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ORIGINAL ARTICLE

Development of 3D Printed Gastroretentive Floating Tablet Devices for Metronidazole

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ABSTRACT

Background: In this study, 3D printed floating tablet devices for Metronidazole (MTZ) were developed to prolong its exposure with *Helicobacter pylori* and eradicate it from causing peptic ulcer.
Objectives: To utilize Quality by Design (QbD) in the development of the tablet devices through Fused Deposition Modelling (FDM) 3D printing. This aimed to develop and construct optimized design dimensions of tablet devices subject for characterization.
Methodology: Tablet designs were established using QbD, Design Failure Mode Effect and Analysis (DFMEA) and 2^2 factorial design. Four floating tablets devices were developed through FDM 3D printing using Polyvinyl alcohol (PVA) filament. Characterization tests determined their dimensions, density, floating mechanism, *in vitro* dissolution rate, drug release kinetics, surface morphology, infill and thermal characteristics. Significance of the QbD model was also assessed.
Results: Density of all devices were less than 1.004 g/cm^3. The floating Lag time (FLT) showed instant floatation and Total Floating Time (TFT) lasted for an average of 1 hour. Drug release kinetics show Korsmeyer-Peppas kinetics. Thermal characteristics fall within 186.12°C-187.27°C. 3D CT X-ray results show accuracy of printing 3D renders. Tablet device 3 exhibited the best surface morphology, longest floating time and slowest drug release.
Conclusion: The study successfully developed 3D printed floating tablet devices for Metronidazole with sustained release mechanism. Thus, utilizing QbD in pre-formulation studies using novel technology is essential in optimizing drug dosage forms. Plots from Design Expert Software show the significant design models.

Introduction

Peptic ulcer disease (PUD) is a persistent inflammation of the gastric mucosa which is usually caused by the excessive use of NSAIDs and the pathogen known as *Helicobacter pylori*. Studies show that bacteria-induced PUD is prevalent in patients with duodenal (73-100% prevalence) and gastric ulcer (65-100% prevalence) [1]. In Asia, the studies published over the last year showed high prevalence rates of *H. pylori* infection ranging from 54% to 76% [2]. It is found that the pathogen resides in the deep parts of the gastric mucosa and resists gastric acid, thus, the failure of eradication of this pathogen results in the recurrence of ulcer.

The treatment regimen consists of antibiotics, bismuth salts, and proton pump inhibitors drugs. However, available drugs have the risk to be metabolized and degraded rapidly by the acid medium and must be absorbed in the small intestine before it can elicit a systemic action [3]. Thus, the transit time of the drug and the elapsed opportunity to eliminate the pathogen at its target site reduces optimal therapeutic outcomes, produces drug side effects, and decreases drug absorption.

To address these, a drug delivery system known as Gastroretentive Drug Delivery System (GRDDS) is explored. They prolong the residence time, enhance bioavailability and effectiveness of orally administered drugs in the stomach or upper gastrointestinal tract (GIT) through floatation. Several studies explored the development of floating devices that encloses a drug through three-dimensional (3D) printing.

3D printing or additive manufacturing, employs layer-wise fabrication, offering design freedom in manufacture compared with traditional manufacture. The technology creates models from a computer aided design (CAD) and slicing software, and from a filament, an object is 3D printed. It enables localized production for pharmaceuticals and uses lesser excipients.

In a study, a 3D printed tablet device comprised a body and a cap printed from polyvinyl alcohol (PVA) and enclosed Metronidazole [3-4]. Their design has an air compartment of 132 mm3 inside for floating and a pore (2.0 mm) for drug release. Their device floated immediately and for 4 hours and had 88% drug release in 8 hours and showed zero-order drug release.

A study also developed a capsule-shaped floating device (CFD) using Fused Deposition Modelling (FDM) for domperidone (DOM) tablets (Motilium-M®) using hydrophilic PVA cap and hydrophobic polylactic acid (PLA) filament [5]. PVA allowed easy dissolution while PLA prevented abrupt drug release. Increasing the cap thickness increased the total floating time (TFT) while decreasing the size of the holes led to a sustained release. One design with 1.3-mm cap thickness and 1.5-mm hole width had approximately 98% release in 10 h and has zero-order kinetics ($R^2 > 0.95$).

A study used Quality by Design (QbD), specifically, central composite design (CCD) using hot melt extrusion-based (HME) FDM 3D printing and evaluated the structure-function relationship of various 3D printed tablets [6]. The shell thickness and infill densities were significant (p-value < 0.05) to the tablet's weights and mechanical properties, and the Design of Experiments (DoE) on *in vitro* drug release showed that the selected individual variables had a significant effect on the amount of drug released at a certain time point as well as drug release rate. A preliminary paper by the author also considered the technical aspects, optimal CAD and 3D printer settings of the tablet devices [7].

From these, this study applied Quality by Design (QbD) in the development of the gastroretentive floating tablet devices for Metronidazole from a PVA filament through FDM 3D printing. It is aimed to construct dimensions and optimize the design of the tablet floating device.

This study significantly aims to increase compliance among patients with PUD and to improve dosage form of Metronidazole while exploring the potential of 3D printing in pharmaceuticals [8]. The need for a localized

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manufacture is also explored due to the limitations brought by the Covid-19 pandemic. To date, there are no 3D printing studies pharmaceutical development published in the Philippines, thus, this study can serve as a reference for future research on 3D printing.

