Original article

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FABRICATION OF A NOVEL HIGH-DENSITY THREE-DIMENSIONAL (3D)-PRINTED DEVICE FOR DOMPERIDONE TABLETS

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ABSTRACT

In conventional high-density tablets, a large amount of high-density material must be directly added to the tablets. Therefore, it may lead to undesired tablet properties. The aim of this study was to develop novel high-density three-dimensional (3D)-printed devices (HPDs) for a gastro-retentive drug delivery system (GRDDS). The HPDs were fabricated from iron powder-loaded polylactic acid (PLA) filaments using fused deposition modeling (FDM). A commercial domperidone (DOM) tablet was utilized as a model drug and placed into HPDs. To enable different drug release characteristics, the devices were fabricated with different hole diameters (1.0, 1.5, and 2.0 mm). The appearance, weight variation, and density of the HPDs were evaluated. *In vitro* dissolution of DOM from the HPDs was conducted to obtain the drug release characteristics. The kinetics of DOM release from HPDs was examined to elucidate the release mechanism. The printed HPDs had similar physical appearances to the designed 3D models. The HPDs had a density of more than or equal to 2.4 g/cm^3 with a slightly rough texture due to the original texture of iron powder-loaded polylactic acid (PLA) filaments. The HPD with hole diameters of 1.5 mm showed an optimal sustained-release profile, with 98.8% of the drug released in 12 h because of the limit of the tablet's surface area exposed to the medium. Moreover, zero-order kinetics was achieved from all HPDs. It can be concluded that HPDs successfully modified the drug release of regular DOM tablets to GRDDS without adding high-density excipients into the tablet directly and may be applied to other commercial drugs as a high-density drug delivery system.

Keywords: high-density gastro-retentive drug delivery system, 3D-printing device, domperidone, tablet, iron powder-loaded polylactic acid, fused deposition modeling

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Introduction

Oral dosage forms are the most popular formulation for humans due to easiness of administration, safety, and pain avoidance.[1] However, some drugs are not suitable to be prepared in conventional oral dosage forms because of the narrow absorption window, basic labile, and low solubility in a basic environment (intestinal tract).[2] Therefore, gastro-retentive drug delivery systems (GRDDS) have been developed to overcome these limitations. The GRDDS is a type of drug delivery system that can remain in the stomach for an optimal period in order to prolong the drug release in the stomach and increase the bioavailability of the drug. In addition, this system is suited for a drug that acts locally within the stomach. Generally, the gastric emptying time of humans is 2 h. Thus, the GRDDS was designed to prolong the stomach's drug release for more than 2 h.[3] GRDDS can be achieved using floating, high-density, bioadhesive, and expandable/swelling systems.[4]

Three-dimensional (3D) printing technology has attracted lots of attention from pharmaceutical companies due to the approval of the world's first 3D-printed levetiracetam tablets (Spritam®) by the United States Food and Drug Administration (USFDA) in 2015.[5,6] Currently, many types of 3D printers have been used to fabricate pharmaceutical products. For example, digital light processing (DLP) and stereolithography (SLA) were employed to fabricate microneedle formulation.[7,8] A powder-based 3D printer was employed to produce a fast-dissolving tablet.[9] An extrusion-based 3D printer was utilized to develop a dipyridamole floating tablet.[10] Among various 3D printer types, fused deposition modeling (FDM) 3D printers are the most popular ones owing to cost-effectiveness, guaranteed quality parameters, and printing accuracy.[11,12]

