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Novel self-floating tablet for enhanced oral bioavailability of metformin based on cellulose

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ABSTRACT

Metformin has several problems such as low bioavailability, short half-life, and narrow absorption window, sustained and site-specific drug delivery system is required. Floating drug delivery systems are very useful to achieve these purposes. However, conventional floating systems have several limitations; lag time, a high proportion of excipient in the tablet, using non-biocompatible excipient, and requirement of a complicated procedure. To overcome these obstacles, we developed a hollow-core floating tablet (HCFT). The HCFT immediately floated in pH 1.2, 4.0, 6.8 medium, and even distilled water. The floating duration time of HCFT was>24 h. From the *in vitro* release study, it was confirmed that HCFT showed the sustain release profile of metformin for 12 h. Water uptake and matrix erosion were evaluated for predicting the buoyancy and drug release kinetics of HCFT in the body. Factor analysis was applied to optimize the formulation. There were significant ($p < 0.05$) differences in metformin plasma concentration of 4 h and 6 h between two groups. Compared with Glucophage® XR, the relative bioavailability of metformin HCFT was 123.81 ± 3.52%. The X-ray imaging of optimized formulation revealed that HCFT was constantly floating in the stomach region of the rabbit, thereby indicating improved gastric retention for>6 h. Consequently, all the findings indicate that HCFT could be an effective gastric retention system and applied extensively to other drugs with narrow absorption windows.

1. Introduction

Despite rapid advancements in parenteral drug delivery technologies, the oral route is still favored because of its convenience, low cost, painless and most widely accepted by patients. However, some drugs have poor oral bioavailability due to low water solubility, limited stability, and rapid clearance and metabolism. Oral drug delivery system is, therefore, developed to deliver drug to target sites for enhanced bioavailability and reduced side effects (Li et al., 2019a). However, commercial oral tablets are also limited by their poor absorption profiles due to variability in their gastrointestinal transit times. Thus, patients are expected to adhere strictly to their medication regime to reap the full pharmacological benefits for their medical conditions.

The residence time of the drug at the optimal absorption site is one of the most important factors affecting the bioavailability (Ulker and Erkey, 2014). Gastric drug delivery system (GDDS) is a technique for maintaining the release of the drug while the therapeutic agent stays in the gastrointestinal tract (GIT) (Baek et al., 2016; Shah and Prajapati, 2019). GDDSs are divided into several types depending on the mechanism; floating system, mucoadhesive system, high-density system, swelling system, and magnetic system (Tripathi et al., 2019). Among them, floating systems having a density of<1.0 g/cm^3 have been most actively studied (Chen et al., 2018).

Floating systems are divided into effervescent and non-effervescent systems (Singh and Kim, 2000). As the name suggests, the effervescent system contains a foaming agent such as $NaHCO_3$ (Guguloth et al., 2011; Pasa et al., 2019). The foaming agent reacts with the acidic components of gastric juice or the organic acids (citric acid or tartaric acid) in the tablet to produce CO_2 gas, which allows the tablet to float. Bubble generation necessarily requires an environment of low gastric pH, but it varies depending on the patient's variables characteristics, for example, age, gender, disease status, races and the degree of gastric juice secretion

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(Pawar et al., 2011). Also, the foaming agent requires sufficient time to have the floating ability, so this can lead to a problem that the formulation would be transferred to the small intestine before floating (Elzoghby et al., 2015). The non-effervescent system, on the other hand, contains low-density excipients to give itself a low density, thereby allowing the tablets to float in the stomach. This leads to overcome the problems of the effervescent system mentioned above. Nevertheless, several limitations have not yet been solved in the previous studies using the non-effervescent system, for example, the high proportion of excipient in the tablet and using non-biocompatible excipient (Essa et al., 2015; Fitriani et al., 2017; Fukuda et al., 2006; Rahamathulla et al., 2019; Wang et al., 2019). Various research about the development of the floating system and metformin loaded floating system has been reported (Thapa and Jeong, 2018; He et al., 2014; Ali et al., 2007; Upadhyay et al., 2014; Simons and Wagner, 2019; Iglesias et al., 2020). However, most of the studies mentioned above require the use of sodium bicarbonate or low density floating polymers to implement gastric retention systems. Also, a complex and energy-intensive manufacturing method such as hot melt extrusion is required to develop gastric retention system tablets. To overcome the limitations described above, a novel floating system is needed.

Nowadays, a number of researches have widely investigated on pharmaceuticals using 3D printers (Awad et al., 2018). By using 3D printers, researchers can make a single tablet containing multiple active pharmaceutical ingredients or tablets of various shape (Khaled et al., 2015; Kyobula et al., 2017). The morphological variety of the tablet prepared by 3D printers may result in unique drug release or zero-order drug release (Li et al., 2019b; Sadia et al., 2018). Floating tablets also can be prepared with 3D printers by changing fill rates, shapes, or developing tablets in device (Fu et al., 2018). The only downside to prepare drug formulations using 3D printers is that it takes too much time to make one tablet (>10–15 min). The production time using the 3D printer might be shorter than that using the mold system in the case of single tablet production. If the large scale mold is used, the production efficiency is dramatically increased. However, the 3D printer still has limitations to apply the scale-up process.

Nevertheless, it is undeniable that studies using 3D printing have played an important role in pharmaceutics. In particular, some studies have shown that the unique shape that tablet compression machines cannot make gives tablet special properties (Abramson et al., 2019; Gong et al., 2018). However, the 3D printing system has limitations such as the high expense and difficulty of application in large scale production. Thus, the simple and large-scale applicable method is needed to enhance the producibility, also the new system needs to have the gastroretentive and sustained release properties for the clinical application. Given this, when developing a floating system, by forming an empty space inside the tablet, as like swimming ball, tablets can be easily floated in the stomach, thereby stayed there. While similar attempts have been made previous, it has been still challenging to use in the industry due to a sublimation process that requires a lot of energy (Asada et al., 2018; Oh et al., 2013; Saab et al., 2016; Strusi et al., 2008).

In this study, we have introduced a novel and innovative floating tablet design without 3D printers. The main property of the tablet is a hollow-core, allowing it to float in the stomach, prolong gastro-retentive time and enhance oral bioavailability. Hollow-core floating tablet (HCFT) loading metformin hydrochloride (metformin) as a model drug was manufactured and evaluated in terms of matrix erosion and *in vitro* drug release. To further evaluate the robustness of this delivery system, the pharmacokinetic study and *in vivo* x-ray imaging were subsequently performed in albino rabbits. The results ascertained the prolonged residence time of HCFT in the stomach. As such, HCFT released the drug to the main absorption site with a sustained-manner, whereby the oral bioavailability was significantly enhanced.

