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FORMULATION DEVELOPMENT OF FAMOTIDINE FLOATING TABLETS USING HOT-MELT EXTRUSION COUPLED WITH 3D PRINTING TECHNIQUE.

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FORMULATION DEVELOPMENT OF FAMOTIDINE FLOATING TABLETS USING HOT-MELT EXTRUSION COUPLED WITH 3D PRINTING TECHNIQUE.

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ABSTRACT

The main goal of this study is to develop a floating tablet of famotidine using hot melt extrusion coupled (HME) with Fused deposition modeling FDM 3D printing technology. Seventeen different formulations were prepared to obtain printable HME filaments. Hydroxypropyl cellulose (HPL-LF), hydroxypropyl cellulose (HPLC-EF), Hydroxypropyl Methylcellulose (HPMC-E5), and Ethyl Cellulose (EC) were used as polymeric carriers with 10% (w/w) famotidine. Polyethylene Glycol 1500 (PEG-1500) was used as a plasticizer. The resulting physical mixtures were then extruded using an 11 mm twin-screw co-rotating extruder (Thermo Fisher Scientific, Waltham, MA, USA). The HME filaments were then printed using an FDM-3D printer (Prusa i3 3D desktop printer, Prusa Research, Prague, Czech Republic) with a thickness of 0.4mm, line pattern, and 100% infill at 180 °C printing temperature.

Famotidine, polymeric carriers, other excipient, filaments, and 3D printed tablets were analyzed to determine the physical state of famotidine by using a Differential Scanning Calorimetry (DSC). The *in-vitro* drug release profile of the printed tablets was evaluated. Five filaments (M10, M11, M15, M16, M17) out of seventeen were successfully printable. The tablets were printed in a line pattern and 100% infill with a hollow shape to have a low-density tablet that may reach the target of floating on the surface of the stomach for a more extended time.

The famotidine DSC thermograms showed an endothermic melting peak at 163.5 °C. This endothermic peak disappeared in the extruded filament and the 3D-printed tablets. The

disappeared peak indicates complete solubilization of famotidine in the polymeric carrier for all Five formulations.

Drug content tests were performed from the best-printed tablets for M10, M11, and M17. The accepted formulations for further investigation were M10 and M17, respectively, which showed a release for 9 hours and 8 hours. The floating profile for M10, M11, and M17 was successful for around 8 hours.

HME revealed the great potential to develop suitable filaments for FDM-3D printing. The formulation compositions and printing design and pattern are the keys to developing 3D printed floating tablets for famotidine.

DEDICATION

This work is dedicated to my beloved husband, Dr. Mohammad Alkhatib, who keeps me passionate and motivated, supports me through the tough and good times. To my parents, Abdel Rahman Al Shawakri and Khadeja Najim, supported me throughout the whole journey in my study and life. To my sweet twins, who made my study life intense yet enjoyable. To my sisters and brothers who picked me as their mentor and were motivated by my success. My family in law is considered my second family for all the care and enthusiasm.

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CHAPTER I
INTRODUCTION

Three-dimensional (3D) printing is an advanced technology that involves the layer-by-layer deposition of materials to create a final desired product [1]. 3D printing is a highly revolutionary technology within the pharmaceutical area. Since 3D printed drug was first approved by the US Food and Drug Administration (FDA) Spiritam in 2015, research in 3D printing for drug manufacturing has been expanding. The overall 3D printing types are illustrated in figure 1. 3D printing is considered as an additive manufacturing technology which is used for fabricating parts layer-by-layer directly from a computer-aided design (CAD) data file.

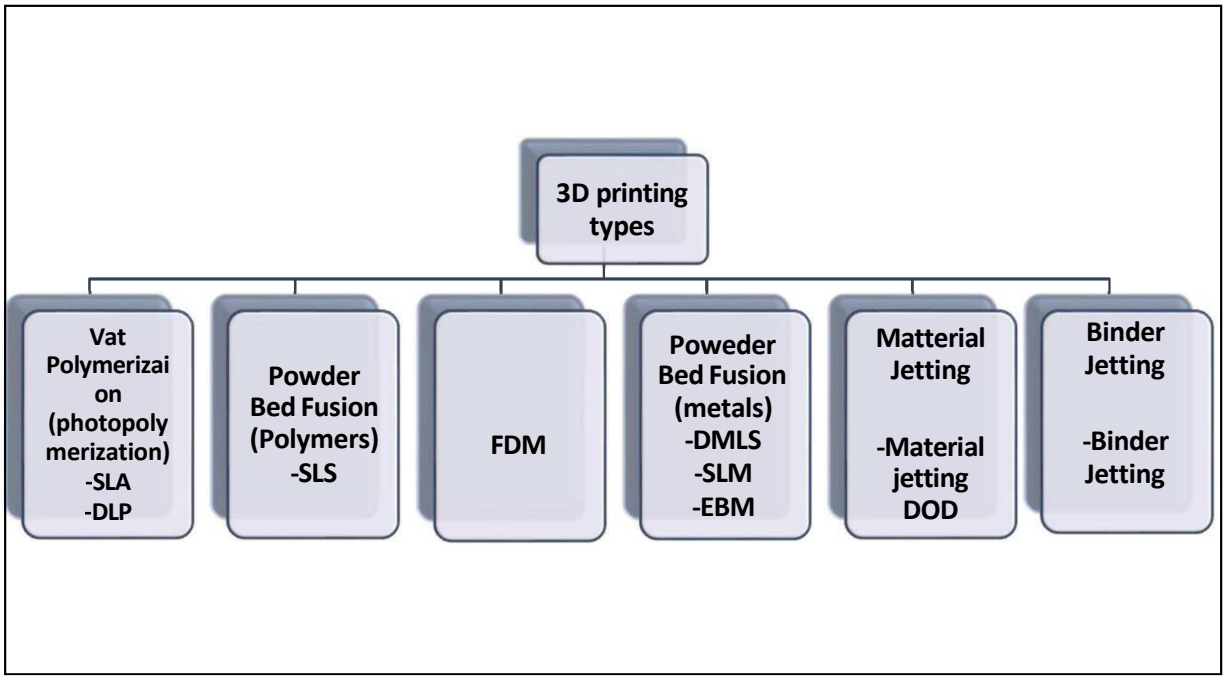


Figure 1: Different 3D printing types.

