Colon-targeted Delayed Release Drug Delivery Tablet Fabricated by MED® 3D Printing Technology

Huan Chi, Meng Ji, Lihua Cao, Feihuang Deng, Senping Cheng, Xiaoling Li, Yulian Zhang

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

CONTACT INFORMATION: zhangyulian@triastek.com

BACKGROUND

Ulcerative colitis is a multifactorial chronic inflammatory bowel disease of mostly unknown etiology. The resulting pathogenesis involves mucosal inflammation initiating in the rectum and extending proximally in the colon in a continuous fashion. Delivery of therapeutic agents to the lower GI tract to provide local drug exposure in the colon may be beneficial for intestinal inflammatory treatment.

A (3D)-printed, delayed release colon-targeted tablet fabricated with Melt Extrusion Deposition (MED®) three-dimensional (3D) printing technology was programmed to deliver drug to the colon. These 3D printed tablets were designed and fabricated with a sequential two-step (pH- and time-based) mechanism to control release. The candidate tablet contained an enteric layer to prevent drug release within the stomach to minimize inter- and intra-patient variation in stomach transit time. Beneath the enteric layer resides a time-based delay layer of appropriate thickness to delay drug release until the tablet reaches the colon.

METHODS

Two prototypes of model drug-containing (3D)-printed tablets with different delay layer thicknesses were fabricated by MED® 3D printing technology. A schematic drawing of the tablet 3D structure and dimensions is shown in Figure 1 and Table 1. The contrast agent barium sulfate (tracking loop and tracking stripe) was incorporated into the drug layer to make the candidate tablet could be visible under X-ray allowing assessment of the tablet transit and drug release in gastrointestinal tract.

In vitro dissolution study parameters: USP Apparatus I; 0.1N hydrochloric acid, 750 mL, 100 rpm for 2 h and then switched to pH 6.8 medium, 1000 mL, 100 rpm for following hours at a temperature of 37 ± 0.5°C. The two candidate tablets were administered to healthy subjects to validate the colon-targeted drug delivery *in vivo*. The study was an open label, randomized, single dose, three period, three sequence, three-way crossover X-ray imaging and pharmacokinetic study in healthy subjects. Twelve healthy volunteers were enrolled into the study. Candidate tablet 1 and 2, and the reference of the model drug were administered in the morning under fasted conditions according to randomization plan. There were at least 4 days wash-out between each treatment. X-ray images and PK samples were collected at the predetermined timepoints. Tablet intestinal transit and drug release properties were evaluated based on X-ray images. The drug plasma concentration was determined by an LC-MS/MS analytical method.

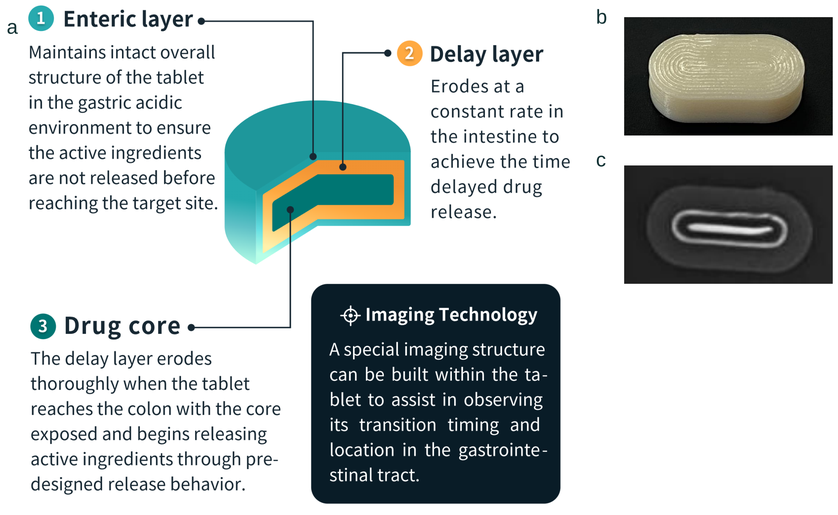

Figure 1. Schematic drawing of the 3D structure and images of candidate tablet: a) 3D structure of tablet comprising enteric layer (green), time-based delay layer (orange), drug core (dark green) (tracking layer incorporated into the drug core is not shown); b) image of 3D-printed tablet; c) X-ray image of top view of 3D-printed tablet (shows the tracking layer: one loop and one stripe).

Table 1. Dimensions of two candidate tablets.

Formulation	Tablet 1	Tablet 2
Dimensions	15.0 mm × 7.6 mm × 4.3 mm	15.0 mm × 7.6 mm × 2.7 mm

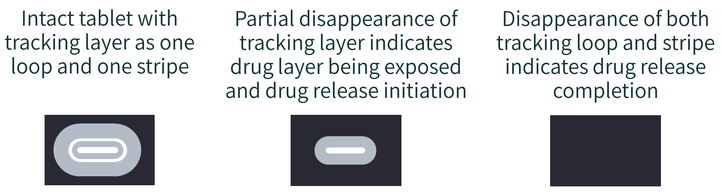

Figure 2. Schematic diagram of tracking layers and disintegration process of candidate tablet.