2. Materials and methods

2.1. Materials

Metformin was supplied by Korea United Pharm, Inc. (Seoul, Korea). Hydroxypropyl methylcellulose (HPMC, Benecel®) E50, K4M, K15M, K100M, and K250M was a gift from Ashland (Mumbai, India). Microcrystalline cellulose (MCC, Avicel® PH102) was provided by FMC (Brussels, Belgium). For the determination of metformin, the LC-MS/MS system was used and high-performance liquid chromatography (HPLC) grade acetonitrile were purchased from Sigma-Aldrich (St. Louis, MO, USA). Ammonium acetate was obtained from Samchun Pure Chemical (Pyeongtaek, Korea).

2.2. Preparation of HCFT

Firstly, metformin was accurately weighed, along with MCC and HPMC (Table 1). The entire ingredients were mixed. After that, distilled water (DW) was added dropwise in powder blend till the damp mass prepared. The above damp mass then filled in tablet triturates mold. After drilling a 1 cm hole at the center using a small rod (i.d. 1.1 mm), this mold was dried at a 40℃ hot air oven for 2 days until hollow-core formation. It was taken about 1 or 2 days. The prepared tablets were evaluated and packed in the container. The production process of HCFT was briefly illustrated in Scheme 1.

2.3. In vitro buoyancy study

In vitro buoyancy of HCFT was conducted following the USP Apparatus II (paddle) method. The dissolution apparatus was filled with 900 mL of pH 1.2 dissolution media maintained at 37 °C under 50 rpm of stirring speed. The floating lag time (FLT) means the required time for floating onto the surface of the media, and the floating duration time (FDT) indicates the time before the HCFT sank down or disintegrated. The preparation method was slightly modified from the literature (Qin et al., 2018). The FLT and FDT were evaluated for three replicates of F1-F5 to determine the *in vitro* buoyancy tendency according to the viscosity of HPMC.

2.4. In vitro release test

In vitro release test was conducted according to the USP Apparatus II (paddle) method using the dissolution tester (DST-610, Labfine, Suwon, Korea). The dissolution test was carried out at 37 °C of 900 mL pH 1.2 media under 50 rpm. At the predetermined time points of 10, 20, 30, 60, 120, 240, 360, 480, 720, and 1440 min, 5 mL of medium was collected and filtered through a 0.45 μm filtration membrane. The collected volume was replaced by a fresh medium for the sink condition. The released metformin was assayed by HPLC.

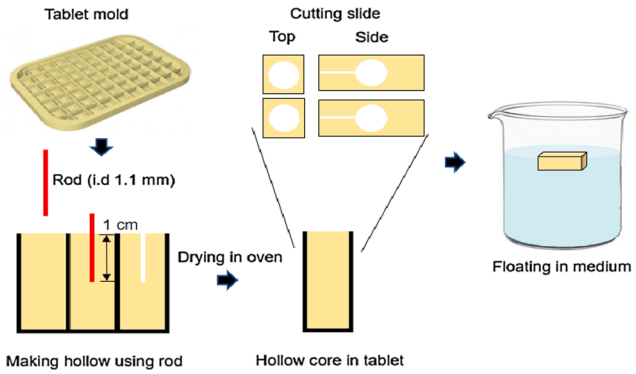
Shimadzu LC-2030C 3D HPLC system (Shimadzu Corporation, Tokyo, Japan) accompanied with Kinetex C18 (Phenomenex, Torrance, CA, USA) (4.6 mm × 250 mm id, 5 μm) was used for the HPLC analysis and the column temperature was 30℃ with 1.0 mL/min of flow rate. The mobile phase consisting of acetonitrile and 10 mM potassium phosphate monobasic (30:70, v/v) was used, and the injection volume was 10 μL. The UV detection wavelength for metformin was set at 234 nm.

2.5. Release kinetic model

In case of *in vitro* released metformin, subsequent models (zero-order kinetics, first-order kinetics, Higuchi and Korsmeyer-Peppas) were applied for a better investigation of the drug release mechanism. The R-square was considered to decide which model fits the best. In particular, the values of n were also calculated in the Korsmeyer-Peppas models, and the relationship between released metformin and matrix erosion in HCFT was determined.

Table 1
The composition of metformin HCFT (F1-F11).

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11
Metformin	500	500	500	500	500	500	500	500	500	500	500
HPMC E50	100	–	–	–	–	–	–	–	–	–	–
HPMC K4M	–	100	–	–	–	–	–	–	–	–	–
HPMC K15M	–	–	100	–	–	150	50	–	–	–	–
HPMC K100M	–	–	–	100	–	–	–	150	50	–	–
HPMC K250M	–	–	–	–	100	–	–	–	–	150	50
MCC	100	100	100	100	100	50	150	50	150	50	150
Total	700	700	700	700	700	700	700	700	700	700	700



Scheme 1. The HCFT production process using a tablet mold.

2.6. Water uptake and matrix erosion

The water uptake and matrix erosion experiments were carried out with a similar method and devices for *in vitro* release test. Briefly, each tablet was firstly weighed (W_1) and transferred to 900 mL of simulated gastric fluid (pH 1.2) with a rotation speed of 500 rpm at 37 ± 0.50 °C. At predetermined time intervals, the tablet was collected from the medium. The covering media around the HCFT was wiped with a filter paper and weighed (W_2) (Qin et al., 2018). After then, the HCFT was dried at hot dry oven for 24 h and weighed (W_3). The degree of water uptake (F_w) and matrix erosion (F_e) were worked out using the following equations:

$$F_w = \frac{W_2 - W_1}{W_1} \times 100\%$$

$$F_e = \frac{W_1 - W_3}{W_1} \times 100\%$$

Higher F_e values represent a high degree of matrix erosion.

2.7. Optimization of metformin HCFT formulations

The multilevel category design was conducted based on the *in vitro* release, water uptake and matrix erosion results (Guguloth et al., 2011; Upasani et al., 2014; Venkata Srikanth et al., 2012). Minitab® 18 (Minitab Ltd., Coventry, UK) was used for experimental design and statistical evaluation. As a categoric factor, two factors (HPMC viscosity and amount) were used as independent variables (Table 2). Three kinds of levels (HPMC K15M, K100M, K250M) were used for the HPMC viscosity (X_1). The HPMC amount (X_2) was carried out using three levels (50, 100, 150 mg). The evaluation of each formulation is based on the friability (Y_1), % metformin release at 2 h (T_2,Y_2), % metformin release at 8 h (T_8,Y_3), time required to release 50% of the metformin (Q_{50},Y_4), % matrix erosion at 12 h (M_{12h},Y_5) (Guguloth et al., 2011).