Stereolithography (SLA) is an industrial 3D printing procedure known as the most common resin 3D printing process. It is used to create concept models, cosmetic prototypes, and complex parts with sophisticated geometries in a brief period [2]. Selective Laser Sintering (SLS) is a subcategory of powder bed fusion 3D printing; it uses a laser beam to create solid items by heating power particles and fusing them at their surfaces.[3]. Inkjet printing is like other 3D printing methods, which continues through layer-by-layer deposition by using low temperature and low pressure to depose liquid materials or solid suspensions[4].

Fused Deposition Modeling (FDM) 3D printing is our research objective type with Hot Melt Extrusion (HME). FDM 3D printing is overall compatible with printing drug products and polymer filaments as materials for drug carriers [5],[6].FDM implies building objects by adding material in a layer-by-layer fashion to create a 3D part, benefiting from generating any design. It provides efficient models in various thermoplastics due to its ability to produce complex geometrical sections nearly and safely in an office-friendly or lab environment[7].

The importance of 3D printing lies in producing small batches of medications with specific dosages, shapes, sizes, and release profiles. The production of drugs using 3D printing may finally lead to the model of personalized medicines becoming a promising target [8].

Hot-Melt Extrusion (HME) began as a novel processing technology in developing solid dispersions of active pharmaceutical ingredients (APIs) into a various polymer or/and lipid matrices [8] Several published reports on the different HME applications in the pharmaceutical area involve solid dispersions, targeted drug delivery systems, sustained-release formulation, films, microencapsulation, nanotechnology, floating drug delivery systems, taste masking, and implants.[9]

Hot Melt Extrusion (HME) is one of the industry's most extensively used processing procedures. It is pumping raw materials with a screw under high temperature and pressure through a heated barrel into a uniform shape and density product. The HME usually consists of one or two screws inside a stationary cylindrical barrel, either co-rotating or counter-rotating. Regardless of the type and complex process, the HME must rotate the screw at a pre-determined speed while balancing the torque and shear produced from both the extruded material and the screw configuration.

A standard HME setup consists of a motor that acts as a drive unit, an extrusion barrel, a rotating screw, and an extrusion die. A central electronic control unit is connected to the extrusion to monitor and control the parameters such as screw speed, temperature, and pressure (figure 2).

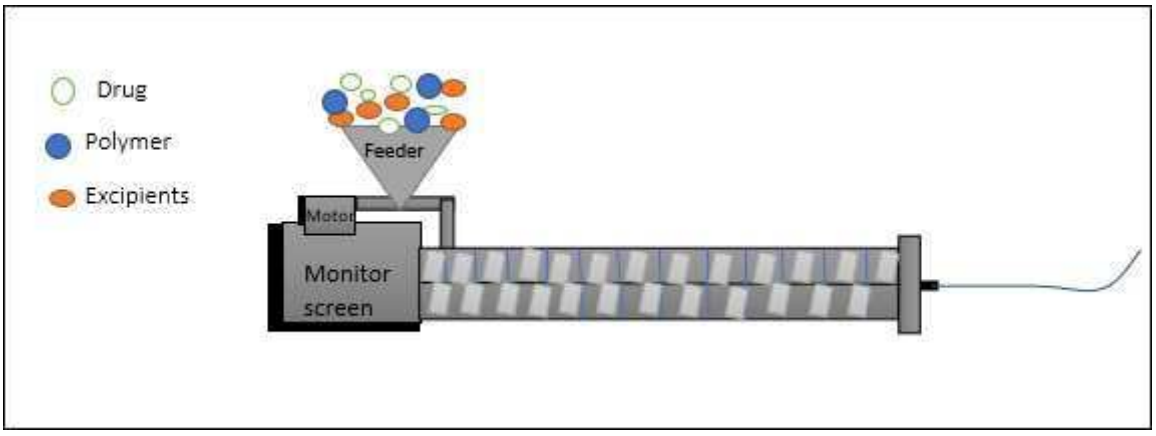


Figure2. Schematic diagram of Hot Melt Extruder.

The extrudates' physicochemical and mechanical characteristics are influenced by temperature, the thermal stability of materials, feeding rate, screw speed, the viscosity of materials, shear rate, and elasticity of materials [9].

The thermoplastic materials used in FDM 3D printers need to be in the form of a filament. However, most filaments available are not suitable for pharmaceutical applications[10]. Aside from this issue, most traditional polymer/ excipients used in pharmaceutics do not have the appropriate thermal and mechanical properties that can be used to make filaments needed for FDM 3D printing[11]. Some of the most common grades of pharmaceutical polymers which can be prepared into filaments are Polyvinylpyrrolidone (PVP), Polyvinyl alcohol (PVA), and Polylactic acid (PLA)[12]. These are suitable for their excellent mechanical and thermal properties and have been used to extrude drugs to yield filaments that can be used in an FDM 3D printer to create different dosage forms.