Methodology

2.1. Materials And Equipment

PVA (eSUN Industrial Co., Ltd., Shenzhen, China) procured from Makerlab (Makerlab Electronics, Manila, Philippines) is the feedstock material used to develop a 3D tablet device. A benchtop 3D printer (Ender 3 Pro, Creality, Shenzhen, China) is used for 3D printing. The tablet devices were also printed in course of few days to a week to ensure that the quality of the filament is retained and prevent the risks of hygroscopicity. When not in use and following its storage condition, the filament is stored in a cool dry place in tightly closed container in a well-ventilated environment.

The device shall enclose a commercial tablet, Metronidazole (Flagyl forte) 500 mg, procured from a community pharmacy. The medium used was 0.1 N HCl will be utilized for floating and dissolution tests. The pH shall be determined through a pH meter (Starter 3100, Ohaus, Germany).

This study used an estimated amount of 65 Metronidazole tablets. This study performed triplicate testing of the floating ability of 5 prototype designs with 4 variations and each enclosed Metronidazole. Lastly, extra Metronidazole (Flagyl forte) tablets were used as necessary in other tests.

2.2. Quality by Design (QbD) Formulation

Following US Food and Drug Administration (FDA) and International Council on Harmonization (ICH) on the development of novel pharmaceuticals, this study utilized a QbD approach [8-11].

First, was to develop a Quality Target Product Profile (QTPP) to have a guideline of the target formulation. Secondly, Critical Quality Attributes (CQAs) were constructed to develop controls. Then, risk assessment is performed using Design Failure Mode Effect Analysis (DFMEA). The DOE used a 2^2 factorial design with main factors (x_1, x_2) and responses (y_1, y_2). This determined the total number of formulations, 12 runs (4 devices, triplicate tests) will be performed in this study and will be plotted in the Design Expert software (ver. 13.0.7.0).

2.2.1 3D Printing And Tablet Device Design

SolidWorks (ver. 2021-2022) software will be used to design the templates of the tablets and exported as a stereolithography (.stl) file into the 3D slicing software, Cura (ver. 4.10.0).

2.2.2. 3D Printing Post Processing

After printing, the tablet devices were cooled down before their removal from the glass build plate using a steel spatula. Their skirt adhesion was cut and the tablet devices were cleaned accordingly and stored in amber colored bottles. The quality control techniques must still be explored, but for this study, the cap and body were fused while using gloves to prevent moisture adherence.

2.3. Quality Control (QC) Tests

Most QC tests were conducted at laboratories in the College of Pharmacy, University of the Philippines, Ermita, Manila. The surface morphology through Scanning Electron Microscopy (SEM) was conducted in Phenom Lab, De La Salle University, Taft Ave., Manila. The tests for infill characteristics through Computed Tomography (CT) Scanning and thermal analysis through Differential Scanning Calorimetry (DSC) were conducted in Advanced Device and Materials Testing Laboratory (ADMATEL), Department of Science and Technology (DOST), Taguig. All tests were done in triplicate.

2.3.1. Tablet Device Dimensions

Tablet dimensions were measured through the use of a Vernier caliper. The dimensions of the tablet device were designed through the SolidWorks Software (ver. 2021-2022). Their visual appearance is recorded accordingly.

2.3.2. Tablet Weight and Tablet Density

Density can be utilized to test and establish floating mechanism. The tablet radius (r) and height (h) in millimeters are measured by vernier caliper. The tablet weight (W) in grams are measured through a weighing balance (ATY224R, Shimadzu, Japan). From references, the density must be ± 1.004 g/cm3. The volume of the cylindrical tablet devices is computed as: $V = \pi r2h$. The density is calculated as: p = mass (m)/volume (v).

2.3.3. *In Vitro* Buoyancy Characterization

Floating Lag Time (FLT)

Floating lag time is the time period which a dosage form requires to rise to the surface of the dissolution medium after being immersed into the liquid [12]. Floating behavior was determined in the same way as the vitro drug release studies USP apparatus II (Varian VK 7000, Agilent, USA) with a paddle speed of 75 rpm [3]. The protocol is to cast a test tablet 3D printed tablet into the 900 ml dissolution media or simulated gastric fluid (0.1 N, pH 1.2) and start the timer, stop and note until the tablet floats up for equal or less than 60 seconds and remains stable on the surface of the relative medium. The total floating time was then recorded.

Total Floating Time (TFT)

This is to measure the floating duration or time period in which the dosage form floats constantly in the experimental setup [12]. The determination was carried out as in FLT and vitro drug release studies. Time during which the tablet keeps floating constantly on the surface of the medium is recorded [13].

2.3.4. *In Vitro* Dissolution

Metronidazole release from floating housings are investigated using a USP dissolution apparatus II with paddles, which were operated at a speed of 75 rpm. The 900-ml volumes of simulated gastric fluid (0.1 N HCl) were used as dissolution media are placed into glass vessels, the apparatus is assembled and the dissolution medium is equilibrated to 37 °C ± 0.5 °C.

Aliquots of test fluid (5 ml) are then taken using a 5 ml syringe after 5, 10, 15, 30, 60, and 120 min and were replaced with similar volumes of fresh media to maintain sink concentrations. The study utilized a UV spectrophotometer (Genesys 10S, Thermoscientific, USA) at about 278 nm of filtered portions of the solution under test, suitable diluted with 0.1 N HCl, in comparison with a standard solution having a known concentration of Metronidazole in the same medium.

Metronidazole concentrations were calculated using a standard curve. *In vitro* release studies were conducted in triplicate, and mean percentage drug release was plotted against time [13].

2.3.5. Kinetics of drug release

Kinetic models were computed and assessed to several kinds of kinetic models (zero-, first-order, Higuchi, Korsmeyer-Peppas) applied to elucidate drug release behaviors. The optimal fit was determined with the model with the highest correlation coefficient (R) which were computed using the excel add-in, DD solver.