Table 2
Factors and responses used in multilevel category design.

Categoric factor	Factors		Levels		
			1	2	3
	X_1: HPMC viscosity (cps)		15,000	100,000	250,000
	X_2: HPMC amount (mg)		50	100	150
Response	Y_1 Friability (%)	Y_2 T_2 (%)	Y_3 T_8 (%)	Y_4 Q_{50} (h)	Y_5 M_{12h} (%)
Goals	Minimize	Minimize	Minimize	Maximize	Minimize

2.8. In vivo pharmacokinetic study in rabbits

In vivo pharmacokinetic study was applied to figure out the floating and sustained release aspect of the HCFT *in vivo* using rabbits under fasted conditions. The rabbits were randomly divided into two groups: Group I: The animals were administrated the commercial product (Glucophage® XR 500 mg). Group II: The animals were administrated the optimized HCFT formulation (F8, metformin 500 mg per tablet). The rabbits were fasted for 12 h with the free access to water before the oral administration. After first administration, the rabbits had a washout period for the enough time to excrete the metformin of at least two weeks between the experiments. Two hundred microliters of blood samples were collected at predetermined time intervals from the rabbit marginal ear vein. After that, the samples were centrifuged at 4000 rpm for 10 min, and the supernatant plasmas were collected stored at –70 °C. The metformin concentration was analyzed by high performance liquid chromatography-electrospray tandem mass spectrometry (HPLC-MS/MS).

2.9. HPLC-MS/MS analytical condition

For analyzing metformin in plasma samples, 50 μL of plasma was put into the microcentrifuge tube, following 5 μL of internal standard (IS, phenformin hydrochloride, 1 μg/mL) solution was added. The tubes were vortexed for 5 s, and 1 mL of acetonitrile was added for the protein precipitation. The samples were mixed at 1,000 rpm for 10 min and then centrifuged at 17,000 g for 5 min. The obtained supernatant was transferred to micro vials for analysis.

The instrument was actuated in positive multiple reaction-monitoring (MRM) mode and was combined to an Agilent 1290 capillary LC system. The detector was an Agilent 6495 triple quad mass spectrometer (TQ-MS), and it was controlled by MassHunter software. The TQ-MS condition was a gas temperature of 200℃, gas flow of 14 L/min, nebulizer pressure of 20 psi, capillary voltage of 3000 V, and cell accelerator voltage of 5 V. The collision energy (CE) was optimized for metformin. The Hypersil GOLD column (4.6 mm × 50 mm, 3 μm) was used for the separation and maintained at 30℃. Positive MRM was used to analyze metformin. For the quantification of metformin, the isocratic conditions were used. The flow rate was optimized at 0.4 mL/min, and the injection volume of sample was 1 μL. The mobile phase was consisted of DW containing 10 mM ammonium acetate (pH 6.8 adjusted by

ammonia solution) and acetonitrile.

The assay showed great linearity at the range of 25–5,000 ng/mL for metformin. The correlation coefficients (R^2) were higher than 0.99, and this result shows that the developed analytical method is very suitable for the determination of metformin concentration in the plasma.

2.10. In vivo buoyancy studies (X-ray imaging)

In vivo buoyancy study by X-ray image was conducted to show that HCFT actually can be floated and remained in the stomach. Animal diagnosis radiation equipment (SM-120HF, Sam mi medical, Seoul, Korea) was used for visual identification of HCFT. Optimal exposure factors were set at 50 kV and 14 mAs, respectively. HCFT, including with 450 mg metformin and 50 mg barium sulfate as an X-ray marker, was used for this study (Guguloth et al., 2011). Before the test, the rabbits were fasted overnight. However, they were freely excess to water that can make the HCFT floated in the stomach during the whole experiment. X-ray photograph of the rabbit before HCFT administration was taken, and it was indicated be as 0 h. X-ray photograph was taken in the lateral and ventral position of the rabbit at predetermined time intervals at 1, 6, and 24 h using an X-ray machine. In order to confirm that the HCFT was floated and not attached to the gastric wall, the location of the HCFT in the ventral position as well as the lateral and dorsal position of rabbit was observed.

2.11. Statistical analysis

The analysis of the pharmacokinetic data was conducted by non-compartmental analyses using Winnolin (Certara, Princeton, USA). The maximum plasma concentration of metformin (C_{max}) and the time to reach the maximum plasma concentration of metformin (T_{max}) were estimated. The AUC of the pharmacokinetic profile from 0 h to infinite time ($AUC_{0-\infty}$) was estimated by extrapolating the time to infinity. The oral relative bioavailability (F) of the HCFT was calculated as: F (%) = 100 × $AUC0_{-\infty}$ of HCFT/ $AUC_{0-\infty}$ of metformin. The student's *t*-test was employed to compare the difference in the dissolution rate and metformin plasma concentration. Differences in results of $p < 0.05$ were considered significant.

3. Results and discussion

3.1. Preparation of characterization of HCFT

HCFT was designed by the inspiration of the swimming tube or glass bottle's ability to achieve passively floated. The HCFT could autonomously float and remain in the upper GIT where metformin is mainly absorbed (Stepensky et al., 2001). In the early stages of the study, 3D printing was considered to create a void inside the tablet (Tan et al., 2018). However, due to limitations such as excessive time required to make tablets and the use of limited materials, 3D printing still faces challenges in scale-up production (Goole and Amighi, 2016). In particular, when we tried to make a tablet using a 3D printing, it is difficult to maintain the inner hollow-core structure of the tablet (data not shown). This is the reason why 3D printing produces tablets by stacking layers (Quan et al., 2015).

To overcome this problem, HCFT was fabricated using molds made of various components and shapes. As a result, it was confirmed that the polypropylene mold is better than polystyrene mold due to its moderate hydrophobic property. The hole depth and oven drying time were also optimized to form a hollow core (Table S1) with a hole depth of 1 cm and an oven drying time of 2 days. Since the same mold was used, similar thickness (8.50 mm) and height (15.00 mm) were found in HCFT. Fig. 1 (a) shows the images of the whole and excised HCFT. The images revealed that a hollow cavity was successfully created. Also, the weight variation was very low (<5.00 of %RSD). Overall, it was considered that all the formulations were formed uniformly. The friability was slightly

