Ileum Delivery of Budesonide by 3D Micro-structure Design for the Treatment of IgA Nephropathy

Xianghao Zuo

Triastek, Inc. No. 24 Building, Max Science Business Park, 99 Lize Road, Nanjing, Jiangsu, China

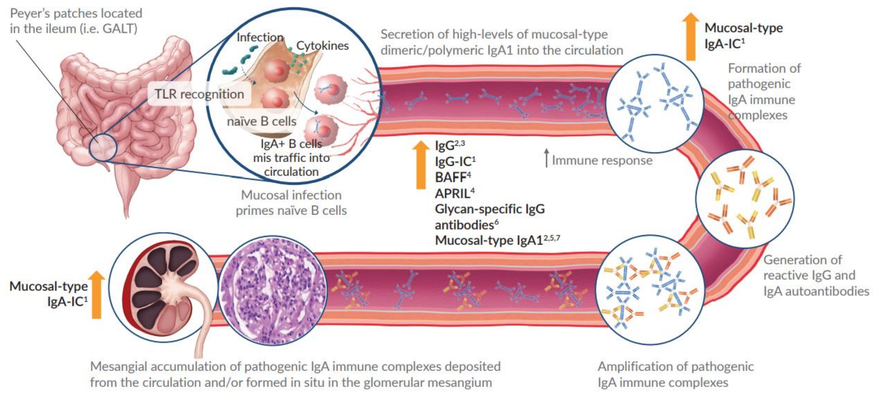
CONTACT INFORMATION: xzuo@triastek.com

Abstract

IgA nephropathy is a leading cause of chronic kidney disease (CKD) and kidney failure, characterized by chronic, progressive autoimmune kidney damage[1]. 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, reduces the amount of IgA1 antibodies, and treats IgA nephropathy at its source.
Triastek developed an improved oral delayed-release budesonide tablet using the globally pioneering Melt Extrusion Deposition (MED®) technology[2-3] and the 3D Microstructure for Modified Release (3DμS®-MR) platform. The tablet consists of drug cores and a delayed release layer. The delayed release layer ensures the drug reaches the ileum intact and starts releasing there. The core is precisely delivered to the mucosal B cells at the end of the ileum, where the drug particles quickly disperse and continuously release budesonide, achieving high concentrations throughout the target area. Compared to the larger Nefecon capsule (size 1), this MED® delayed-release tablet improves drug load capacity, reducing tablet size or dosage frequency, thereby lessening the medication burden on patients and enhancing treatment compliance and quality of life.

Introduction

The pathophysiology of IgAN[4]