2.3.6. Surface Morphology

Surface morphology of the tablet devices were evaluated by SEM (SEM Phenom XL, Thermo Fisher, USA) which features a newly designed chamber including a compact motorized stage that allows analysis of samples of up to 100 mm x 100 mm. In this study, the magnification used was 300x. Since the sample was not conductive, gold has been sputtered in the sample.

2.3.7. Infill Characteristics

A high-resolution 3D Computed Tomography X-ray scanner (NSI X5000, North Star Imaging, USA) was utilized to check the internal structure of the tablets.

2.3.8. Thermal Analysis

Samples (raw materials, extruded filaments and printed tablets) were characterized using differential scanning calorimeter (DSC 4000, PerkinElmer, USA). The samples (5-10 mg) are placed in a standard aluminum pans and covers and heated over the temperature range of 30–430 °C at a purge gas pressure at 2.0 to 3.0 bar (typically at 30 to 40 psi in the regulator).

2.3.9. Statistical Analysis

All experiments were carried out in triplicate. The results are reported as the mean standard deviation (SD). Depending on the data gathered, one-way ANOVA and ANOVA were measured to determine the significance of the difference of the characterization tests and factorial design. The significant level was set at $p < 0.05$.

Results

3.1. Quality by Design (QbD) Formulation

3.1.1. Quality Target Product Profile (QTPP)

In Table 1, all QTPP elements have been achieved. Although some elements may not have been achieved perfectly, the data gathered in this study is sufficient to optimize the drug devices further.

Table 1. Summary of quality target product profile (QTPP) for gastroretentive tablet devices for Metronidazole

QTPP ELEMENT	TARGET	JUSTIFICATION	COMPLIANCE (YES/NO)	NOTES
Formulation				
Dosage form	Gastroretentive tablet device	Prolong gastric residence time Increased therapeutic efficacy by improving drug absorption Allows targeted delivery in the stomach until the drug is completely released from the dosage form To increase contact time of Metronidazole with *H. pylori* To enclose Metronidazole tablet	Yes	Oral dosage form, GRDDS tablets developed through 3D printing
Route of administration	Oral	Dosage form designed to be administered orally	Yes	Oral tablet device is developed
Dosage strength	500 mg	Dosage strength of Metronidazole to eradicate *H. pylori*	Yes	Metronidazole (Flagyl forte) used has 500 mg dosage strength
Drug product quality attributes				
Physical Attributes Density Dissolution	No physical defect $\leq$ 1.004 g/cm^3 Sustained release	Meeting the compendial or other applicable (quality) standards To render floatation Sustained release for decreased drug administration	Yes Yes Yes	No physical defect, infill characteristic intact Density lower than 1.004 g/cm^3 Floatation is achieved equating to sustained release mechanism
Floating lag time Total floating time	Minimum lag time, 0-3 mins Maintains its floating force until complete drug release & exhibits a floating force decrease to zero	Increased possibility of prolonged gastric residence time of tablet device Tablet should continuously float in the medium. If not, gastric emptying of device is likely to occur, which can be considered as a failure	Yes Yes	Tablet devices float instantly. PVA tablet device dissolves prematurely while Metronidazole tablet is still undergoing release.
Drug release kinetics	Correlation coefficient ($R^2 > 0.9$) and release exponent ($n > 0.89$)	To determine the best fitted release kinetic	Yes	The best fitted model of the devices closest to 1 fall under Korsmeyer- Peppas mechanism.
3D Printing Characteristics				
Surface morphology	Smooth surface	Decreased degradation Meeting the compendial or other applicable (quality) standards Better resolution of 3D printing	Yes	Tablet 3 exhibits most consistent tablet layer
Degradation products	Minimal degradation	Increased thermal stability	Yes	Thermograms are within limits (190 ^{o}C-210^{o}C)
Infill Characteristics	Assess tablet internal structure	3D design accomplished	Yes	3D render is printed based on CAD design

3.1.2. Risk Assessment

The initial design runs and dimensions were tested to assess optimal dimensions (air holes, height, thickness, infill density, and size). The parameters with the highest risks priority numbers (RPN) were wall thickness (RPN= 75) and the design (RPN= 60) itself presented challenges in the formulation. We also need to take into account the variables, total floating time (TFT) and % drug release at the maximum time the tablets cease to float.

In summary from the DFMEA, the following are notable design failures encountered:

1) Tablet devices with infill less than 100 % floated shortly and some runs did not float at all. This is because the incomplete infills makes the walls thinner and allows the solvent to permit easily.
2) Devices with wall thicknesses lesser than 2.0 mm did not float optimally. Wall thickness larger than this made the device heavier and sunk instantaneously.
3) Designing air holes on the sides or lock of the tablet device increased solvent penetration.
4) Omitting air holes prevent the release of the enclosed drug.
5) Tight fitting tablet designs only seem as a secondary tablet coating and made the devices sink. The devices should have dimensions larger than the enclosed tablet to encourage drug release and floatation as voids in the spaces allows buoyancy.
6) Air pockets are important in creating buoyancy of the tablet devices.

3.1.3. Design of Experiments (DOE)- 2^2 Factorial Design

The factors and responses deemed to affect the overall essence of the floating devices are the TFT (min) and drug release (%). Due to the limited feasibility of conducting multiple runs in this study, it is suggested that other factors and responses must also be assessed for future studies.

3.2. Tablet Device Dimensions

The design for 3D printed devices was based on optimization of QbD results. The 3D renders and the actual printed models are shown in the next sections.