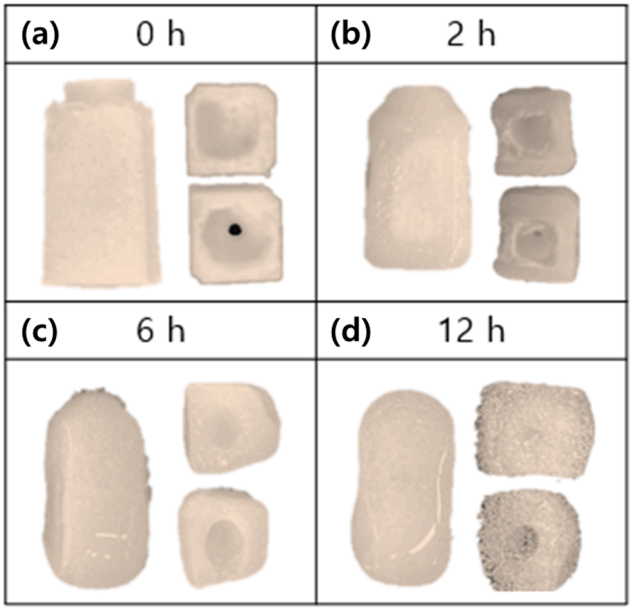


Fig. 1. The morphologies of the whole (left) and excised (right) HCFT (F8) after (a) 0 h, (b) 2 h, (c) 6 h and (d) 12 h of release in the release medium (pH 1.2) at 37 °C.

increased when the higher amount and viscosity of HPMC was used. However, all the formulations prepared showed very low value (<0.50%), and it was considered acceptable (Table S2).

The biggest issue of mold tablets is that its hardness is too low. Due to the reason, mold tablets are generally used for fast disintegration tablets due to the low hardness resulting in, rapid disintegration and dissolution of tablets. However, in this study, the hardness of the HCFT was higher than the maximum hardness that can be measured by hardness tester. This result is possible because HCFT was created using the proper ratio of HPMC and MCC.

When using other sustaining agents such as polyethylene oxide or other diluents such as lactose, it took too much time for the tablets to dry, and the tablets had a mild hardness or sticky property. DW was optimal to form the damp mass. In the case of using ethanol, on the other hand, the damp mass was not properly formed, and the hardness of the tablet was weak even after drying. This may be explained by the following reasons. When HPMC comes in contact with water, the viscosity rises to maintain the tablet form. On the other hand, when ethanol was used, the hardness of the tablet was not sufficiently strong (Table S1).

3.2. In vitro buoyancy study

In vitro buoyancy study in terms of FLT and FDT was performed for all the formulations. Since the major absorption of the metformin is in the stomach and upper GIT, the floatability would be advantageous. The excretion of tablets into the small intestine can be prevented by the immediate rise and maintained flotation achieving local drug absorption. The FLT and FDT data of different formulations are illustrated in

Table 3
The FLT and FDT of various formulation of metformin HCFT (n = 3).

Formulation	Floating lag time (FLT; s)	Floating duration time (FDT; h)
F1	0	<1
F2	0	<12
F3	0	>24
F4	0	>24
F5	0	>24

Table 3 and Fig. S1. Regardless of the viscosity of the HPMC, all formulations immediately floated upon contact with the medium (FLT = 0 s). As for the FDT, F1 and F2 disintegrated rapidly in the medium as the tablets were fabricated with low viscosity of HPMC (Sangalli et al., 2004). Therefore, the FDT of F1 and F2 was shorter than 1 h and 12 h, respectively. This could be the result of fast drug release. In addition, tablet breaking induced by incorporating lower viscosity grade material could be another reason. Thus, a sufficient FDT over 24 h could be ensured when using HPMC with the viscosity above the appropriate level. Therefore, subsequent experiments were conducted using the formulations except for F1 and F2. As shown in Fig. 1, the hollow cavity was not impaired up to 12 h, correlating the buoyancy of the HCFT for the prolonged period. Baek et al. reported the floatable microcapsule enabled enhanced oral bioavailability (Baek et al., 2018). Strusi et al. demonstrated some *in vivo* studies for confirmation that the *in vitro* floating ability of void configuration was maintained also in the human stomach (Strusi et al., 2008). Considering this, HCFT can be expected to float in the stomach in proportion with the FDT from the *in vitro* results.

To evaluate the effect of hollow core on buoyancy, the non-hollow core table (F8 without hollow core) was compared to the HCFT (F8) in terms of *in vitro* buoyancy. When the non-hollow core tablet was placed in pH 1.2 medium, the tablet was immediately sink (Fig. S2(A)). In contrast, the HCFT (F8) was floated in pH 1.2 medium (Fig. S2(B)). It indicates that the presence of hollow core plays important role in the buoyancy of the tablet developed in this study.

3.3. In vitro release study

Metformin is an extremely hydrophilic drug. Under physiological conditions, the existing form is mostly positively charged. Therefore, release retarding agents, such as HPMC, have to be incorporated in the formulations to achieve a sustained drug release. As the floating ability was confirmed in the previous study, a prolonged-release would be a synergistic effect with the great buoyancy for enhanced bioavailability.

As shown in Fig. 2, *in vitro* release behavior of F3, F4, and F5 has no significant difference among the formulations tested. This result means that the different types of HPMC have no substantial influence on the release behavior of the drug (Fig. 2b and c). This is because the viscosity of HPMC only affects the lag time before quasi-stationary diffusion but not the rate of release (Ford, 2014). In the formulations using HPMC K15M or K100M obviously, the release of metformin significantly slowed down at 2 h and 4 h with the increasement of the percentage of the polymer into the formulations. It was assumed that the sufficient sustained release of metformin might require a certain level of amount or viscosity of HPMC. Due to the porous surface and hydrophilic property of metformin, the dissolution was not quite slow, and the dissolution rate was 40–80% in 2 h. These results indicate that HCFT is the metformin sustained-release tablet suitable for the gastro-floating delivery system. Therefore, a high bioavailability of metformin would be expected in HCFT when the floating and sustained-release property is further confirmed even *in vivo*.

3.4. Release kinetic model

To elucidate the release pattern of the drug from these tablets, the drug release data were fitted to zero-order, first-order, Higuchi and Korsmeyer-Peppas release kinetics (Okunlola and Ghomorai, 2018). As listed in Table 4, the best fit model was Korsmeyer-Peppas model for the drug release profile. In this model, the value of n characterizes the release mechanism of the drug. In the case of HCFT, $0.45 \leq n$ corresponds to the Fickian diffusion mechanism and $0.45 < n < 0.89$ corresponds to non-Fickian transport (Dash, Murthy, Nath, and Chowdhury, 2010).

Interestingly, the release exponent n of formulations with high viscosity or the large amount of HPMC (F4, F5, F6, F8, F10) was within the range of 0.45–0.89, indicating a non-Fickian or anomalous transport. Besides, the drug release was controlled by both diffusion and matrix erosion. Meanwhile, the release exponent n of other formulations (F3, F7, F9) was lower than 0.45, suggesting that the drug release from the tablets occurs primarily via diffusion (Dash et al., 2010).