FDM 3D printers have been employed to produce many oral dosage forms. Sadia and coworkers designed an immediate-release tablet.[13] The immediate-release tablets were fabricated with channels to accelerate the drug release. Additionally, a budesonide-loaded delay-release and extended-release tablet was fabricated from polyvinyl alcohol (PVA) filaments and coated with Eudragit® L100 to obtain a delay-release manner.[14] Moreover, a fluorescein sodium-loaded controlled-release tablet was produced from PVA, followed by a thermal crosslinking process.[15] However, the systems mentioned above were conducted by direct loading of the heat-resistant drug into the formulations using the hot-melt extrusion technique. Therefore, the heat-labile drug becomes the limitation of this process. To overcome this limitation, several studies have investigated the incorporation of a drug formulation into a device to create a GRDDS. By that, heat-intolerable drugs can be delivered via a GRDDS device to enhance gastric retention time for better absorption and efficacy. Maroni and coworkers produced 3D-printed multi-compartment capsular devices for two-pulse drug release using different wall thicknesses and polymer types.[16] FDM is also used to fabricate floating devices by creating an air chamber inside the devices. Recently, Fu and coworkers developed a tablet-in-device (TiD) system of riboflavin as a floating drug delivery system (FDDS) using polylactic acid (PLA) filaments.[17] This device had two chambers, consisting of an air chamber and a tablet chamber. Our group also successfully produced a capsular-shaped crosslinked 3D-printed device as an FDDS of amoxicillin capsules.[2] Moreover, a tablet-shaped crosslinked 3D-printed device as an FDDS of domperidone (DOM) tablet was fabricated.[18] In addition, a 3D-printed device fabricated from two polymers with different properties was designed as FDDS.[9] These studies illustrate the feasibility of FDM for the production of floating devices. However, to obtain the floating devices with a suitable floating time, the buoyancy force of the devices is crucial. The floating device could not sink before the drug was fully released. On the other hand, some devices remained floating in the stomach for a long time even though the drug was completely released. Hence, a high-density system was considered to be used as GRDDS to overcome the hindrance because the drug is released completely before being moved to the intestinal tract.

In general, a high-density GRDDS should have a density close to 2.5 g/cm^3 to be retained in the stomach and resist peristaltic movements.[19,20] This system usually sinks in the lowermost part of the stomach (antrum) and stays in the stomach longer than the gastric emptying time. The formulation with high density can be achieved using a high-density compound such as zinc oxide, barium sulfate, iron powder, or titanium dioxide. However, it is challenging to manufacture high-density tablets with high drug content in the formulation.[4] In this study, DOM tablets were used as a model drug because DOM is poorly soluble in the intestinal environment but has good solubility in the stomach environment.[21] Despite various high-density compounds, the modified filament that was commercially available was loaded with iron powder. Therefore, iron powder-loaded PLA filament was selected to fabricate a novel high-density 3D-printed device (HPD) using FDM for delivering commercial DOM tablets as GRDDS.

Materials and Methods

Materials

Domperidone (DOM) 10 mg tablets (Motilium-M®) were a product of Janssen-Cilag (Thailand) Limited. Iron powder (Fe)-loaded polylactic acid (PLA) filaments (eSTEEL filament, 1.75-diameter) were supplied from Shenzhen Yun Industrial Co., Ltd. (Shenzhen, China). Methanol (MeOH) and sodium chloride (NaCl) were supplied from Honeywell (North Carolina, U.S.A.) and Sigma-Aldrich (Steinheim, Germany), respectively. Ammonium acetate (AmAc) and hydrochloric acid fuming 37% (HCl) were supplied from Merck KGaA (Darmstadt, Germany).

Methods

Design of high-density 3D-printed device)HPD(

The HPDs were designed using the Autodesk® Fusion 360TM Design program (V. 2.0.7421). A capsular shape of the HPDs was selected as it provides a higher volume than the tablet shape. The HPDs were composed of two parts, the body and the cap, with a chamber containing a Motilium-M® tablet. Eight holes were generated on the wall of the body with a fixed length of 2.9 mm (Figure 1). Each device had different hole widths (1.0, 1.5, and 2.0 mm) for controlling the drug release. The cap was designed to fit the body. The HPD design is illustrated in Figure 1.

Printer setting

Prusa i3 MK3®, an FDM 3D printer (Prusa Research SRO, Czech Republic), was employed to fabricate the HPD from the eSTEEL filament. Printer parameters and conditions for HPDs were presented in Table 1.