The tablets are larger than what is accepted in the market because the available tablet enclosed is large in nature (dimension). In other studies, they presented accepted tablet devices because they either manufactured pills or enclosed pills but due to the time constraints of the pandemic, this has not been possible to explore in this study. This gives the formulator the opportunity to fine tune and enlarge the device without making the tablet unpalatable.

Table 2. A) Slicer Settings; B) Dimensions of the tablet devices; C) 3D renders of the tablet devices; D) Actual images of the tablet devices.

3.3. Tablet Weight And Tablet Density

3.3.1. Tablet Weight

The tablets are weighed with or without enclosed Metronidazole tablets. The heaviest tablet is the tablet device 3 (wall thickness= 2 mm, airhole diameter= 5 mm) at 1.99 g without Metronidazole and 2.70 g with Metronidazole. Tablet device 2 (wall thickness= 1.5 mm, airhole diameter= 10 mm) is the lightest at 1.53 g without Metronidazole and 2.29 with Metronidazole which is due to its thin walls at 1.5 mm and airhole diameter of 10 mm cutting out more surface of the device.

Table 2A. Slicer settings

SLICER SETTINGS	PARAMETER
Layer Height	0.1 mm
Infill Density	100 %
Printing Temperature	190 ºC
Printing speed	50 mm/s
Build plate adhesion	Skirt
Fan speed	100 %

Table 2B. Dimensions of the tablet device

TABLET DEVICE	DIMENSIONS (mm)			
	OUTSIDE DIAMETER	INSIDE DIAMETER	WALL THICKNESS	AIRHOLE DIAMETER
1	17.5	15	1.5	5
2	17.5	15	1.5	10
3	17.5	14	2	5
4	17.5	14	2	10

Statistical analysis: In Appendix 1a, it shows the results of the One-way Analysis of Variance for weight. Alpha value of 0.05 was used in the study. The mean weight of the tablet as well as the standard deviation are presented. The standard deviations (SD) obtained signify the homogeneity. Weights of tablets 3 and 4 are found to be significantly different from tablets 1 and 2 in terms of the tablet's body.

3.3.2. Tablet Density

The tablet densities are presented in table 3. In this study, tablet device 3 floated the longest at an average of 76 mins because its wall thickness of 2.0 mm helped in slowing down the penetration of the dissolution medium. Thus, careful consideration of other factors such as thickness, airhole diameter, infill density and the filament used is important in the improvement of the desired formulation. In 3D printing parameters, "infill density" can be interchanged with density. It is the parameter utilized when making a 3D structure hollow, and weigh lighter and a characteristic taken into account in risk analysis (DFMEA).

Statistical analysis: The mean densities of the tablets are shown in Appendix 1b along with the corresponding standard deviations. SD was found to be homogeneous. In terms of the body of the tablet, the density of tablet 4 was found to be different from tablets 1, 2 and 3.

3.4. *In Vitro* Buoyancy Characterization

3.4.1. Floating Lag Time (FLT)

The floating lag time (FLT) of the devices instantaneously at 0 min, which supports floatation of Metronidazole. The Metronidazole tablet sank at the bottom of the vessel. Immediate floatation can be also attributed to several factors of the tablet design such as the presence of air pockets, wall thickness and density of the devices. Similarly, a patent US 1990/0629918 in the development of an extended release Metronidazole capsule composed of a layer which provides floating of the system, this can be attributed similarly to the air pocket present in the tablet design. The force of dissolution may vary from the actual forces governing our gastric system, thus, *in vivo* floating studies are also recommended.

3.4.2. Total Floating Time (TFT)

In Table 3, the total floating time of the tablet devices were close to 1 hour while the Metronidazole sank at the bottom. Among the tablets, tablet device 3 floated the longest for 76 mins. This mechanism helps in the prolongation of the exposure of the drug, Metronidazole, to *H. pylori*. There is also no specific target floating time for the devices since limited actual data were present.

Although multiple structural specifications were considered, the main variable that may have caused short floating time is the filament. Indeed, there are types of destruction at the solid-liquid interfaces observed for different combinations of polymeric materials and solvents [14].