3.5. Tablet swelling behavior

Drug release is affected by both diffusion and erosion properties of

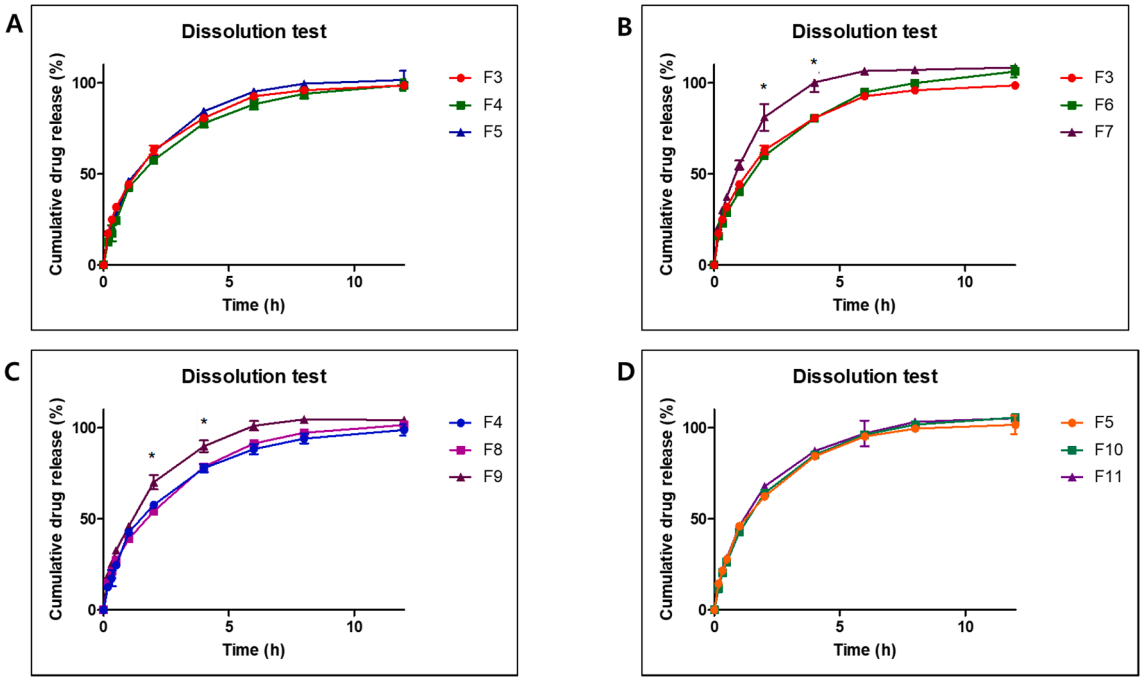


Fig. 2. Effect of type and amount of sustained-release agent on the release profiles of metformin from the HCFT in pH 1.2 medium (n = 3). (a), type of HPMC; (b), amount of HPMC K15M; (c), amount of HPMC K100M; (d), amount of K250M. *$p < 0.05$.

Table 4
Fitting results of drug release profiles.

Formulations	Zero order	First order	Higuchi	Hixon-Crowell	Korsmeyer-Peppas		Mechanism of drug release
	R^2	R^2	R^2	R^2	R^2	n	
F3	0.7904	0.9909	0.9337	0.9398	0.9758	0.4225	Fickian
F4	0.8085	0.9978	0.9439	0.9674	0.9677	0.5082	Non-Fickian
F5	0.7824	0.8853	0.9285	0.9981	0.9674	0.4774	Non-Fickian
F6	0.8402	0.7864	0.9611	0.9939	0.9867	0.4633	Non-Fickian
F7	0.7030	0.7427	0.8739	0.8238	0.9517	0.4042	Fickian
F8	0.8398	0.9907	0.9599	0.9858	0.9874	0.4718	Non-Fickian
F9	0.7608	0.8635	0.9139	0.8909	0.9707	0.4333	Fickian
F10	0.7955	0.9354	0.9367	0.9572	0.9638	0.5222	Non-Fickian
F11	0.7758	0.9296	0.9245	0.9448	0.9620	0.4903	Non-Fickian

tablet, the tablet swelling behavior and matrix erosion at 12 h were evaluated. We used the different types of HPMC to evaluate the interaction between the viscosity of HPMC and matrix erosion of the tablet. Fig. 3 showed the effect of type (HPMC K15M, K100M, K250M) and amount (50, 100, 150 mg) of HPMC on the matrix erosion at 12 h of HCFT. Matrix erosion (M_{12h}) was highest (95.80%) in the HCFT containing 50 mg of HPMC K15M, and it was decreased to 75.06% with 150 mg of HPMC K250M for manufacturing the HCFT. As such, the M_{12h} was lowered when using high viscosity and large amount of HPMC. In summary, when the HPMC with high viscosity and the high amount was used, the matrix erosion of the tablet was decreased. The swelling behavior of the tablet is significant as it could influence drug release kinetics and buoyancy. The degree of matrix erosion of the tablet may affect to the presence of hollow-core and the floating retention time (Thapa and Jeong, 2018). If the tablet matrix erosion increases, HCFT is not able to maintain its own shape while staying on the stomach. It directly results in the disintegration and moving from the stomach into the small intestine of tablet before the drug is totally released from the tablet. By choosing the formulation with the lowest M_{12h}, the buoyance of HCFT can be maintained *in vivo* for a sufficient time.

3.6. Optimization of HCFT

Minitab software was used to analyze all the experimental data statistically. If the developed model has statistical significance was determined by the analysis of variance. The *p*-values of all models were < 0.0001, indicating that these models are statistically significant (Jyoti, 2019). The adequacy of all the models was forecasted by R^2, adjusted R^2, and predicted R^2. The R^2 value represents the maximum squared regression coefficient. It is an indication of how well the model fits the experimental data and can be achieved by a model using only the variables in it. $R^2 > 0.75$ indicates aptness of the model (Chauhan and Gupta, 2004). The adjusted R^2 considering the number of terms used within the model compared with R^2 and the predicted R^2 could estimate how well the model predicts a response value. The difference between adjusted R^2 and predicted R^2<0.2, the model was recommended. In terms of R^2, adjusted R^2, and predicted R^2, it was found out that these models described the data well (Table 5).

