIs was achieved by controlling the thickness of the soluble shell. Tablet G (Figure 1. d, e, f) was printed using the drug core intermediate with a 55% infill density (blue). Dissolution study parameters: USP type II dissolution apparatus; FaSSGF, pH 2.0, 90mL, 100rpm for 0.5 h and then convert to FaSSIF ,150mL, 100rpm for another 3 h. Dog PK study was carried out to compare the bioavailability of the capsules filled with ASD powders and Tablet G.

Table 1. Dimensions and formulations of tablet C and tablet G.

Prototype	Dimensions	Formulation	
		Component	Composition
Tablet C	20.0 mm × 8.0 mm × 4.0 mm	Soluble Shell	HPC SSL:TEC=9:1
		Core	BI 02:HPMC AS M=23:77
Tablet G	20.0 mm × 8.0 mm × 3.5 mm	Core	BI 02:HPMC AS M=23:77

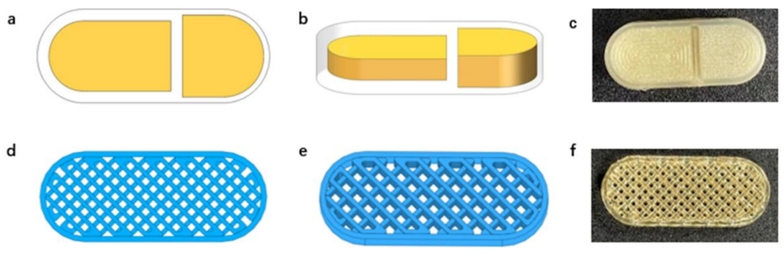

Figure 1. Design of two-compartment tablet (Tablet C) comprising soluble shell (transparent) and drug core (orange): a) top view, b) upper front view, c) 3D-printed tablet:); and design of grid tablet (Tablet G) comprising drug core (blue) only: d) top view; e) upper front view, f) 3D-printed tablet.

INTERMEDIATES DEVELOPMENT

➢ DSC and TGA characterization of BI02

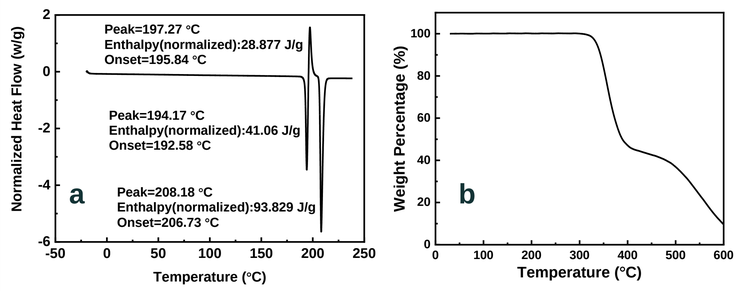

Figure 2. DSC(a) and TGA(b) characterization of BI02

➢ DSC and PXRD characterization of the core intermediate

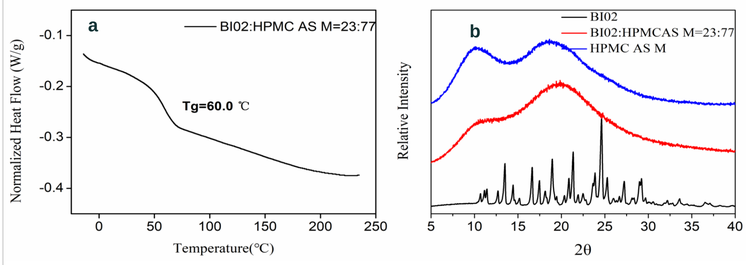

Figure 3. (a) DSC curve of the drug core intermediate. (b) PXRD characterization of the pure drug (black curve), excipient HPMCAS MG (blue curve), and the drug core intermediate (red curve).

➢ Solubility and supersaturation of the ASD intermediates

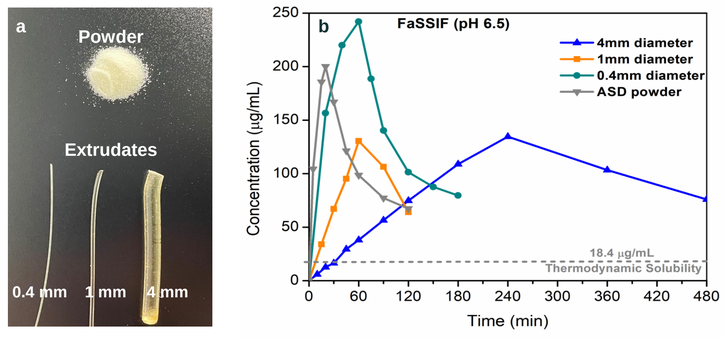

Figure 4. (a) Picture and (b) solubility study of ASD intermediates with different surface area (powders, 0.4mm, 1.0mm and 4.0mm extrudates)

Solubility of the API powders was 18.4 μg/mL in FaSSIF, which increased to 200 μg/mL in the ASD system (Figure 4b). Filaments with 0.4 mm diameter showed higher API concentration and slower crystalline rate than ASD powders. The API concentration decreased with increasing filament diameter, but the supersaturation time prolonged, indicating surface area played an important role in balancing the dissolution rate and crystallization rate. MED® 3D printing platform can be utilized to manipulate the surface area to achieve desire dissolution profile.

IN-VITRO AND IN-VIVO STUDY

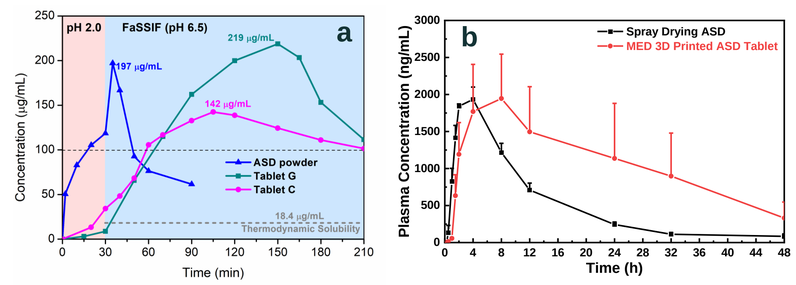

Figure 5. (a) In-vitro gastrointestinal conversion dissolution of ASD powders, Tablet C and Tablet G; (b) In-vivo dog PK study of ASD powders and Tablet G (n=4, mean±SE)

Tablet G performs showed a highest concentration and longest supersaturation time compared to ASD powders and Tablet C in the dissolution study, which was selected for dog PK study to compare with ASD powders.

Dog PK results indicated MED prototype tablet G showed an enhanced solubility, prolonged supersaturation time and improved in-vivo bioavailability (doubled the AUC of the ASD powders).

CONCLUSION

Present work demonstrated that by using MED® 3D printing technology, amorphous solid dispersion can be used to develop the tablets with structures for the enhancement of the in vitro solubility. Different tablet structures can be designed to enhance the in-vitro dissolution behavior of the API. MED® 3D printed tablets can prolong the supersaturation time of poorly soluble APIs, and the dissolution can be controlled by specific tablet designs. In vivo dog PK study demonstrated that the designed tablet G improved the bioavailability when comparing to spray drying ASD powders.

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