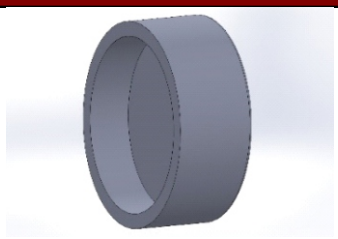
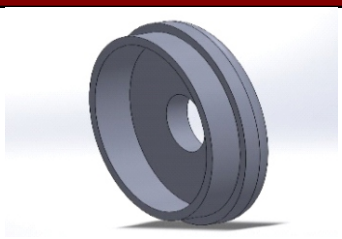
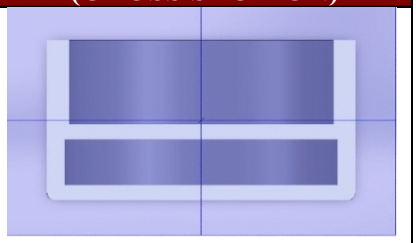
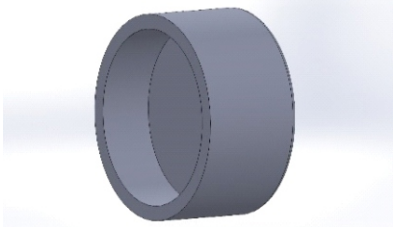
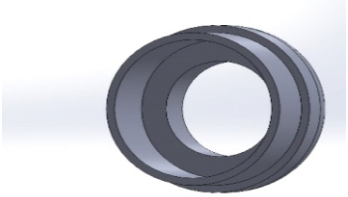
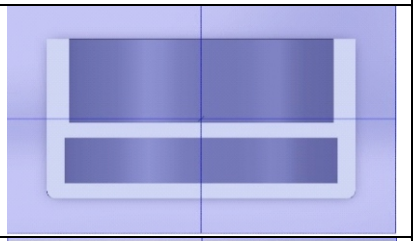
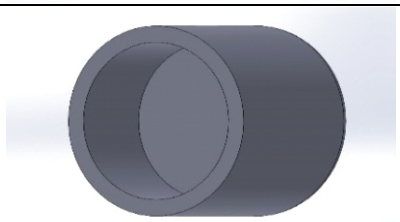
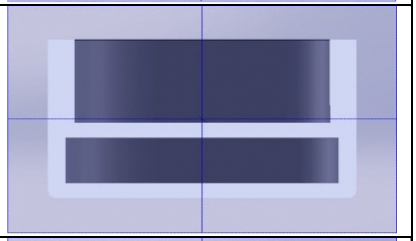
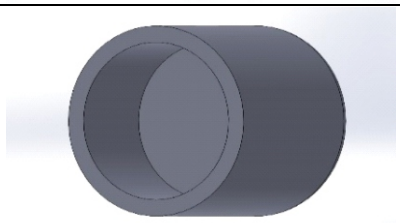
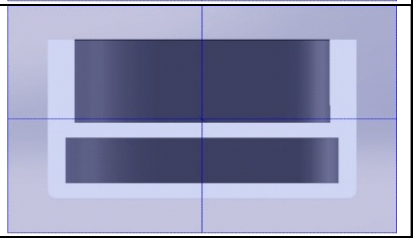
Statistical Analysis: In appendix 1c, the floating time of the four tablets was compared using one-way Analysis of Variance. A p-value of 0.012 (F= 7.093) revealed that there is a significant difference between the floating time but no statistical difference among the four tablets.

3.5. *In Vitro* Dissolution

As seen in Table 3 and Figure 1, ranking them according to the fastest to slowest drug release is as follows the order of Tablet device 2, Tablet device 1, Tablet device 4 and Tablet device 3.

The tablet devices 1 & 2 with thinner walls, are expected to dissolve faster than tablet devices 3 & 4. Tablet devices with narrower air holes (Tablets 1 and 3) are also expected to have lesser % drug release versus tablet devices (Tablets 2 and 4) with wider air holes. Thus, the thicker the wall and the narrower the airhole diameter is, the more prolonged the drug release is.

Table 2C. 3D renders of the tablet devices

TABLET DEVICE	BODY	CAP	BODY (CROSS SECTION)
1			
2			
3			
4			

On the specifications for test procedures and acceptance criteria of new drug products, the acceptance criteria should be established on the basis of available batch data. Since this study focused on the development and exploration of 3D printed floating tablet devices, only a small batch was produced. Although the drug release rate for the tablets from 5 mins to 30 minutes did not exceed a variability of +/-10% of the labeled content of drug substance, more data and bioequivalence tests must be made to arrive and develop an acceptance criterion for dissolution [14-16].

Statistical Analysis: In Appendix 1d, results revealed a p-value of <0.01 for the first 5 to 60 minutes of the drug release. This indicates that the tablets significantly differ on the basis of drug release time within 5, 10, 15, 30 and 60 minutes. This indicates that the drug release time of the 5 tablets do not significantly differ after 2 hours.

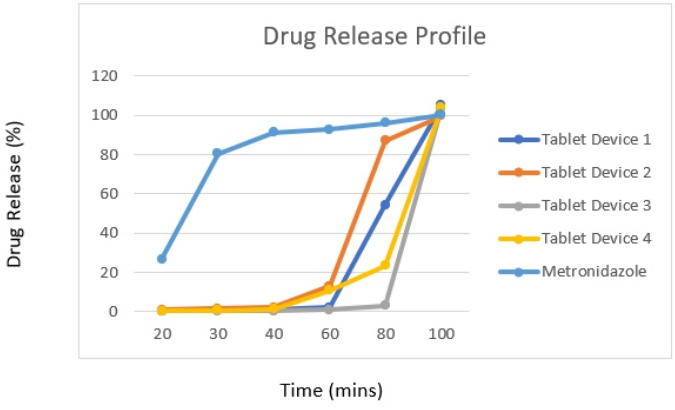


Figure 1. Drug release profile of tablet devices

3.6. Kinetics of Drug Release

In Table 3, using the drug release excel add-on DDsolver [17], it is found that the R^2 and n values of the devices correspond to Korsmeyer-Peppas (Supercase II) drug release kinetics. On the other hand, Metronidazole exhibited R^2 of 0.8545 and n of 0.197 falling under first order kinetics.