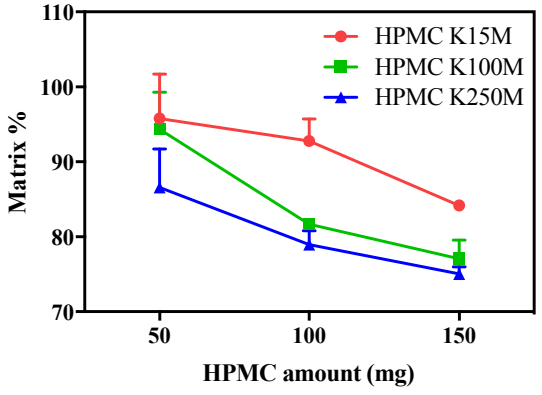


Fig. 3. Effect of type and amount of sustained-release agent on the matrix erosion at 12 h of the HCFT (n = 3).

The desirability function approach was influenced by more than one independent variable and predicted by multiple response applications. In this study, five responses were available, and they were directly influenced by the viscosity and amount of HPMC. In order to obtain the highest bioavailability of HCFT, Y_1, Y_2, Y_3, and Y_5 were to be minimized, and Y_4 was to be maximized. Minitab response optimizer was used to optimize the formulations (Unal, 2016). The optimum parameters were found to be HPMC viscosity of K100M and HPMC amount of 150 mg (F8). According to these optimized values, the overall desirability was evaluated as 0.8665.

3.7. In vivo pharmacokinetic study in rabbits

For pharmacokinetic evaluation, a commercial product (Glucophage® XR 500 mg, Merck Santé, Lyon, France) or the optimized HCFT formulation (F8) was administered to rabbits. The plasma concentration of metformin against time following the oral administration of HCFT is shown in Fig. 4. Various pharmacokinetic parameters are listed in Table 6. In the HCFT and commercial product groups, the mean plasma concentrations of 4 h were 3183.10 ± 61.51, 2127.03 ± 264.81 ng/mL and 6 h were 2371.91 ± 550.98, 1358.40 ± 205.06 ng/mL, respectively. There were significant differences in metformin plasma concentration of 4 h ($p < 0.01$) and 6 h ($p < 0.05$) between two groups. Also, the mean plasma concentration of HCFT formulation was superior to that of metformin since after 4 h of administration. So, the superior plasma concentration of metformin could prolong the anti-diabetic effect of metformin. Compared with Glucophage® XR, the relative bioavailability of metformin HCFT was 123.81 ± 3.52%. The analysis of the PK data indicates that the oral bioavailability of HCFT is superior to that of the commercial product. Firstly, the floatability of the HCFT possibly extended the gastro-retentive time of the metformin. This is unlike the situation where most oral formulations including the commercial product used in the study reside only ~ 2 h in the stomach (Baek et al., 2018). In addition to the prolonged GRT, the controlled release of the metformin is another key factor to explain the enhanced bioavailability. HCFT could stay in the stomach and release the drug in the sustained manner. Through the pharmacokinetic study, it was confirmed HCFT is a

Table 5
Summary of model *p*-value and statistical analysis.

Response (unit)	Model *p*-value	R^2	Adjusted R^2	Predicted R^2
Y_1: Friability (%)	< 0.0001	0.8305	0.7552	0.6186
Y_2: T_2 (%)	< 0.0001	0.9012	0.8573	0.7778
Y_3: T_8 (%)	< 0.0001	0.9221	0.8874	0.8247
Y_4: Q_{50} (h)	< 0.0001	1.0000	1.0000	1.0000
Y_5: M_{12h} (%)	< 0.0001	1.0000	1.0000	1.0000

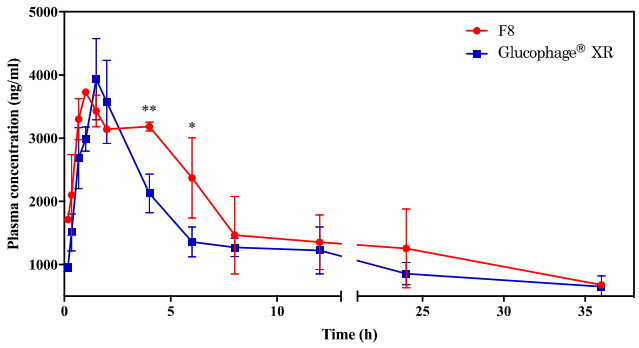


Fig. 4. Mean metformin plasma concentration (ng/mL) after oral administration of floating tablet (F8) and Glucophage® XR (mean ± SD) (n = 4). (**$p < 0.01$ and *$p < 0.05$).

Table 6
Pharmacokinetic parameters of commercial product (Glucophage® XR) and HCFT (F8) (n = 4).

Parameters	Glucophage® XR	HCFT (F8)
C_{max} (ng/mL)	4,074.63 ± 402.19	3,751.98 ± 27.65
T_{max} (h)	1.75 ± 0.25	0.92 ± 0.14
$AUC_{0\rightarrow\infty}$(h·ng/mL)	43,830.95 ± 3011.12	54,266.72 ± 10,605.81
F (%)	–	123.81 ± 3.52

C_{max}, maximum concentration; $AUC_{0-\infty}$, area under the curve from zero to infinity; t_{max}, time to reach C_{max}; F, relative bioavailability.

useful system because of a steady state of plasma level that is therapeutically effective and non-toxic for an extended period of time (Razavi et al., 2017).

3.8. *In vivo buoyancy studies (X-ray imaging)*

In order to prove the floating HCFT enabling the enhanced bioavailability of HCFT visually, a radiological method was used to monitor the developed HCFT contained 50 mg of barium sulfate and 450 mg of metformin in the stomach (Diós et al., 2016; Widmark, 2007). The rabbits used in the study were under the fasting state. As shown in Fig. 5, X-ray imaging made it simple to identify the interior space of the HCFT. This study also demonstrated that, even in the fasted state under the influence of strong acidity and gastric activity, the shape and floating ability of F8 was not impaired at least 6 h. When it considered that the gastric emptying time is 2–6 h, HCFT showed the property of gastric-retention (Cathy, 2006). Therefore, it can be assumed that this property came from the floating ability of HCFT. Hence, it was confirmed that HCFT was successfully floated and remained in the stomach by introducing a hollow cavity in the HCFT. The X-ray image at 24 h showed that HCFT was disintegrated and excreted from the body, indicating the biodegradability of the HCFT regarding toxicity.

4. Conclusion

To develop the gastroretentive sustained-release tablet, we designed the metformin loaded tablet which has the hollow core system using a mold. The HCFT was successfully fabricated by the mold system, which is a simple and inexpensive system. The tablets could immediately float in all the media tested regardless of pH and release the drug with sustained-manner depending on the amount and viscosity of HPMC. The optimal formulation of HCFT was chosen based on the results of friability, *in vitro* release and matrix erosion. Pharmacokinetics study on the HCFT exhibited improved bioavailability of the drug against the commercial product. Notably, it was confirmed that HCFT could remain in the stomach with the controlled release of metformin by the pharmacokinetic study and *in vivo* X-ray images. In conclusion, the novel floatable HCFT may be a promising delivery platform to improve the oral bioavailability of the narrow absorption window drug through the gastroretention of drug in the stomach.