Conjugating HME and FDM 3D printing are viable for fabricating medicines based on patient needs[13]. These two technologies can rationalize the complex processes of conventional manufacturing methods to develop pharmaceutical products. Thus, there has been some investigation into combining these two technologies into one continuous process to achieve a more valuable and efficient manufacturing procedure. The coupling of HME with FDM 3D printing into one single process opens up the possibility of creating any dosage forms in a pharmacy/hospital for immediate use. Blending these two processes makes the fabrication of dosage forms more cost-effective, efficient, and economical.[10]

Famotidine (Figure 3) is a competitive histamine H-receptor antagonist (H2RA) that binds to the H-receptors located on the basolateral membrane of the parietal cell in the stomach, effectively blocking histamine action. Famotidine is used to treat acid-related gastrointestinal conditions, and the pharmacological activity developed by inhibiting gastric secretion by suppressing acid concentration and volume of gastric secretion. [14]– [16]

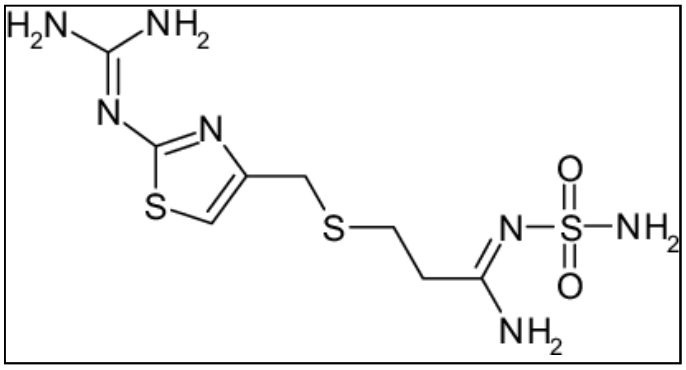


Figure 3. Famotidine chemical structure

Famotidine is (3-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl] methylsulfanyl]-*N*'-sulfamoylpropanimidamide), has a molecular weight of 337.5 g/mol, a crystal with a white to an off-white color. The melting point is 163.5ºC[17]. Solubility at 20 °C 800 mg/mL in DMF; 500 mg/mL in acetic acid; 3mg/mL in methanol; 1mg/mL in water; <0.1mg/mL in ethanol, ethyl acetate, and chloroform.[18]

After the oral administration of famotidine tablets, the absorption is dose-dependent and incomplete. The oral bioavailability varies from 40 to 50%, and the Cmax is reached in 1-4 hours post-dosing. The elimination half-life is about 2 to 4 hours [19]–[21].

Famotidine dosage forms are available both over-the-counter (OTC) and prescription (Rx). The US FDA approved treating duodenal ulcers, gastric ulcers, and gastroesophageal reflux disease (GERD) [22] Dosage forms and strengths of famotidine available in US market for adults are illustrated in table 1[23].

Table1. List of dosage forms and strengths of famotidine in the US markets for adult use.

Dosage From	Prescribed / OTC	Strength
Injection Solution	Prescribed	10 mg/ml 0.4 mg/ml
Oral Suspension	Prescribed	40 mg/ml
Tablet	OTC	10mg 20mg 40 mg
Tablet (chewable)	OTC	10 mg 20 mg

The oral route is the predominant and most desirable route for drug delivery, although drug absorption is sometimes incomplete and variable between individuals regardless of excellent in vitro release patterns[24], [25]. The major problem in the oral dosage form is the variation because of gastrointestinal transit and gastric retention time (GRT). These attributes lead to developing a drug delivery system that will stay in the stomach for a prolonged and predictable time.

One of the possible approaches is to control GRT using a gastroretentive dosage form (GRDF) that will provide new and essential therapeutic options. GRDF can be retained in the stomach and improve the sustained oral delivery of drugs that have an absorption window in specific areas of the gastrointestinal tract. These systems help release the drug continuously before it reaches the absorption window, ensuring optimal bioavailability[26].

Floating drug delivery systems (FDDS) is one of the GRDF types, which was described by Davis in 1968 [27]as a low-density system with enough buoyancy to float over the gastric area and remain in the stomach for a sustained period. As the system floats over the gastric contents, the drug is released slowly at the desired rate, which results in increased gastro-retention time and reduces fluctuations in absorption. The advantages of FDDS are many, which makes it a unique drug delivery system for various illnesses.

FDDS used to enhance the bioavailability of some drugs, sustain drug delivery, reduce the frequency of dosing, target therapy for local effects in the upper GIT, minimize the fluctuation of drug concentration, minimize adverse mechanism of action in the colon. Finally, FDDS are considered site-specific systems. [28]

Further, FDDS is the most practical approach to prolonging the gastric retention time of a dosage form [14] .Recently, FDM 3D printing has been utilized to fabricate floating aid devices [30], floating pulsatile tablets [31], and floating control release matrixes[32][33]

HME coupled with 3D printing technology has been used to manufacture floating tablets. X. Chai *et al.* studied in 2017 the Domperidone intragastric floating tablets for sustained release. Domperidone is a dopamine (D2) receptor antagonist used in treating gastroparesis. X. Chai. Et al. prepared cylinder-shaped tablets with different infill percentages and shell numbers to investigate the floating capability of their tablet. They concluded that the buoyancy of the hollow structure of tablets was directly related to their densities [34]