Appearance and weight variation of HPDs

The appearance of printed HPDs was observed by Dino-lite®, a digital microscope (AnMo Electronics Corporation, New Taipei City, Taiwan). A digital caliper (Zhejiang Deqing Syntek Electronic Technology CO., LTD, Deqing, China) was used to measure the actual dimension of HPDs. The weight variation of HPDs was determined using an analytical balance (Sartorius®, Data Weighing Systems, Inc., Illinois, United States). Twenty HPDs were individually weighed and recorded. The results are presented as mean ± standard deviation (SD).

Density evaluation

Motilium-M® tablet-incorporated HPDs were weighed (W) and recorded in grams. The whole volume (V) was calculated in cm3 using slicer software. The density (D) of Motilium-M® tablet-incorporated HPD was calculated according to Equation 1, and the results are presented as mean ± SD.

$$D = W/V \quad \text{..................................(1)}$$

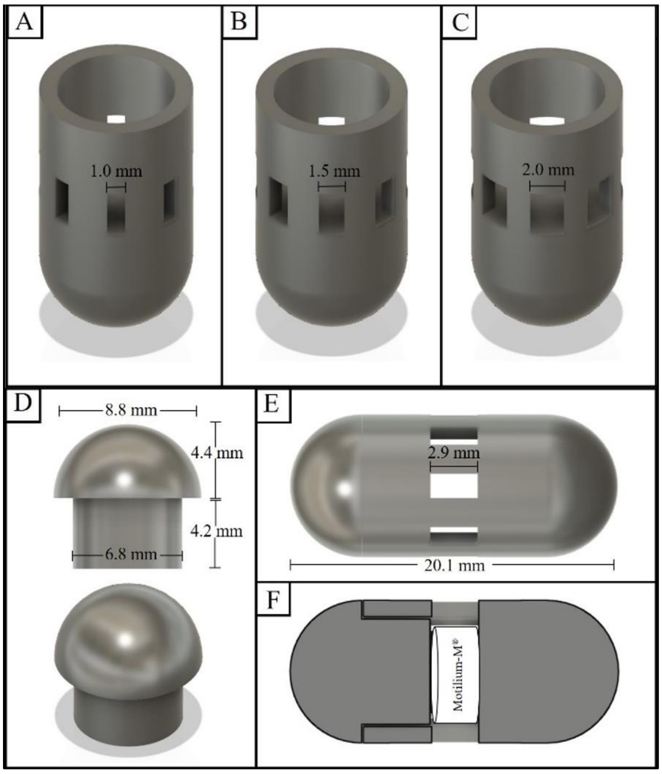

Figure 1 Illustration of HPD; the dimension of the bodies with a hole width of (A) 1.0 mm, (B) 1.5 mm, and (C) 2.0 mm. (D) The dimension of the cap. (E) The whole device's dimension and (F) the vertical cut view of HPD shows a chamber area containing a Motilium-M® tablet.

Table 1 The parameter setup of the FDM printer.

Parameters	Condition
Extruder temperature	190°C
Bed temperature	60°C
Nozzle diameter	0.4 mm
Layer height	0.15 mm
Vertical shells	2
Infill density	100%
Infill pattern	Rectilinear
Speed while printing	45 mm/s
Speed while traveling	180 mm/s
Brim	5 mm

In vitro dissolution of DOM from HPDs

The dissolution of DOM from HPDs was evaluated using a USP dissolution apparatus II (paddle). Each vessel contained 900 ml of simulated gastric fluid (SGF) (0.1 N HCl, pH 1.2) as the dissolution medium. The paddle rotation speed was set at 75 rotations per minute (rpm), and the testing environment was controlled at 37 ± 0.5°C. The dissolution medium (3 ml) was taken at different time intervals (0.25, 0.5, 1, 2, 4, 6, 8, 10, and 12 h), and the same volume of fresh medium was immediately replaced to maintain the sink condition. The sample solution was filtered with a 0.45-µm syringe filter, and DOM content was analyzed by high-performance liquid chromatography (HPLC)[22] (Model: 1260 infinitely series, Agilent Technologies Inc., California, USA) using a reversed-phase C-18 column (VertiSepTM, particle size was 5 µm, 4.6 mm × 15 cm). A solvent mixture of 0.5% w/v AmAc and MeOH was used as the mobile phase with gradient elution. The mobile phase ratio (0.5% w/v AmAc:MeOH) was linearly changed from 70:30 to 0:100, by volume, in 10 minutes. The injection volume and the flow rate were set at 10 µL and 1.5 ml/min, respectively. The eluent was detected with a UV detector operated at a wavelength of 280 nm. The approximate retention time was 8.5 min.