MED® 3D Printing Technology

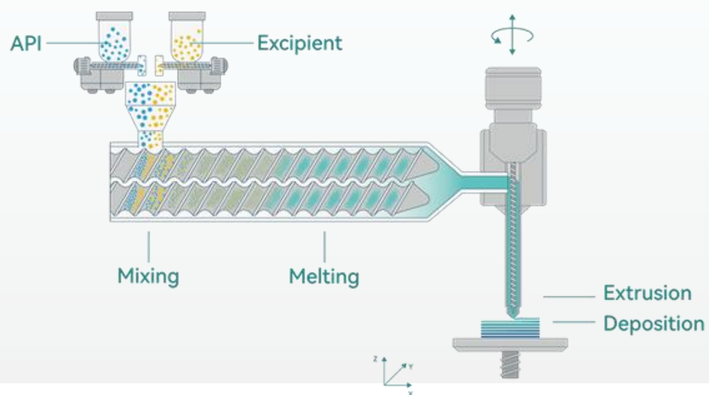


Illustration of MED® 3D printing technology and process

Methods

3DμS®-MR for Precise GI Delivery

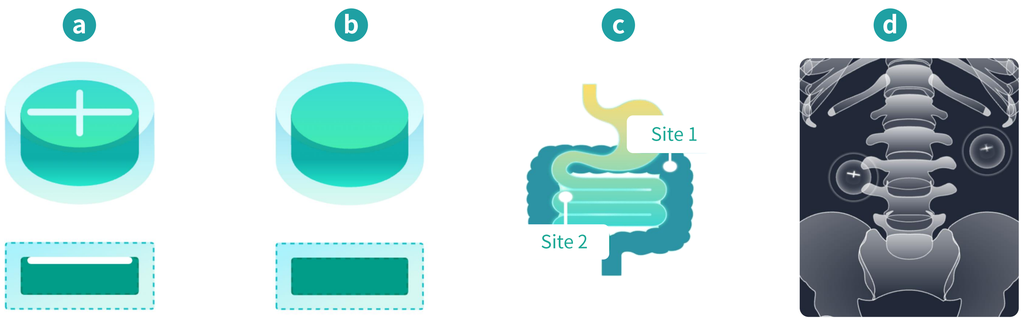
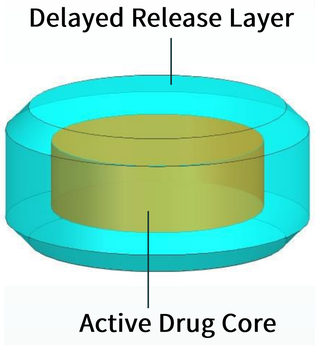


Figure 1. (a) tablets in the R&D stage (tracking material is 3D printed in the tablets to track tablet GI transition and API release), (b) drug products in the commercialization stage (tracking material is removed from the tablets), (c) schematic of the drug release site, and (d) schematic of the captured X-ray images showing the location of the tablets in GI tract.

Model design



1. Delayed Release Layer

The delayed release layer can protect the amorphous solid dispersion (ASD) for a long time in vivo and prevent premature crystallization. Through adjustment of its thickness, precise control over the site and timing of initial drug release can be achieved.

2. Active Drug Core

The active drug core consists of an amorphous solid dispersion and a water-soluble matrix. By uniformly dispersing the ASD of ultrafine particle drug-containing ingredients in a water-soluble matrix, rapid release at the target site can be achieved.

Conclusion

1. A delayed-release tablet was developed using a 3D microstructure design and MED® 3D printing technology.
2. X-ray images captured in dog PK study demonstrated that 3D-printed Budesonide delayed-release tablets can be delivered to and release their contents in the distal small intestine.
3. Results from the dog PK study demonstrated that 3D-printed Budesonide delayed-release tablets reduced the in-vivo variability in release and absorption compared with Nefecon.

Reference

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Results and discussion

The core formulation development

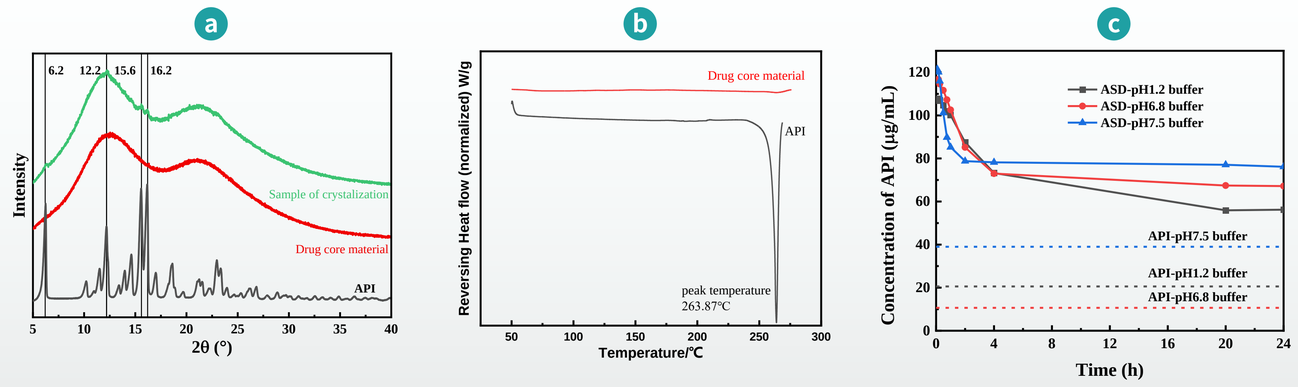


Figure 2. (a) XRD patterns and (b) DSC patterns of the ASD drug core material. (c) Solubility study of the ASD drug core material and API in buffers with different pH values.