In another study, Vo A et al. investigated cinnarizine using HME FDM 3D printing to develop HPC-based floating tablets. They observed an improvement in the physical properties of the filaments and printing process when using VA-64 Kollidon® as a co-matric-forming polymer. [35]

The concept of famotidine floating tablets was introduced in 2007 by M. Jaimini et al., using an effervescent technique using different grades of Methocel (HPMC) based on viscosity. Sodium bicarbonate was combined as a gas-generating agent. Citric acid's effect on famotidine drug release profile and floating properties was studied. The in vitro buoyancy study noted that the tablet persisted buoyant for 6-10 hours Methocel K 100 was observed to float for a longer duration than formulations Ethocel 15M [36]

The current research aims to develop a floating tablet of famotidine using HME coupled with FDM 3D printing. To accomplish this target, polymeric carriers were selected (HPC with different grades, PEO N80, HPMC E5, EC), Other excipients (PEG 1500) were screened to operate printable hot-melt extruded filaments with 10% w/w famotidine.

CHAPTER II
MATERIALS AND METHODS

2.1 Materials

Famotidine was purchased from Thermo Fisher Scientific (Waltham, MA, USA). Hydroxypropyl cellulose (HPC-LF) and hydroxypropyl cellulose (HPC-EF) were gifted from Ashland Inc. (Wilmington, Delaware, USA). Polyethylene glycol (PEG 1500) was gifted from Thermo Fisher Scientific (Waltham, MA, USA). Hydroxypropyl Methylcellulose (HPMC-E5) was gifted from DOW (The DOW chemical company, Midland, Michigan, USA). Ethylcellulose (EC) N.F. Premium was purchased from DOW (The DOW chemical company, Midland, Michigan, USA). Polyethylene oxide (PEO N80) was gifted from Colorcon (Ruth Road Harleysville, PA, USA). PLA filaments and all other chemicals and solvents were of analytical grade and purchased from Fisher Scientific (Hanover Park, IL, USA).

2.2 Methods

2.2.1 Formulation compositions

As listed in Table 2, formulations were set to achieve printable filaments. HPC-LF, HPC-EF, HPMC-E5, and EC were used as polymeric carriers. PEG-1500 was used as a plasticizer.

Table 2. Famotidine formulations compositions

Formulation code	Famotidine (% w/w)	klucel™ HPC-EF (% w/w)	klucel™ HPC-LF (% w/w)	Polyethylene glycol™ PEG 1500 (% w/w)	Methocel E5® HPMC-E5 (% w/w)	Ethocel® EC (% w/w)	Polyox™ PEO N80 (% w/w)
M1		94.1%		5.9%			
M2		73.5%		5.4%	21.1%		
M3		70.6%		5.9%	23.5%		
M4			100%				
M5			90%		10%		
M6			85%	10%		5%	
M7	10%	62.5%		5%	22.5%		
M8	10%		80%		10%		
M9	10%		70%		20%		
M10	10%		60%		30%		
M11	10%		55%		30%	5%	
M12	10%		75%		10%	5%	
M13	10%		65%		20%	5%	
M14					50%		50%
M15					33%		67%
M16					67%		33%
M17	10%				60%		30%

2.2.2 Hot-Melt extrusion

Famotidine (10 % w/w), HPC, HPMC-E5, PEO N80, and EC, and PEG excipient of each formulation (18-40 g) were blended homogenously using a V-Shell blender (Globalpharma, Maxi blend, New Brunswick, NJ) for 10 minutes at 25 rpm. Then the resulting blends were fed into an 11 mm co-rotating, twin-screw extruder (Thermo Fisher Scientific, Waltham, MA, USA) with a 1.5 mm round die to achieve the desired 3D printing filament diameter. The extrusion temperature was set at 115-160 ° C except for the first zone at which the temperature was set at 90 °C. The feeding rate was 2-3 g/min. The screw speed was set at 100 rpm.

2.2.3 Fused deposition modeling (FDM) 3D printing

The floating tablet design was created using the TINKERCAD 3D modeling program. The desired design was saved as stl. File and then, Cura© software from Ultimaker (Utrecht, Netherlands) was utilized to link the designed floating tablets to the 3D printer (figure 4) and operate all the printing settings. The First 3D printing attempt used PLA as a standard filament with a 1.75 mm diameter to examine the 3D printed design and floating profile. The 3D printing parameters for the tablets were maintained among all the formulations, as shown in table 3.

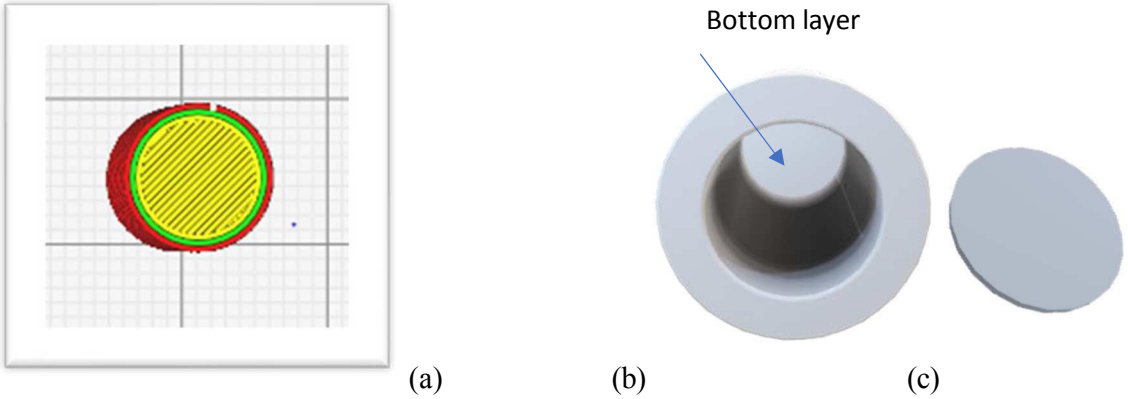


Figure 4. The floating tablet design (a: software cylinder design, b: 3D shape hollow cylinder design with bottom layer attached, c: top layer)

Table 3. Printing setting for the successful formulations.