RESULTS

➢ *In-vitro* dissolution

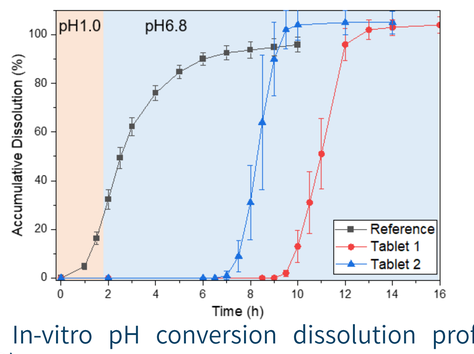

Figure 3. In-vitro pH conversion dissolution profiles (n=6, mean±SD).

Candidate tablet 1 and tablet 2 exhibited an approximately 9.5 hour and 7.0 hour delay, respectively, in drug release initiation as expected for colon-targeted formulations.

➢ *In-vivo* PK results in healthy volunteers

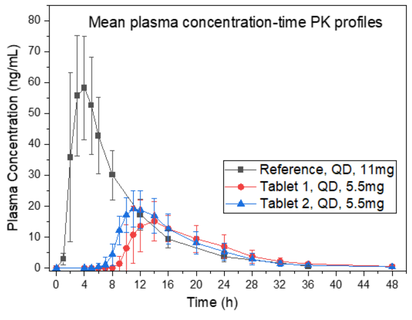

Figure 4. Mean plasma concentration-time profiles in healthy volunteers (n=12 for Reference and tablet 2, n=9 for tablet 1, mean±SD).

Table 2. Pharmacokinetic parameters (mean±SD)

PK parameters[a]	Reference	Tablet 1	Tablet 2
T_{lag} (h)	0.0 (0.0-0.0)	8.0 (7.0-11.0)	7.0 (5.0-8.0)
T_{max} (h)	3.0 (2.0-5.0)	14.0 (11.0-16.0)	11.0 (9.0-14.0)
C_{max} (ng/mL)	65.8 ± 22.7	17.2 ± 5.53	20.0 ± 5.80
AUC_{0-t} (ng/mL×h)	525 ±140	206 ± 69.2	231 ± 74.8
AUC_{0-inf} (ng/mL×h)	530 ± 141	211 ± 70.7	234 ± 75.3

a: n=12 for Reference and tablet 2, while n=9 for tablet 1 since the plasma concentration for three subjects were below the lower limit of quantification.

RESULTS (CONTINUED)

➢ X-ray imaging results

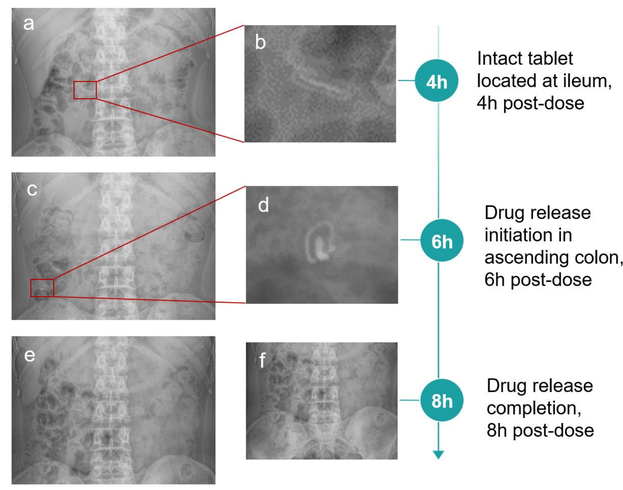

Figure 5. Representative X-ray images of one subject following Tablet 2 administration (a,c,e) whole abdomen images; (b,d,f) zoom in images.

The X-ray imaging results showed that the candidate tablet could be tracked in the gastrointestinal tract. Results from the majority subjects (8 out of n=12 for both test treatments) suggested that both candidate tablets released the drug within the colon region: Tablet 1 (3 subjects at ascending colon, 2 subjects at transverse colon, 1 subject at transverse to descending colon, 1 subject at descending colon, 1 subject at descending to sigmoid colon) while tablet 2 (7 subjects at ascending colon, 1 subject at transverse colon).

The pharmacokinetic results reflected the delayed release properties of the candidate tablets with a median (range) absorption T_{lag} of 8.0 h (7.0-11.0 h), 7.0 h (5.0-8.0 h) and 0.0 h (0.0-0.0 h) for tablets 1, 2 and the reference tablet, respectively, which confirmed the colon release property of 3D printed test formulations.

CONCLUSIONS

The drug release and tracking agent images demonstrated that the release location/time occurred as predicted for the 3D printed tablets. The MED® 3D printed tablets with a sequential two-step control mechanism can precisely deliver drug to the colon in human, suggesting its potential application in IBD therapy.

REFERENCES

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