The ASD drug core material was prepared using hot-melt extrusion (HME) technology to enhance the solubility of the API and ensure its complete release upon ingestion.

The tablet development

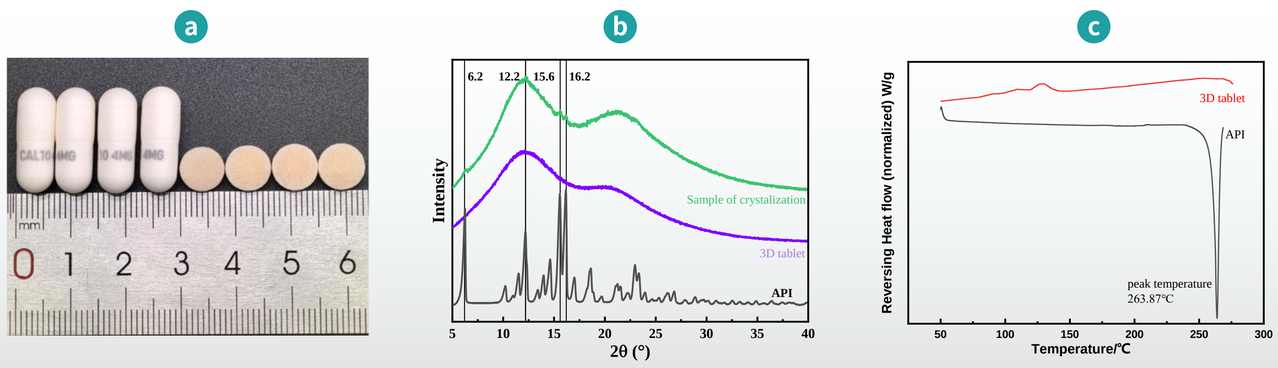
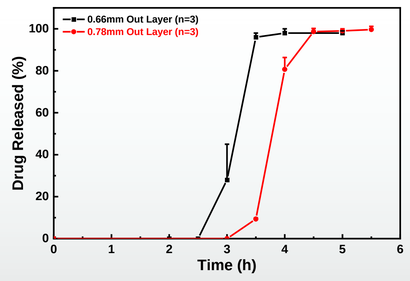


Figure 3. (a) Size comparison chart of the RLD capsule and the 3D tablet. (b) XRD patterns and (c) DSC patterns of the 3D tablet.

In vitro dissolution studies



Apparatus	USP Apparatus 1 (Basket)
Buffer	pH-6.8 phosphate buffer
Volume	900ml
Temperature	37 °C
rotation speed	100 rpm

Figure 4. (a) Comparison of in vitro dissolution curves of tablets with different outlayer thicknesses. (b) Conditions for in vitro dissolution testing.