Parameter	Values
Thickness (mm)	Course 0.4
Outer Wall linewidth (mm)	0.4

Infill line width (mm)	0.4
Wall thickness (mm)	0.8
Wall line count	2
Infill Density (%)	100
Infill Pattern	Line
Printing Temperature (°C)	180
Build Plate Temperature(°C)	60
Printing Speed (mm/s)	60

2.2.4 Weight variation

Five 3D printed tablets were weighed using an analytical balance, and the average weight and relative standard deviation were recorded.

2.2.5 Differential scanning calorimetry (DSC)

Famotidine, polymers, excipients, and physical mixtures of some formulations using a DSC system (TA Instruments, New Castle, DE, USA) to examine the drug's physical state and determine the drug-polymer miscibility. A 3-5 mg sample was weighted in an aluminum T-zero pan scaled using a T-zero lid and then installed into the DSC beside a reference empty pan. The samples were heated from 25 to 200 °C at a rate of 10 °C. TA Instruments TRIOS software was used to analyze the data.

2.2.6 Drug assay

The drug assay evaluated the drug content and uniformity of physical mixtures, HME filaments, and FDM 3D printed tablets. Sample (25-50 mg) of the physical mixture, HME filaments, and 3D printed tablets were dissolved in 20 mL methanol, then mixed using vortex to help solubilize the sample in methanol. Samples were diluted ten times and then analyzed using HPLC.

2.2.7 *In-vitro* drug release study

The *in-vitro* drug release profile of 3D printed tablets was evaluated using a United States Pharmacopeia (USP) dissolution apparatus II (paddle) (Hanson Research Virtual Instruments SR8 Plus, Los Angeles, CA). The dissolution medium was 900 mL 0.1 N HCL (pH 1.2) and was maintained at 37± 0.5 ºC and 50 rpm. A sample volume of 2 mL was withdrawn using a dissolution cannula topped with a filter tip of 10 µm for DISS 1000 (Thermo scientific) at time points 0, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours. The samples were replaced with a fresh dissolution medium to maintain the total volume in the apparatus. Later the withdrawn samples were analyzed using HPLC.

2.2.8 HPLC analysis

The samples of drug content and drug release were analyzed using the HPLC method with The Waters HPLC-UV system (Waters Corporation, Milford, MA, USA). The column used was a Luna 5u C18 column (5 microns, 150* 4.60 mm). The test conditions were set up: column temperature 25 °*C*, flow rate 0.4 mL/min, injection volume 10 µL, and detection wavelength 267 nm. It was indicated in the literature that the best separation was achieved in the mobile phase composed of methanol (a) and 1% acetic acid aqueous solution (b) in the ratio of 30:70 (v/v).

[30]. The calibration curve is prepared using concentration (5, 10, 25, 50, and 100 μg/mL), R2 ~ 0.9999.

2.2.9 Floating profile

The floating tablets profile was performed directly after the 3D printed tablet was created into 20 ml Glass Scintillation Vials using bottled water to test the floating duration. The duration of time that the 3D printed tablet constantly remained on the surface was determined as the total floating time.

CHAPTER III
RESULTS AND DISCUSSION

3.1 Formulation Composition

The characteristics and thermal properties of the polymers used are shown in Table 4. HPC is a cellulose derivative with plasticity, hydrophobicity, hydrophilicity property, and low Tg (depending on the moisture content). A high swell ability property makes it appropriate for modified drug release kinetics. EC was used in this research to enhance the mechanical properties of the filament. It possesses excellent thermal plasticity in some polymeric matrixes, which means softening or fusing when heated up and hardening and turning rigid again when cooled. HPMC-E5 is a swellable hydrophilic polymer that helps control a modified release formulation. PEO N80 as a polymeric carrier. PEO has different grades, and the N80 grade is one of the low grades with a molecular weight of 200,000 [38]. PEO N80 has a history of being used for successful extended-release applications of osmotic pump technologies, gastroretentive dosage forms (GRDF), hot-melt extruded products, hydrophilic matrices, and other drug delivery systems. PEO N80 has a thermoplastic property and is highly crystalline with a low melting temperature characteristic for hot melt extrusion; it was assumed to be a good choice for this research [34].

Table 4. The characteristics and thermal properties of the polymers.

The chemical name of the polymer	Used in FDA approved drug product	Melting temperature (Tm) ℃	Glass Transition Temperature (Tg) °*C*
Ethylcellulose (EC) N.F. premium	Yes	240-255	130-133[39]
Hydroxypropyl cellulose (HPC-LF)	Yes	Amorphous	0 and 120 [40]
Polyethylene oxide (PEO N80)	Yes	63- 67	-50[41]
Polyethylene Glycol (PEG1500)	Yes	Amorphous	-67.15[42]
HPMC E5	Yes	Amorphous	154[41]

In this current research, the aim is to create a famotidine floating tablet using HME with FDM 3D printing and the integrated role of polymers and excipients within the formulations to have a longer time in the stomach.