This is a conclusive drug release kinetic for the devices because this mechanism describes drug release from polymeric systems with prolonged release [18]. In the computation of the values, the structural modifications and geometrical characteristics of the system are involved. The n is the exponent of release (related to the drug release mechanism) in function of time

3.7. Design of Experiments (DOE)

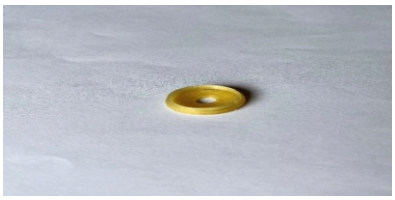
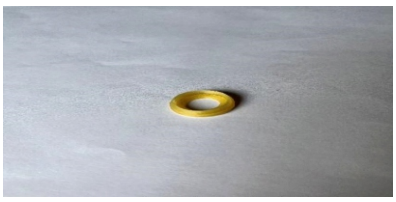
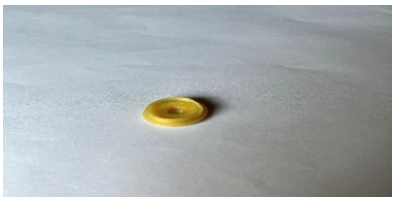
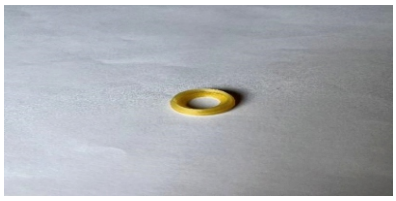
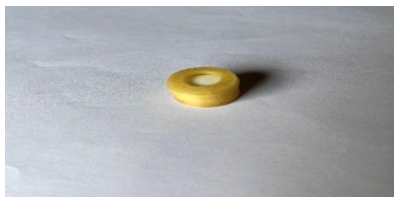
The results from characterization tests are plotted in the Design Expert Software (ver. 13.0.7.0) to assess its significance and the correlation between the factors and responses.

3.7.1. Significance of the Model

ANOVA of Total Floating Time: In Appendix 2a, the Model F-value of 11.34 implies the model is significant. There is only a 0.35% chance that an F-value this large could occur due to noise. P-values less than 0.05 indicate model terms are significant. The Lack of Fit F-value of 0.32 implies the Lack of Fit is not significant relative to the pure error. Non-significant lack of fit is good as we want the model to fit.

Fit Statistics on Total Floating Time (TFT): In Appendix 3a, the Predicted R^2 of 0.4948 is in reasonable agreement with the Adjusted R^2 of 0.6527; i.e. the difference is less than 0.2. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 7.060 indicates an adequate signal. This model can be used to navigate the design space.

Table 2D. Actual images of the tablet devices

TABLET DEVICE	BODY	CAP	CLOSED
1			
2			
3			
4			

ANOVA of Drug Release at 1 hour: In Appendix 3b, the Model F-value of 29.15 implies the model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.05 indicate model terms are significant. In this case A, B are significant model terms. The Lack of Fit F-value of 0.55 implies the Lack of Fit is not significant relative to the pure error. Non-significant lack of fit is good since we want the model to fit.

Fit Statistics on Drug Release at 1 hour: In Appendix 3b, the Predicted R^2 of 0.7623 is in reasonable agreement with the Adjusted R^2 of 0.8366; i.e. the difference is less than 0.2. Adequate Precision measures the signal to noise ratio. A ratio greater than 4 is desirable. The ratio of 11.6981 indicates an adequate signal. This model can be used to navigate the design space.

Optimized model: As computed in the design expert software, the optimized model has the total floating time (TFT) of 75.500, drug release at one (1) hour of 0.106 % with the highest desirability of 0.892 resulting with dimensions designed into Tablet device 3.

3.8. Surface Morphology

As shown in table 4, Tablet device 3 shows the consistent filament layers without cracks and tears. Notably, tablet device 3, with the best morphology exhibited the longest drug floatation among the devices. The surface morphology of the tablets is important with reference to its drug release as inconsistent layers present structural defects and consistent layers help in achieving better drug release due to much improved mechanical strength, adhesion bonding and resistance against the solvent (0.1N HCl). Surprisingly, all of the devices followed the same slicer settings (Table 2a).

3.9. Infill Characteristics

Table 4 shows the most acceptable X-ray images among the 3D printed tablet devices for Metronidazole. The X-ray images show the presence of the air pocket which allows the floatation of the device. The cap and body also fit snugly with each other, enabling a suitable enclosure of the tablet.

Although the printer showed accuracy in printing desired tablet devices, it should be noted that there are filament strands present between the air holes and inside the air pockets. This may be attributed to the sudden change of design structure or the direction of the nozzle as it works its way up when forming the body. The filament may have also not solidified well during the 3D printing. This also shows that the tablet devices are indeed created layer-by-layer, from top to bottom. Although PVA filament displays biocompatibility with drugs, drug-filament interaction between Metronidazole must be explored [18-20].

3.10. Thermal Analysis

The melting temperature of the blank and the PVA was observed at about 170 °C (166.55 °C). The printed tablet devices were at about 186 °C (186.12

Table 3. Summary of Characterization Tests

CHARACTERIZATION TESTS	TABLET DEVICE			
	1	2	3	4
3.3. Tablet Weight and Tablet Density				
3.3.1a. Empty Tablet Weight (g)	1.68	1.58	1.99	1.81
3.3.1b. Tablet Weight with MTZ (g)	2.38	2.29	2.70	2.51
3.3.2a. Empty Tablet Density (g/cm^3)	0.55	0.53	0.66	0.60
3.3.2b. Tablet Density with MTZ (g/cm^3)	0.79	0.76	0.90	0.83
3.4. *In vitro* Buoyancy Characterization				
3.4.1. Floating Lag Time (mins)*	0	0	0	0
3.4.2. Total Floating Time (mins)*	62	59	76.33	70
3.5. *In vitro* dissolution (%)				
a. 5 min	0.36	0.87	0.26	0.44
b. 10 min	0.64	1.64	0.35	0.74
c. 15 min	1.18	2.25	0.43	1.41
d. 30 min	2.25	13.07	1	10.76
e. 60 min	54.39	87.16	3.25	23.44
f. 120 min	104.92	99.76	103.48	103.76
3.6. Drug Release Kinetics				
3.6.1. Korsmeyer-Peppas (Supercase II) Drug release Kinetic Model (R^2)**	0.9583	0.856	0.9999	0.997
3.6.2. Korsmeyer-Peppas (Supercase II) Drug release Kinetic Model (n)	1.39	0.976	4.968	2.015

* Metronidazole alone sunk immediately
** Metronidazole exhibited R2 of 0.8545 falling under first order kinetics.