In vivo Dog PK Results

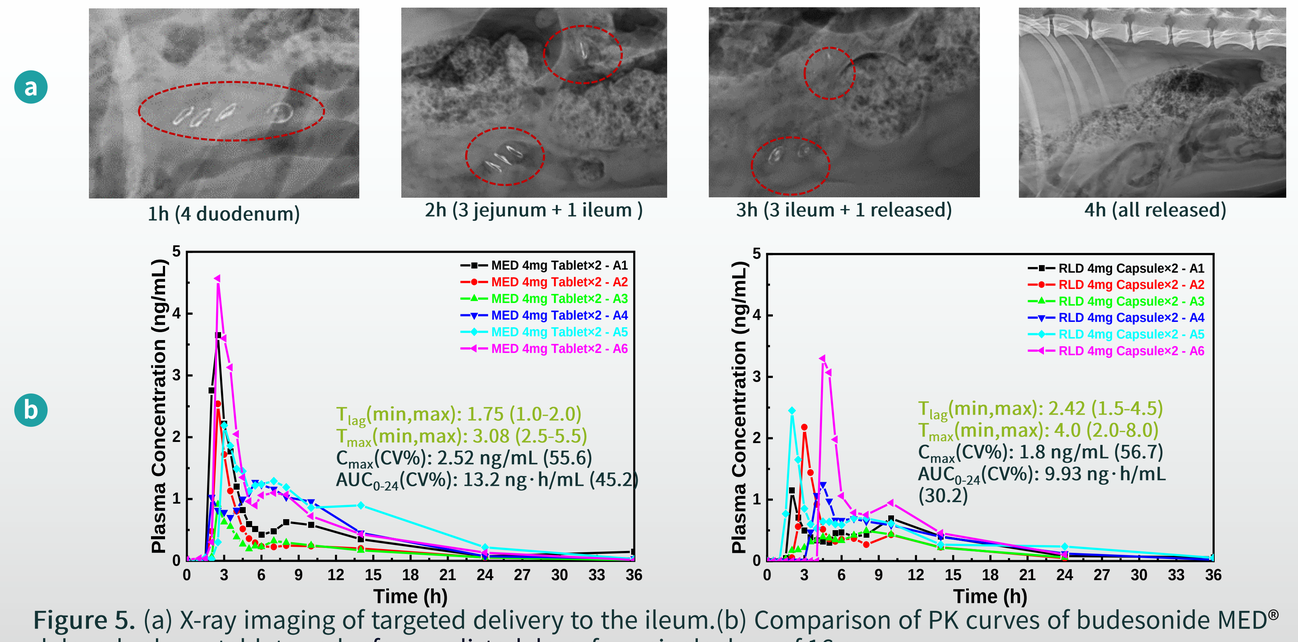


Figure 5. (a) X-ray imaging of targeted delivery to the ileum.(b) Comparison of PK curves of budesonide MED® delayed-release tablets and reference listed drug for a single dose of 16 mg.

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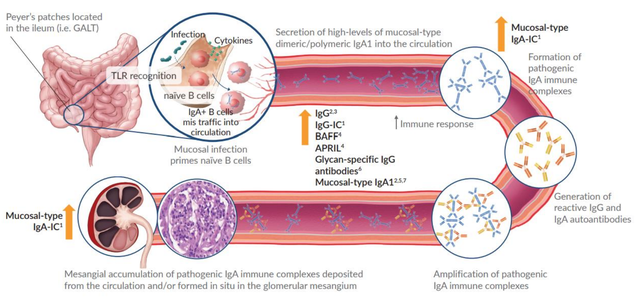

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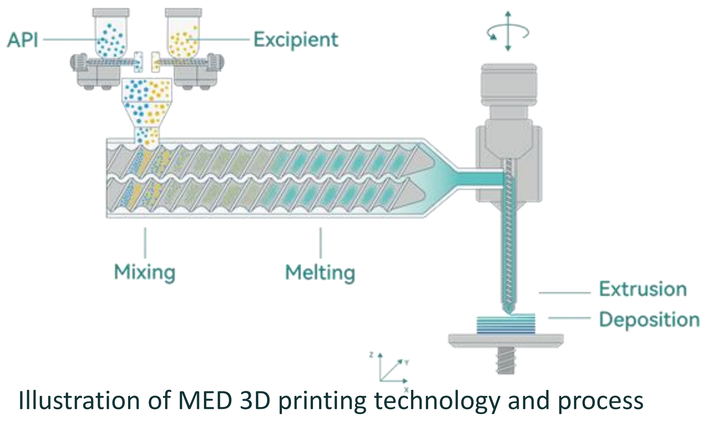