3.2 Hot-Melt Extrusion

All formulations were successfully extruded. The screw configuration consisted of four conveying zones and three mixing zones. A 1.5 mm round die was used, and the diameter of the extruded filaments was ~ 1.7. The increase in the diameter was since there was a swelling of the filaments after leaving the die end, and it reached the desired 1.7 mm. The color of filaments varied from one formulation composition and another, which was white to off-white in most cases. For formulations with EC and PEO, which changed the color of the filaments to dark yellow, This is possible because of the oxidation of EC in the formulation at high temperature(Table 5). The screw speed was set at 100 rpm speed. The justification for using 70-90 °C is to prevent building materials, stop sticking, and ensure smooth feeding to the following zones. The extruded filaments were kept in plastic bags until further use. M17 extrusion temperature parameter was distinct from the other formulations; the extrusion temperature was 150 °C, except the first zone was 25°C to have better flowability and prevent accumulation and building up the material.

Table 5. HME parameters for M1-M17 formulations.

Formulation Code	Torque (Nm)	Die Pressure (Bar)	Extrusion Temperature (°C)	First zone temperature *(°C)*	Screw speed (rpm)	Filament color	Printability
M1	1.2	25	120	70	100	white	Failed
M2	1.3	30	120	70	100	White	Failed
M3	1.7	28	120	70	100	White	Failed
M4	2.9	1	160	160	100	White	Failed
	4.9	13	120	90	100	Transparent	Failed
M5	4.6	14	150	150	100	white	Diameter > 1.7 mm
M6	1.4	61	120	120	100	white	failed
M7	1.4	28	120	70	100	white	Failed
M8	6.7	78	110	90	100	White	Failed
M9	5.9	25	120	90	100	Milky white	Diameter > 1.7 mm
M10	6.7	45	115	90	100	White	Printable
M11	5.6	38	115	90	100	Dark yellow	Printable
M12	4.8	45	115	90	100	Dark yellow	Failed
M13	5.16	41	115	90	100	Dark yellow	Failed
M14	3.6	53	150	150	100	Light yellow	Failed
M15	4.2	51	150	150	100	Light yellow	printable
M16	3.0	50	150	150	100	Light yellow	Printable
M17	3.8	73	150	25	100	Dark yellow	Printable

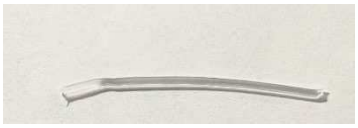
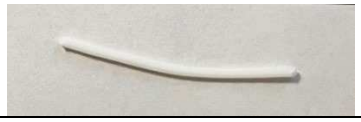
Formulation code	HME Filament	Formulation code	HME filament
M1		**M10**	
M2		**M11**	
M3		**M12**	
M4		**M13**	
M5		**M14**	
M6		**M15**	
M7		**M16**	
M8		**M17**	
M9			

Figure 5: all the Formulations' filaments extruded using a two screw HME.

3.3 Fused deposition modeling 3D printing (FDM)

Printing was initiated by using PLA filaments. There was no significant difference in the density between PLA and the filaments of the successful formulations. Therefore, the printing was started with PLA first to review the design pattern and determine the desired tablet weight. The first dimensions were (X20*Y20*Z10), and the weight of the PLA (480 mg) exceeded the range needed (200-400 mg). Next, the dimensions were reduced to (X10*Y10*Z5), and the weight of PLA was accepted (270 mg) (figure 6).

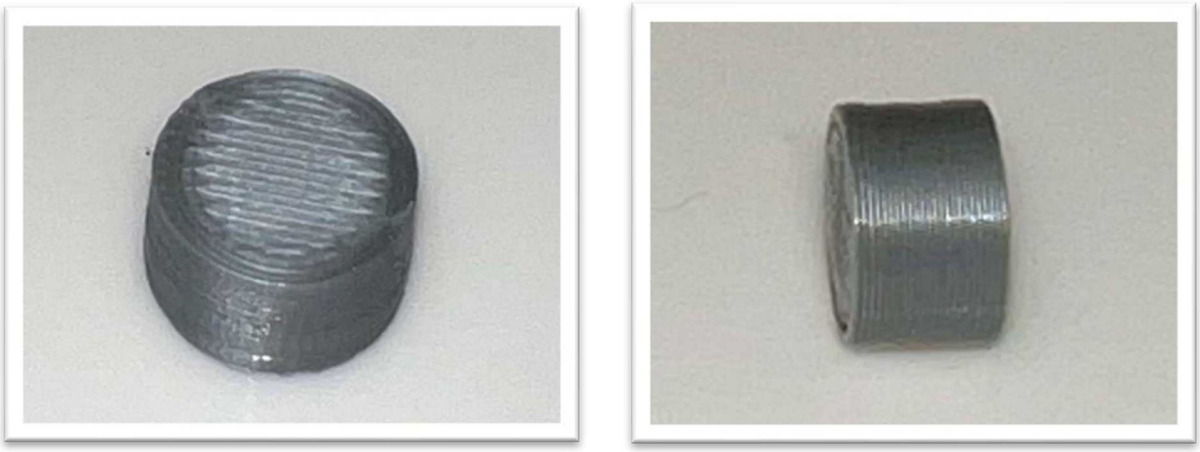
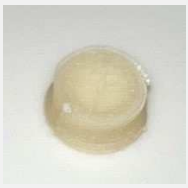


Figure 6: The Floating tablet design using PLA filaments through an FDM 3D printer.

