High-quality Modified-release Drug Product Development with Melt Extrusion Deposition (MED®) 3D Printing Technology

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INTRODUCTION

Triastek has developed 3D Microstructure for Modified Release (3DμS®-MR) platform using melt extrusion deposition (MED®) technology. The 3DμS®-MR platform features a core-shell structure designed with a delay layer and a drug core, enabling precise and programmed controlled release of drugs at designated gastrointestinal (GI) locations. By quantitatively adjusting the thickness of the outer layer, precise control of the release onset time can be achieved. This platform can deliver any active pharmaceutical ingredient (API) to the targeted GI tract, regardless of the API properties. An x-ray imaging agent can be 3D printed on the drug core for animal and early-stage clinical studies to track the GI transition and API release behavior of the formulations. Furthermore, the outer layer materials can be developed with an erosion mechanism to protect the amorphous API from precipitation before reaching the targeted GI location. Continuous manufacturing (CM) process is applied for large-scale production.

METHODS

MED® 3D Printing Technology

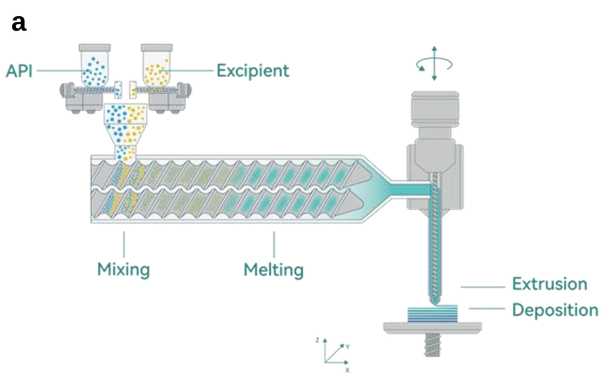
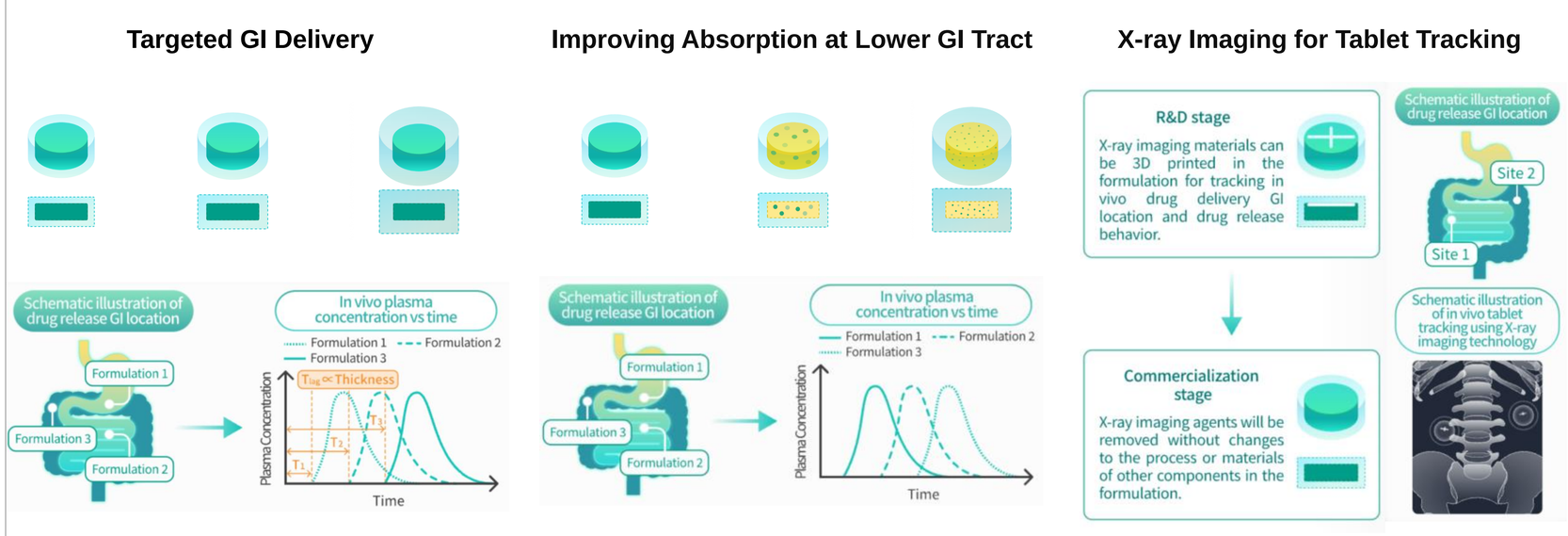