Illustration of MED 3D printing technology and process

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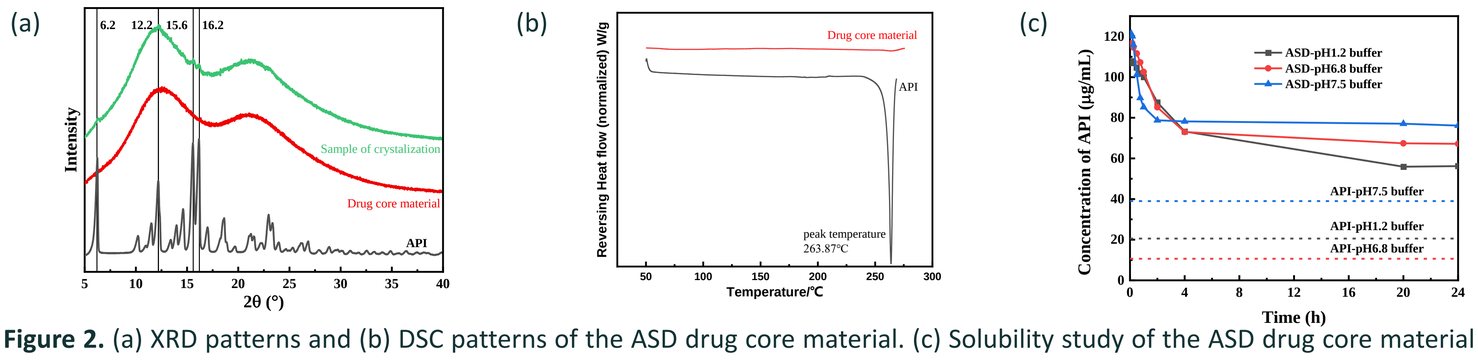

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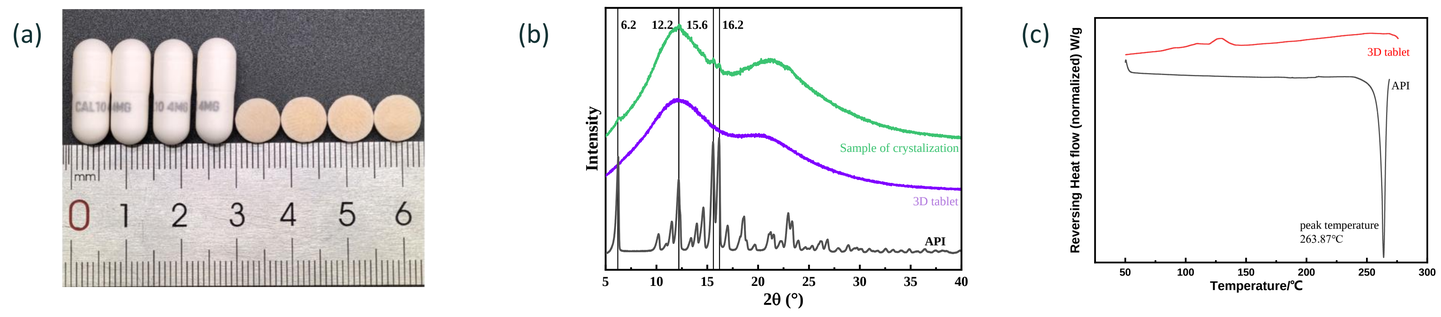