Kinetics of DOM release from HPDs

The kinetic equations of zero-order, first-order, Higuchi, and Korsmeyer-Peppas models were employed to find the release mechanism of DOM from HPDs. The fitting data are reported as correlation coefficients (R^2). The highest R^2 was considered as the best fit.

Statistics analysis

The results are reported as the mean ± SD. The statistically significant differences were assessed by one-way ANOVA (analysis of variance), then followed using a least significant difference (LSD) post hoc test (SPSS version 16.0 for Windows, SPSS Inc., USA). The differences in the dissolution study were significant at p-values < 0.05.

Results and Discussion

Appearance and weight variation of HPDs

The appearance of HPDs was investigated by Dino-lite® microscope, and the results are illustrated in Figure 2. The printed HPDs have a similar physical appearance compared to the designed 3D models. A slightly rough texture of HPDs was obtained due to the texture of the eSTEEL filament, which was PLA loaded with iron powder. The enlarged image (Figure 2E) showed a stripe pattern which is common for FDM since the method prints the filament layer-by-layer. The color of HPDs is metallic gray because of the iron powder that is loaded in PLA of the eSTEEL filament. The brim was the first part of the material that was printed to allow the HDP body to stand while the FDM was printing the device. This part was removed before HPD was incorporated with a DOM tablet. The actual size and weight variation of HPDs were displayed in Table 2. The results of actual size show the consistency and accuracy of FDM since narrow SD values were obtained. Moreover, the weight variation of HPDs emphasizes the printing accuracy of FDM presented by the narrow SD values. These findings are in concordance with previous articles, which reported the narrow SD of actual size and weight variation of a device fabricated by an FDM 3D printer.[2,9] Furthermore, the benefit of consistency and accuracy in printing might affect the dissolution profile to be more precise and reliable.

Density evaluation

The density of the Motilium-M® tablet-incorporated HPDs was calculated, and the results are shown in Table 2. All HPDs had a density of more than or equal to 2.4 g/cm^3, reaching the target density of a high-density formulation for GRDDS. The device's density close to 2.5 g/cm^3 is reported to be capable of resisting the stomach's peristaltic movements.[4] The appropriate range of the density of the dosage form to retain in the lower part of the stomach is 2.4 - 2.8 g/cm^3 and 2.5 - 3.0 g/cm^3.[20,23] With the calculated density in Table 3, HPDs would be able to withstand peristalsis and prolong the residing duration in the stomach.[24] Moreover, if the density was lower than 1.04 g/cm^3, this formulation was classified in a floating drug delivery system that provides a floating property to prolong the drug in the stomach. If the density was close to 2.5 g/cm^3 or more than 2.5 g/cm^3, this formulation should provide a gastro-retentive drug delivery system as a high-density formulation. The printed devices can be assumed to be considered GRDDS using a high-density system. The eSTEEL filament is a finished product used for fabricating HPDs. Thus, the density of the device can be adjusted by changing the device's design such as increasing the length of the bottom and cap part. Moreover, this technique could be applied to other drugs.