Figure 1. (a) Illustration of MED® 3D printing technology and process. (b) MED® 3D Printing System

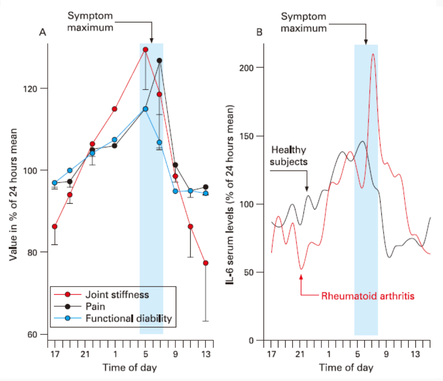
3DμS®-MR Platform



Applications of 3DμS®-MR Platform for Drug Product Development

Delayed- and Extended- Release Tofacitinib (T19)

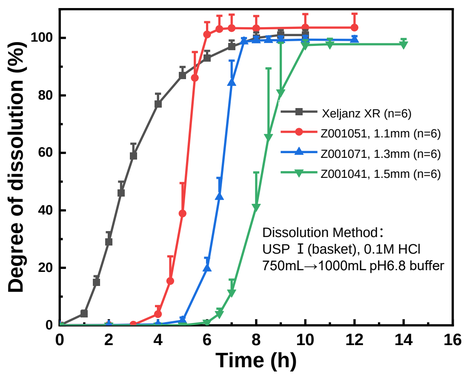
◆ Objective



Rheumatoid Arthritis: IL-6 inflammatory factor reaches highest concentration between 4 am-7 am.

T19 designed based on **3DμS®-MR V1.0.**
With a delayed-and extended release structure, after taken the drug at about 10:00 pm before sleep, the release of active drug will delay by 3-4 hours and make it reach to C_{max} right between 4 to 7 am. Highly improve the patient outcomes.

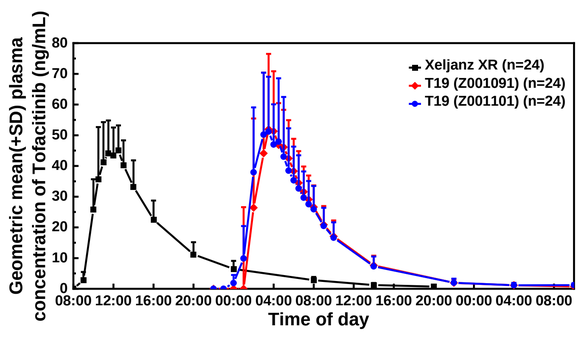
◆ Tablet Design and In Vitro Study



No.	Delay layer thickness (mm)	Lag time (h)
Z001051	1.1	4.5±0.2
Z001071	1.3	5.7±0.1
Z001041	1.5	6.8±0.4

Figure 2. In vitro dissolution profiles of the tablets with different delay layer thicknesses and the reference (Xeljanz XR).

◆ In vivo study



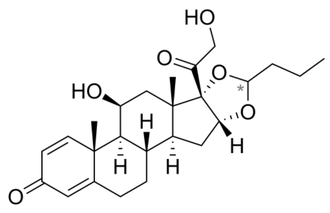
Phase I, randomized, open-label, single-dose, three-period, three-sequence crossover study

Parameter (Unit)	T19 (Z001091) / Xeljanz XR		T19 (Z001101) / Xeljanz XR	
	Ratio of Adjusted Geometric Means (%)	90% CI for Ratio	Ratio of Adjusted Geometric Means (%)	90% CI for Ratio
C_{max} (ng/mL)	130.89	(113.49, 150.95)	116.95	(104.92, 130.35)
AUC_{0-t} (ng·h/mL)	104.24	(100.79, 107.81)	105.60	(102.02, 109.31)
AUC_{0-inf} (ng·h/mL)	104.04	(100.81, 107.38)	105.46	(102.03, 109.38)

Figure 3. In vivo profiles of T19 tablets and the references.

Budesonide Delayed-Release Tablets (D23)

◆ Objective



Budesonide is the first and only FDA-approved treatment proven to reduce the loss of kidney function in adult patients with IgAN. It acts on the terminal ileum.
BCS Ⅱ compound, solubility enhancement is needed.

3DμS®-MR were applied for 1) solubility enhancement, 2) reducing the *in-vivo* variability of drug release and absorption, 3) achieving accurate in vivo delivery.