M1-M9 and M12-M14 failed to print as the filaments were soft and were stuck in the printer and could not pass through. The rationale behind that is the mechanical strength of HPC polymer on the filament. Filaments became sticky inside the printer. Melted material was incapable of pulling through the heater. An uneven flow of materials along the printer nozzle was observed, including some sticking and pausing the printing process. Failure of printing for some of the formulations was correlated to the high content of HPC and possibly moisture absorption, which will affect the flexibility of the filaments.

The filament diameter of M5 and M9 was more than 1.75 mm, which won't allow the filament to go through the printer nozzle. Filaments from M10-M11 and M15-M17 were printable (Table 6); the printing processing starts either the day after the extrusion or 2-days after extrusion. The color of the tablets varied according to the filament color; however, they all shared the same printing pattern, which was a line to make strong support for the hollow space inside the tablet and reduce the gaps and reach the desired weight. The percent of the infill was 100% to prolong the floating tablet's dissolution and increase the strength of the design.

Table 6. Successful formulations Printed tablets using FDM 3D printer

FORMULATION CODE	3D PRINTED TABLET
M10	
M11	
M15	
M16	
M17	

3.4 Weight variation

The 3D printed floating tablets for formulations M10 and M11 were weighed in an analytical balance(Mettler Toledo , model# XSE204) ,and the results are displayed in Table 7. The target weight was between 200-400 mg since famotidine strengths are 20 mg and 40 mg, making our weight range more flexible. All of the printed tablets were within the desired weight range.

Table 7. 3D printed floating tablet weight variations for M10 and M11

Formulation code	**Average weight (mg)**	**RSD**
M11	279.1	1.38
M10	293.7	1.48

3.5 Differential Scanning Calorimetry (DSC)

The analysis of the thermal properties of the drug, polymers, and excipients established a connection between temperature and specific physical properties of the substances using the melting point of the drug and glass transition temperature for polymers and other substances. Famotidine thermograms showed an endothermic melting point peak at 164.76 °C. This endothermic peak disappeared in the extruded filament and printed tablets, indicating complete solubilization of famotidine in the polymeric carriers for all Five formulations studied (Figures 7, 8).

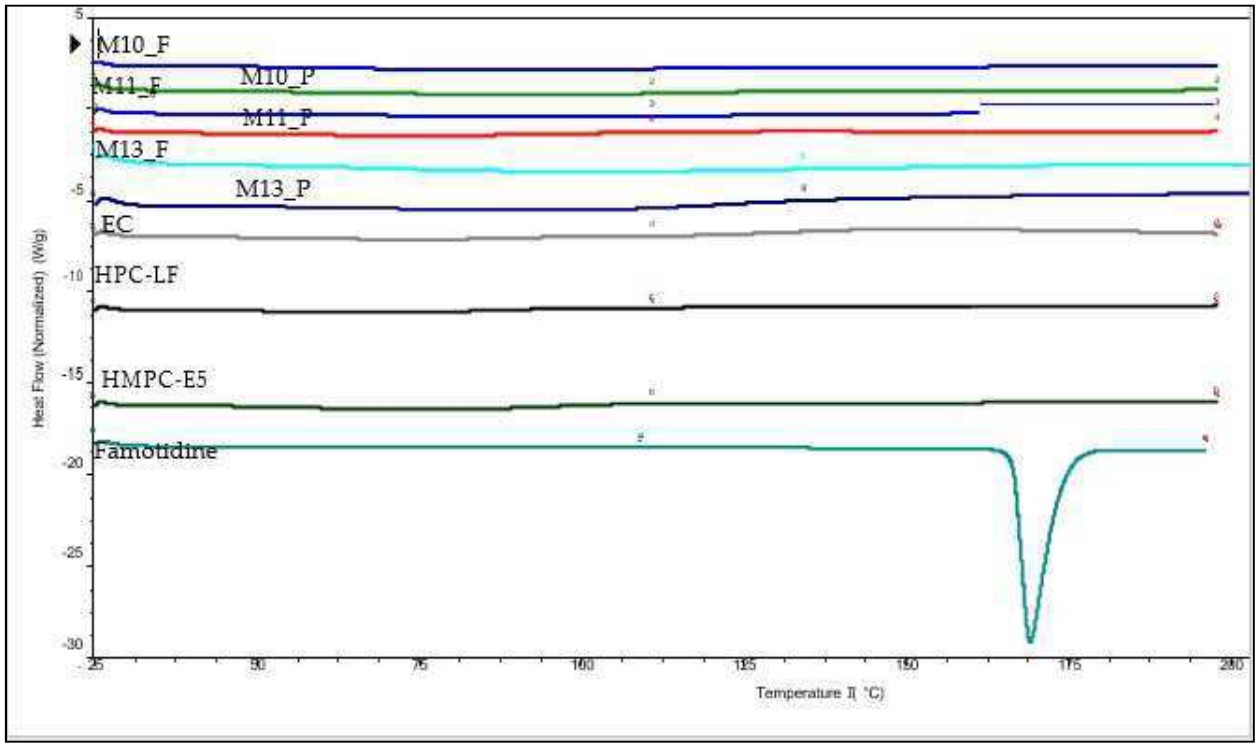


Figure 7. DSC thermogram of F10, 11, 13 for both filaments (F) and printed tablets (P), Famotidine, HPMC-E5 , HPC-LF, EC.