In vitro dissolution of DOM from HPDs

The results of in vitro dissolution of Motilium-M® tablet-incorporated HPDs are presented in Figure 3. The domperidone tablet (control) showed an immediate release profile (approximately 93% in 15 min). This finding agrees with our previous studies and is obvious for the dosage form that was designed to act as an immediate-release tablet.[9] The Motilium-M® tablet-incorporated HPD with a hole width of 2.0 mm showed the fastest release among all other formulations because it has the largest hole width on the device: 99.6% of drug release was obtained in 6 h. At 12 h, the Motilium-M® tablet was completely dissolved. On the other hand, the Motilium-M® tablet-incorporated HPD with the smallest hole size (1.0 mm) presented the slowest drug release: 49.5% of the drug was released in 12 h. The Motilium-M® tablet was partially dissolved and the remaining Motilium-M® tablet was still in the device. This inferred that the dosage form required a longer duration to release from the dosage form-incorporated device and could be considered a prolonged-release system if the dissolution test was

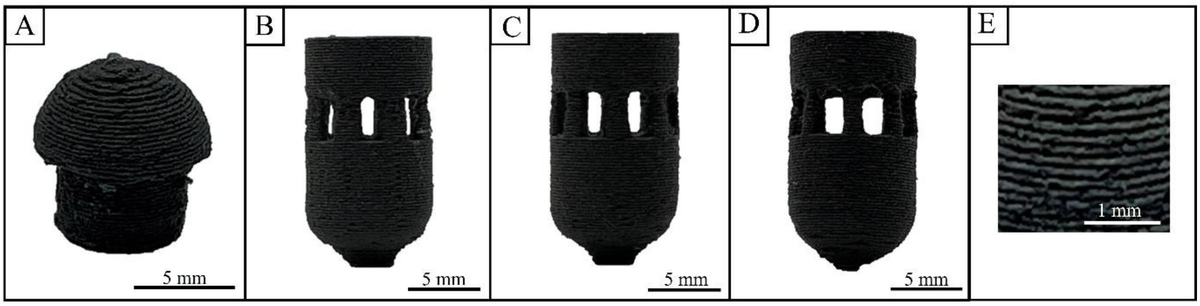

Figure 2 The morphology of HPD. (A) The cap of HPD and the bodies of HPD with different hole widths (B) 1.0 mm, (C) 1.5 mm, and (D) 2.0 mm), and (E) the enlarged image of HPD.

Table 2 Physical properties of HPD

Property	1.0 mm HPD	1.5 mm HPD	2.0 mm HPD
Average weight (g) (n = 20)	1.86 ± 0.01	1.87 ± 0.03	1.85 ± 0.05
Hole width (mm) (n = 3)	0.99 ± 0.02	1.50 ± 0.03	2.00 ± 0.02
Height (mm) (n = 3)	20.15 ± 0.03	20.12 ± 0.02	20.11 ± 0.01
Diameter (mm) (n = 3)	8.78 ± 0.03	8.80 ± 0.02	8.81 ± 0.02
Density (g/cm^3) (n = 20)	2.42 ± 0.00	2.43 ± 0.00	2.40 ± 0.00

further investigated. Furthermore, the optimal release profile was obtained from the Motilium-M® tablet-incorporated HPD with a hole width of 1.5 mm: 98.8% of drug release was achieved and the Motilium-M® tablet was completely dissolved in 12 h. This result is in accordance with Noyes-Whitney's equation as it describes that the dissolution rate depends on the surface area exposed to the medium.[25] Moreover, according to a previous article that fabricated the devices from PLA by varying the hole width, the large hole width exhibited faster drug release than the small hole width.[9] It can be concluded that the main factor in controlling the drug release rate is the hole width. Therefore, the Motilium-M® tablet-incorporated HPD with a hole width of 1.5 mm was found to be the optimal device to extend the release of domperidone to 12 h while acting as a GRDDS device. However, the previous article mentioned that the dose of domperidone for 12-h intervals should be 20 mg.[26] Therefore, the DOM tablet incorporated HPD should be taken for 2 devices at once or redesigned for incorporated 2 tablets into one HPD. Moreover, previous articles investigated high-density GRDDS as pellets. The results show that the high-density pellet leaves the stomach after administration for a while.[27,28] However, the way to eliminate the high-density devices (large pieces) from the body was not reported. Although PLA is a hydrophobic polymer, this is a biodegradable and biocompatibility material.[29] Thus, the HPDs may be eliminated by being biodegraded into small pieces in the stomach, and the device will be excreted to the intestinal part and removed from the body as feces. From the limitation of information, it could be suggested that the in vivo retention period, elimination property, and safety of HPDs should be investigated in further study.