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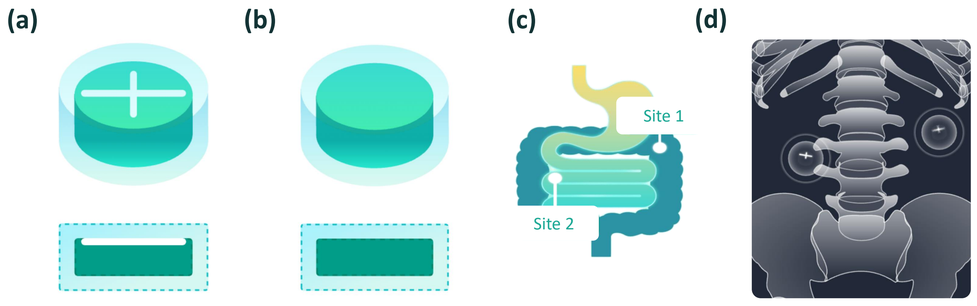

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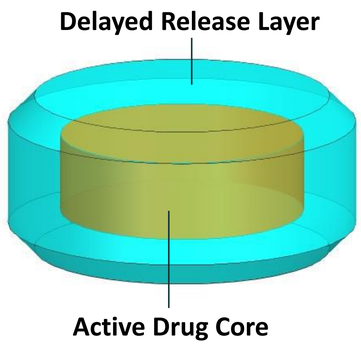

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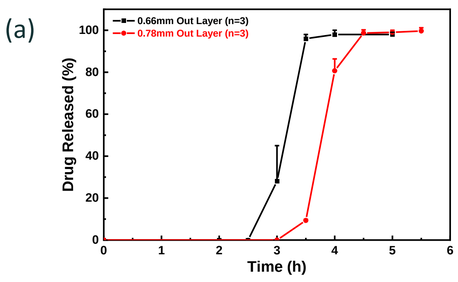

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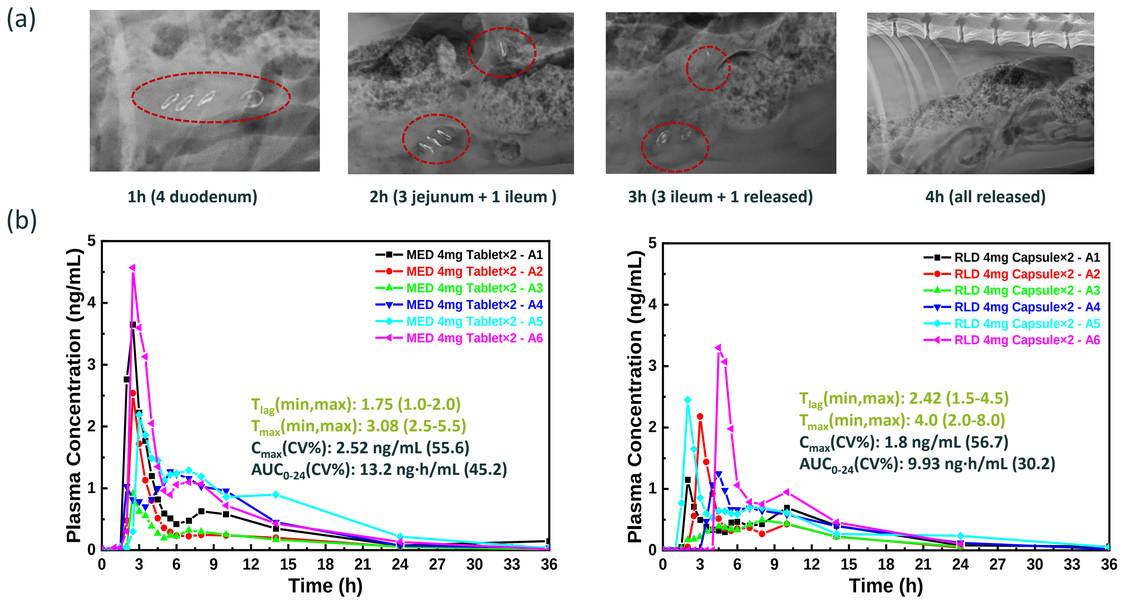

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