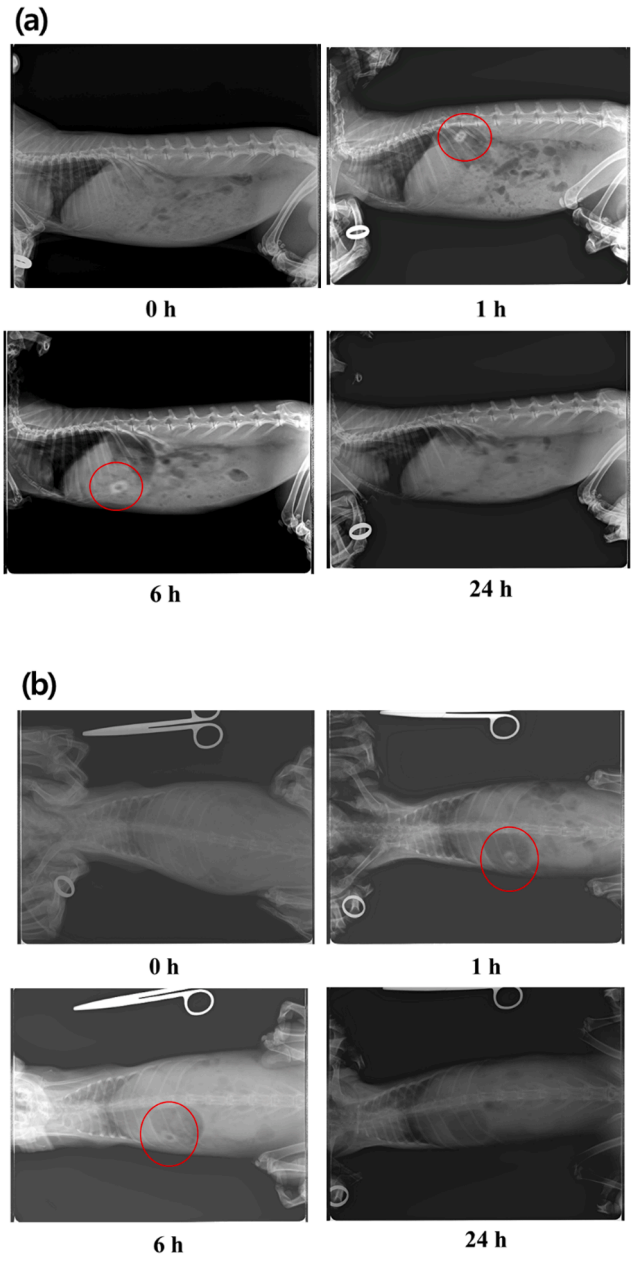


Fig. 5. X-ray photographs of metformin HCFT (F8) in a rabbit at 0, 1, 6, and 24 h. (a), Lateral and dorsal; (b), Ventral.

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CRediT authorship contribution statement

Hyun Wook Huh: Conceptualization, Methodology. **Young-Guk Na:** Methodology, Software. **HeeChol Kang:** Methodology. **Minki Kim:** Validation. **Mingu Han:** Formal analysis. **Thi Mai Anh Pham:** Formal analysis. **Hyeonmin Lee:** Validation. **Jong-Suep Baek:** Writing - original draft. **Hong-Ki Lee:** Methodology, Data curation, Writing - review & editing. **Cheong-Weon Cho:** Conceptualization, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijpharm.2020.120113.

References

Abramson, A., et al., 2019. An ingestible self-orienting system for oral delivery of macromolecules. Science 363 (6427), 611–615.

Ali, J., et al., 2007. Formulation and development of hydrodynamically balanced system for metformin: In vitro and in vivo evaluation. Eur. J. Pharm. Biopharm. 67, 196–201.

Asada, T., et al., 2018. Formulation of a poorly water-soluble drug in sustained-release hollow granules with a high viscosity water-soluble polymer using a fluidized bed rotor granulator. Int. J. Pharm. 541 (1–2), 246–252.

Awad, A., et al., 2018. Reshaping drug development using 3D printing. Drug Discov. Today. 23 (8), 1547–1555.

Baek, J.S., et al., 2016. Multi-Drug-Loaded Microcapsules with Controlled Release for Management of Parkinson's Disease. Small. 12 (27), 3712–3722.

Baek, J.S., et al., 2018. Improved Bioavailability of Levodopa Using Floatable Spray-Coated Microcapsules for the Management of Parkinson's Disease. Neuromolecular Med. 20 (2), 262–270.

Cathy, A.J.-D., 2006. Anatomy and physiology of the rabbit and rodent gastrointestinal system. Proc. 110, 9–17.

Chauhan, B., Gupta, R., 2004. Application of statistical experimental design for optimization of alkaline protease production from Bacillus sp. RGR-14. Process Biochem. 39 (12), 2115–2122.

Chen, K., et al., 2018. Study of controlled-release floating tablets of dipyridamole using the dry-coated method. Drug Dev. Ind. Pharm. 44 (1), 116–124.

Dash, S., et al., 2010. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol. Pharm. 67 (3), 217–223.

Diós, P., et al., 2016. Influence of barium sulfate X-ray imaging contrast material on properties of floating drug delivery tablets. Eur. J. Pharm. Sci. 95, 46–53.

Elzoghby, A.O., et al., 2015. Swellable floating tablet based on spray-dried casein nanoparticles: Near-infrared spectral characterization and floating matrix evaluation. Int. J. Pharm. 491 (1–2), 113–122.

Essa, E.A., et al., 2015. Development and evaluation of glibenclamide floating tablet with optimum release. J. Drug. Deliv. Sci. Technol. 27, 28–36.

Fitriani, L., et al., 2017. Formulation of Metformin HCl Floating Tablet using HPC, HPMC K100M, and the Combinations. J. Sains. Farm. Klin. 4 (1), 79–82.

Ford, J.L., 2014. *Design and evaluation of hydroxypropyl methylcellulose matrix tablets for oral controlled release: A historical perspective.* AAPS Adv. Pharm. Sci. Ser. 16, 17–51.

Fu, J., et al., 2018. Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. Int. J. Pharm. 549 (1–2), 370–379.

Fukuda, M., et al., 2006. Floating hot-melt extruded tablets for gastroretentive controlled drug release system. J. Control. Release. 115 (2), 121–129.