Kinetics of DOM release from HPD

According to the release study, the HPD with a hole width of 2.0 mm provided the fastest release rate due to the largest hole resulting in a complete release within 6 h. The release of DOM from this device was calculated up to the time when the complete release was found. On the other hand, other devices were calculated until the dissolution test was completed (0 – 12 h). The DOM release kinetics from the HPD are shown in Table 3. The highest R^2 values were obtained with a zero-order kinetic model from all HPD formulations. This means that the devices may become the main factor affecting the release of DOM from the system, while the concentration of released DOM may not have an influence on the release. Meanwhile, the release rate was controlled by the whole width. This result demonstrates the potential of HPD for controlling drug release with zero-order kinetics. Moreover, this system could control the rate of drug release without any sustained release agent.

Conclusion

In this study, HPDs were successfully fabricated as GRDDS from iron powder-loaded PLA filaments using an FDM 3D printer. The incorporation of iron into the filament enhanced the density of the system and would allow a high-density GRDDS. The appearance of the printed HPDs was similar to the designed 3D models. All HPDs had a density close to 2.5 g/cm^3, signifying the ability to resist the stomach's peristaltic movements. The hole width of the HDPs affected the release rate of DOM from the device, where the larger size accelerated the drug release and vice versa. The Motilium-M® tablet-incorporated HPD with a hole width of 1.5 mm showed the optimal sustained-release profile and offered zero-order kinetics for 12 h. This device is promising to be applied for gastro-retentive drug delivery.

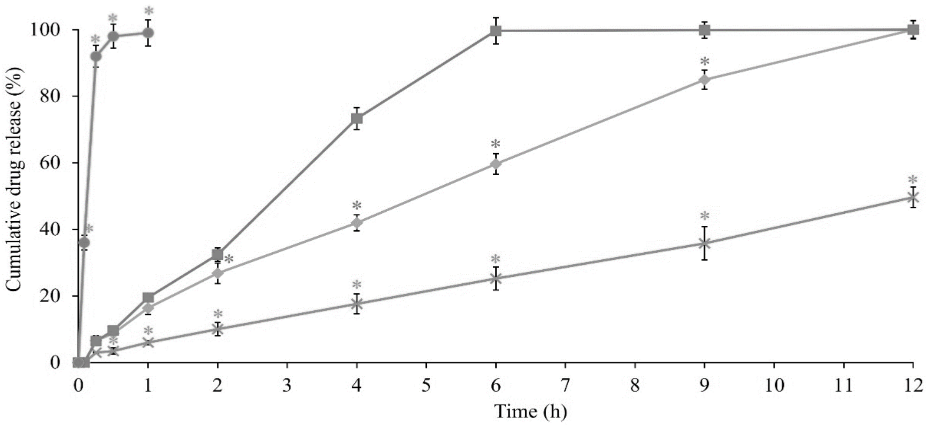

Figure 3 *In vitro* drug release of domperidone from a domperidone tablet (control) (—●—) and the Motilium-M® tablet-incorporated HPD with different hole widths (1.0 mm (—✕—), (C) 1.5 mm (—◆—), and 2.0 mm (—■—). * Statistically significant from HPD with a hole width of 2.0 mm (p<0.05). All experiments were performed in triplicate (n=3).

Table 3 Drug release kinetics and drug release rate of DOM from HPDs

Formulations	Zero-order (R^2)	First-order (R^2)	Higuchi model (R^2)	Korsmeyer-Peppas (R^2)	Drug release rate
1.0 mm HPD	0.9987*	0.0193	0.9456	0.9905	3.9094
1.5 mm HPD	0.9904*	0.4297	0.9747	0.3040	8.1274
2.0 mm HPD.	0.9949*	0.2900	0.9073	0.6079	16.6570

* The highest R^2

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

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