◆ Tablet Design and In Vitro Study

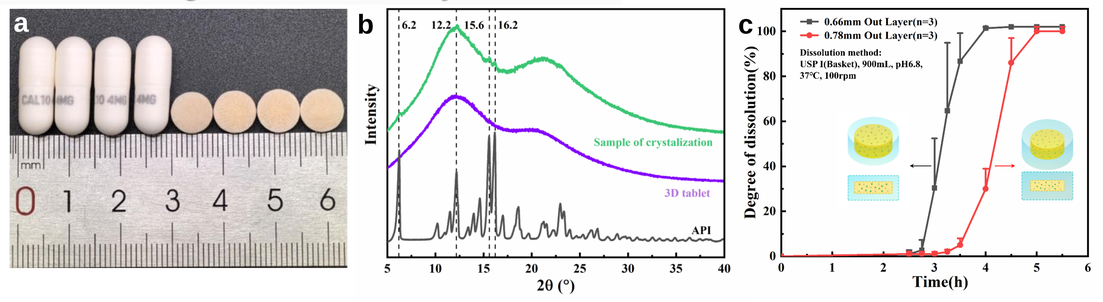


Figure 4. (a) Size comparison chart of the RLD capsule and the 3D tablet. (b) XRD patterns of the 3D tablet (c) In vitro dissolution profiles of tablets with different outlayer thicknesses.

◆ In vivo study

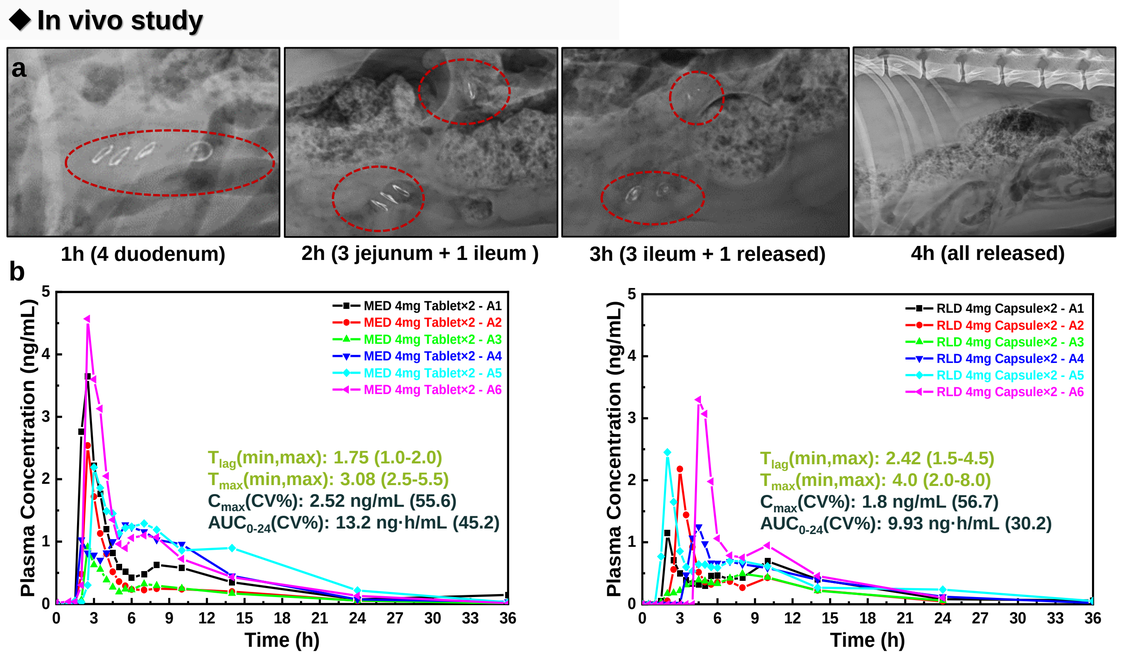


Figure 5. (a) X-ray imaging of targeted delivery to the ileum.(b) Comparison of PK curves of budesonide MED® delayed-release tablets and reference listed drug for a single dose of 16 mg.

References

1. Zheng, Yu, et al. "Melt extrusion deposition (MED™) 3D printing technology–A paradigm shift in design and development of modified release drug products." International Journal of Pharmaceutics 602 (2021): 120639.
2. Timothy Tracy, et al. “3D printing: Innovative solutions for patients and pharmaceutical industry.” International Journal of Pharmaceutics 631 (2023) 122480.