Table 4. a) SEM image of tablet device 3 b) CT X-ray Images of tablet device 3 c) Thermal analysis of tablet devices

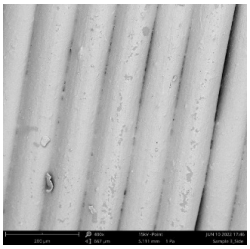
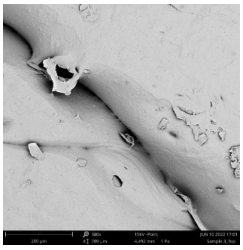
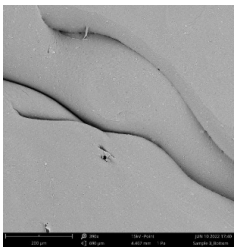
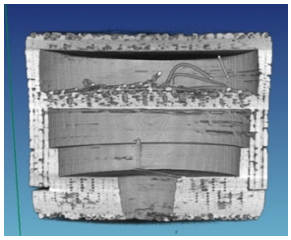
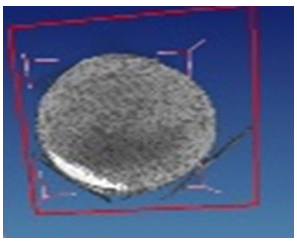
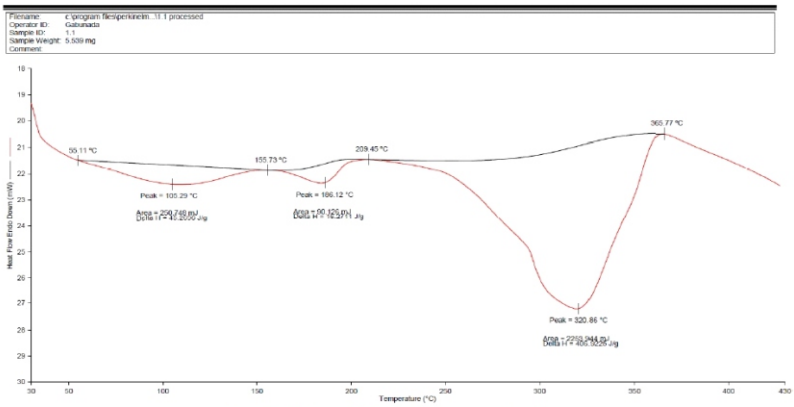
	SIDE	TOP	BOTTOM
a			
b			
c			

Figure 3. DSC Curve of *3D Printed Tablet Device - 1.1* sample.

°C-187.27 °C). In determining glass transition, peaks will show an abrupt and linear rise in signal before quickly leveling out. Glass transition temperatures are 179.65°C for the PVA filament then 155.73°C, 156.75°C, and 156.41°C for the printed tablet devices.

On the endothermic graph, slopes depict the melting point of the PVA. At temperatures of 250 °C and higher, we can see a drastic downward slope which represents PVA degradation. PVA filament should only be prepared in its prescribed range of 180 °C to 210 °C, as this study has observed with 190 °C.

A strict control over the filament diameter and shape is needed, as dimensional fluctuations cause changes in the flow of material through the nozzle and subsequent potential nonconformities in printed part dimension [21-24]. This may also affect the morphology, drug release and kinetics [25-26]. To gauge the thermal degradation, this study also suggests further thermal imaging tests such as thermogravimetric analysis (TGA).

Statistical analysis (Endothermic Peak Temperature): In Appendix 2e, the SD is heterogeneous. The p-value less of <0.01 was obtained. F value was found to be higher than critical value. Tukey test revealed that the endothermic peak temperature of all four tablets are significantly different from each other. Tablet 4 has no results due to lack of available value to compute peaks.

Statistical analysis (Enthalpy): In Appendix 2f, the mean enthalpy tablets are shown along with the corresponding standard deviations. The SD is heterogeneous. The computed F and critical value were found to be 0.016 and 5.14, respectively, while a p-value greater than the alpha was also obtained. There is no significant difference between the tablets in terms of enthalpy.

Conclusion and Recommendations

The development of optimized tablet devices for Metronidazole were established using Quality by Design (QbD) method using Design Failure Mode Effect and Analysis (DFMEA) and 2^2 factorial method.

The characterization tests conclude that density, structural modifications, and filament material greatly affected the floating mechanism, dissolution, and kinetics of tablet devices. Further studies must be also established to standardize *in vitro* dissolution tests for 3D tablets.

Important structural features of a 3D printed floating tablet device are air pockets and optimized thickness for floating and air holes as a drug release pore. Korsmeyer-Peppas (Supercase II) drug release kinetics of the tablet devices coincided with the QTPP.

When formulating a dosage form using novel techniques, it is important to use QbD methods during drug development as this will serve as a guide in pre-formulation studies. Through mindful selection of factors, optimizers and their respective values, an optimized design was indeed achieved as seen on statistically significant and sound results. It is recommended to have further optimization carried out in the design space by adjusting values on wall thickness and air hole diameter while aiming to achieve longer floating time. The enclosure of smaller-sized pharmaceuticals is encouraged to have more freedom designing tablet devices.