Gong, L., et al., 2018. Development and Evaluation of Compression Coating Gastro-Floating Tablet of Alfuzosin Hydrochloride for Zero-Order Controlled Release. AAPS PharmSciTech. 19 (7), 3277–3286.

Goole, J., Amighi, K., 2016. 3D printing in pharmaceutics: A new tool for designing customized drug delivery systems. Int. J. Pharm. 499 (1–2), 376–394.

Guguloth, M., et al., 2011. Development of sustained release floating drug delivery system for norfloxacin: in vitro and in vivo evaluation. PDA J. Pharm. Sci. Technol. 65 (3), 198–206.

He, W., et al., 2014. Gastro-floating bilayer tablets for the sustained release of metformin and immediate release of pioglitazone: Preparation and in vitro/in vivo evaluation. Int. J. Pharm. 476, 223–231.

Iglesias, N., et al., 2020. In-Depth Study into Polymeric Materials in Low-Density Gastroretentive Formulations. Pharmaceutics. 12 (636), 1–49.

Jyoti, G., 2019. Optimization of esterification of acrylic acid and ethanol by box-behnken design of response surface methodology. Indian J. Chem. Technol. 26 (1), 89–94.

Khaled, S.A., et al., 2015. 3D printing of five-in-one dose combination polypill with defined immediate and sustained release profiles. J. Control. Release. 217, 308–314.

Kyobula, M., et al., 2017. 3D inkjet printing of tablets exploiting bespoke complex geometries for controlled and tuneable drug release. J. Control. Release. 261, 207–215.

Li, C., et al., 2019a. Recent progress in drug delivery. Acta Pharm. Sin. B. 9 (6), 1145–1162.

Li, P., et al., 2019b. Flexibility of 3D Extruded Printing for a Novel Controlled-Release Puerarin Gastric Floating Tablet: Design of Internal Structure. AAPS PharmSciTech. 20 (6), 236–313.

Oh, T.-O., et al., 2013. Preparation of highly porous gastroretentive metformin tablets using a sublimation method. Eur. J. Pharm. Biopharm. 83 (3), 460–467.

Okunlola, A., Ghomorai, T., 2018. Development of ibuprofen microspheres using acetylated plantain starches as polymer for sustained release. J. Pharm. Investig. 48 (5), 551–564.

Pasa, G., et al., 2019. Formulation Design and Optimization of Floating Matrix Tablets of Ciprofloxacin HCl by Using HPMC and Ethyl Cellulose with Experimental Design. Asian J. Pharm. Res. Develop. 6, 23–35.

Pawar, V.K., et al., 2011. Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. Drug Deliv. 18 (2), 97–110.

Qin, C., et al., 2018. Design and optimization of gastro-floating sustained-release tablet of pregabalin: In vitro and in vivo evaluation. Int. J. Pharm. 545 (1–2), 37–44.

Quan, Z., et al., 2015. Additive manufacturing of multi-directional preforms for composites: Opportunities and challenges. Mater. Today. 18 (9), 503–512.

Rahamathulla, M., et al., 2019. Development of Valsartan Floating Matrix Tablets Using Low Density Polypropylene Foam Powder: In vitro and In vivo Evaluation. AAPS PharmSciTech. 20 (1), 35–110.

Razavi, M., et al., 2017. Gastroretentive behavior of orally administered radiolabeled tamarind seed formulations in rabbits validated by gamma scintigraphy. Drug Des. Dev. Ther. 11, 1–15.

Saab, M., et al., 2016. Alternative approaches in formulating floating hollow tablets via sublimation technique; a platform tailored drug release profile. Pharmazie. 71 (12), 701–708.

Sadia, M., et al., 2018. Channelled tablets: An innovative approach to accelerating drug release from 3D printed tablets. J. Control. Release. 269, 355–363.

Sangalli, M.E., et al., 2004. Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: a study on process parameters and in vitro performances. Eur. J. Pharm. Sci. 22 (5), 469–476.

Shah, H.P., Prajapati, S.T., 2019. Quality by design based development and optimization of novel gastroretentive floating osmotic capsules of clopidogrel bisulfate. Int. J. Pharm. Investig. 49 (3), 295–311.

Simons, F.J., Wagner, K.G., 2019. Modeling, design and manufacture of innovative floating gastroretentive drug delivery systems based on hot-melt extruded tubes. Eur. J. Pharm. Biopharm. 137, 196–208.

Singh, B.N., Kim, K.H., 2000. Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention. J. Control. Release. 63 (3), 235–259.

Stepensky, D., et al., 2001. Preclinical evaluation of pharmacokinetic-pharmacodynamic rationale for oral CR metformin formulation. J. Control. Release. 71 (1), 107–115.

Strusi, O.L., et al., 2008. Module assemblage technology for floating systems: in vitro flotation and in vivo gastro-retention. J. Control. Release. 129 (2), 88–92.

Tan, D.K., et al., 2018. Advanced Pharmaceutical Applications of Hot-Melt Extrusion Coupled with Fused Deposition Modelling (FDM) 3D Printing for Personalised Drug Delivery. Pharmaceutics 10 (4), 203.

Thapa, P., Jeong, S.H., 2018. Effects of Formulation and Process Variables on Gastroretentive Floating Tablets with A High-Dose Soluble Drug and Experimental Design Approach. Pharmaceutics 10 (3), 161.

Tripathi, J., et al., 2019. Current State and Future Perspectives on Gastroretentive Drug Delivery Systems. Pharmaceutics 11 (4), 193.

Ulker, Z., Erkey, C., 2014. An emerging platform for drug delivery: Aerogel based systems. J. Control. Release 177 (1), 51–63.

Unal, O., 2016. Optimization of shot peening parameters by response surface methodology. Surf. Coat. Technol. 305, 99–109.

Upadhyay, P., et al., 2014. Studies on biological macromolecules lipid-Gelucire based gastroretentive multiparticulate. Int. J. Biol. Macromol. 67, 463–477.

Upasani, A., et al., 2014. Design and optimization of sustained release matrix tablet of opipramol HCL by using quality by design approach. Asian J. Pharm. Clin. Res. 7 (5), 227–234.

Venkata Srikanth, M., et al., 2012. Statistical design and evaluation of a propranolol HCl gastric floating tablet. Acta Pharm. Sin. B. 2 (1), 60–69.

Wang, S., et al., 2019. Formulation and evaluation of gastric-floating controlled release tablets of Ginkgolides. J. Drug Deliv. Sci. Technol. 51, 7–17.

Widmark, J.M., 2007. Imaging-related medications: a class overview. Proc 20 (4), 408–417.