Also, exploration on the use of different filaments must be considered. The development of filaments using industry grade tablet excipients through HME should also be explored. It is also encouraged to assess different 3D printing technologies in the improvement of dosage forms.

For drug release studies, *in vivo* dissolution studies must also be considered. Further studies must be conducted to standardize *in vitro* dissolution test for 3D printed tablet and explore drug-filament interactions of PVA filament and Metronidazole.

As the first study of 3D printed pharmaceuticals in the country, this study serves as a reference for pre-formulation studies for future 3D printed pharmaceuticals.

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Appendix

Appendix 1. ANOVA results of characterization tests

a. One-way ANOVA for Tablet weight						
PARAMETERS	**MEAN**	**SD**	**df**	**SS**	**F**	**p***
1. Empty	1.) 1.67	0.01	11	0.294	204.497	<0.01
	2.) 1.58	0.02				
	3.) 1.99	0.02				
	4.) 1.81	0.03				
2. Cap	1a.) 0.36	0.27	11	0.465	5.967	0.019
	2a.) 0.43	0.01				
	3a.) 0.79	0.01				
	4a.) 0.57	0.01				
3. Body	1b.) 1.16	0.02	11	0.019	6.459	0.016
	2b.) 1.15	0.02				
	3b.) 1.21	0.02				
	4b.)1.24	0.04				
4. with MTZ Tablet	1c.) 2.38	0.01	11	0.288	273.500	<0.01
	2c.) 2.29	0.02				
	3c.) 2.70	0.02				
	4c.) 2.51	0.02				
b. One-way ANOVA for Density						
PARAMETERS	**MEAN**	**SD**	**df**	**SS**	**F**	**p***
1. Empty	1.) 0.55	0.002	11	0.032	204.497	<0.01
	2.) 0.53	0.01				
	3.) 0.66	0.01				
	4.) 0.60	0.01				
2. Cap	1a.) 0.12	0.09	11	0.051	5.967	0.019
	2a.) 0.14	0.004				
	3a.) 0.26	0.004				
	4a.) 0.19	0.003				
3. Body	1b.) 0.39	0.01	11	0.002	6.459	0.016
	2b.) 0.38	0.01				
	3b.) 0.39	0.01				
	4b.) 0.42	0.01				
4. with MTZ Tablet	1c.) 0.79	0.002	11	0.032	273.500	<0.01
c. ANOVA for Total Floating Time of tablet devices and Metronidazole (Flagyl forte)						
PARAMETERS	**MEAN**	**SD**	**df**	**SS**	**F**	**P***
1. Total Floating Time *(in minutes)*	1) 62	1.00	11	763.667	7.093	0.012
	2) 59	5.00				
	3) 76.3	6.43				
	4) 70	6.08				
	N/A					
d. ANOVA for Drug release						
PARAMETERS	**MEAN**	**SD**	**df**	**SS**	**F**	**p***
1. 5 minutes	1) 0.36	0.10	14	1699.704	85.818	<0.01
	2) 0.87	0.49				
	3) 0.26	0.12				
	4) 0.44	0.24				
	(MTZ) 26.64	4.87				
2. 10 minutes	1) 0.64	0.26	14	15244.18	6393.873	<0.01
	2) 1.64	0.42				
	3) 0.35	0.11				
	4) 0.74	0.74				
	(MTZ) 80.52	1.47				
3. 15 minutes	1) 1.18	0.75	14	19523.1	438.015	<0.01
	2) 2.25	0.87				
	3) 0.43	0.11				
	4) 1.41	1.18				
	(MTZ) 91.24	7.26				
4. 30 minutes	1) 2.25	0.94	14	2887.05	273.500	<0.01
	2) 13.07	1.79				
	3) 1.00	0.38				
	4) 10.76	11.53				

Appendix

Appendix 2. ANOVA of the Responses of a) total floating time and b) drug release at 1 hour (Factor coding is Coded; Sum of squares is Type III-Partial)

a) ANOVA of the Responses of Total Floating Time						
SOURCE	**SUM OF SQUARES**	**df**	**MEAN SQUARE**	**F-VALUE**	**p-VALUE**	
Model	546.67	2	273.33	11.34	0.0035	significant
A-Wall thickness	481.33	1	481.33	19.96	0.0016	
B-Airhole diameter	65.33	1	65.33	2.71	0.1341	
Residual	217.00	9	24.11			
Lack of Fit	8.33	1	8.33	0.3195	0.5874	not significant
Pure Error	208.67	8	26.08			
Cor Total	763.67	11				
b) ANOVA of the Responses of Drug Release at 1 hour						
Model	11998.50	2	5999.25	29.15	0.0001	significant
A-Wall thickness	9895.19	1	9895.19	48.08	< 0.0001	
B-Airhole diameter	2103.31	1	2103.31	10.22	0.0109	
Residual	1852.26	9	205.81			
Lack of Fit	118.63	1	118.63	0.5474	0.4805	not significant
Pure Error	1733.63	8	216.70			
Cor Total	13850.75	11				

Appendix 3. Fit Statistics of a) total floating time and b) drug release at 1 hour

a) Total Floating time			
STANDARD DEVIATION	4.91	**R^2**	0.7158
MEAN	66.83	**ADJUSTED R^2**	0.6527
C.V. %	7.35	**PREDICTED R^2**	0.4948
		ADEQUATE PRECISION	7.06
b) Drug release			
STANDARD DEVIATION	14.35	**R^2**	0.8663
MEAN	42.06	**ADJUSTED R^2**	0.8366
C.V. %	34.11	**PREDICTED R^2**	0.7623
		ADEQUATE PRECISION	11.6981