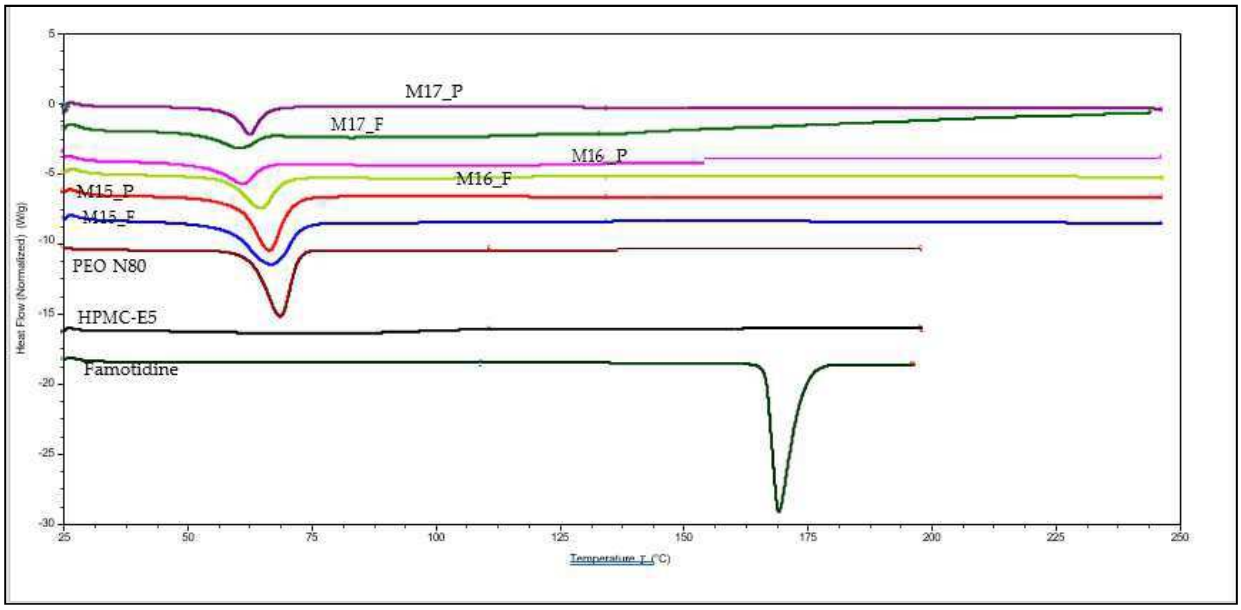


Figure 8. DSC thermogram of F15, 16, 17 for both filaments (F) and printed tablets (P), Famotidine, HPMC-E5, PEO N80.

3.6 Drug content study

Formulations M10 and M11 were examined to analyze the famotidine content in the tablets after to check whether the EC presence or absence influences the results. M10 with no EC exhibited a higher but more variable drug content (Average DC = 99.2 %, RSD= 10.1) than M11 with 5% EC (Average= 62.2, SD=1.7).

3.7 *in-vitro* drug release study

The dissolution of tablets made with the M10 formulations were performed. (Figure 9). Famotidine continued in M10 formulation floating in the media for 9 hours until fully dissolved. That revealed that the 3D printing floating tablet design was successful for M10 towards prolonging the floating and releasing the famotidine.

The release of M17 formulation was for 8 hours until fully dissolved. Resulted release data were low despite the good floating profile. The assumption was that the PEO swelling mechanism around the famotidine increased the duration of releasing famotidine from the dosage form.

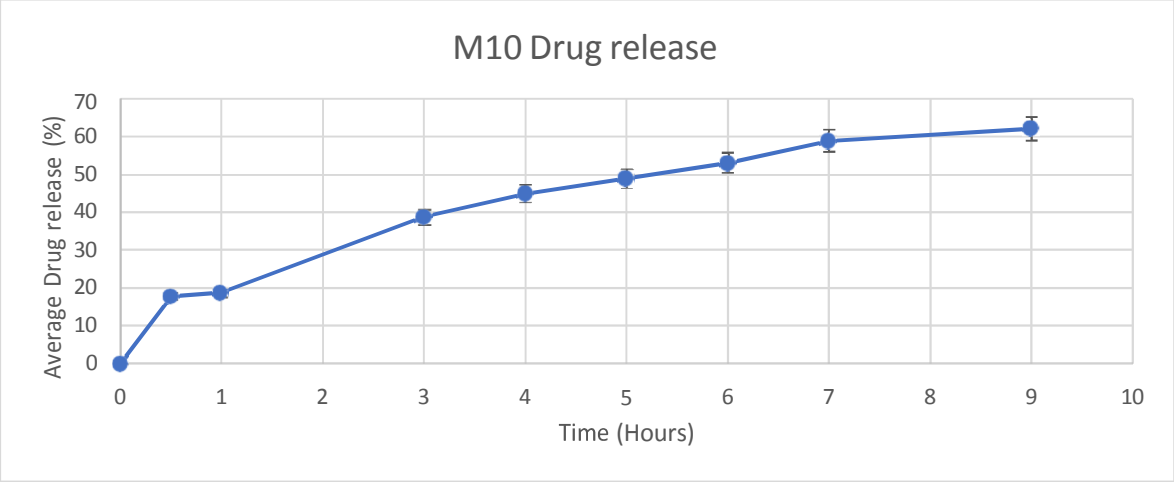


Figure 9. The dissolution profile of 3D printed tablets for M10 in 0.1N HCL (pH 1.2) media, apparatus II

3.8 Floating analysis

Floating tests were examined successfully for printed tablets for formulations M10, M11, and M17 (Figure 11 and 12, respectively). The floating test was performed in 20 mL cantillation vial directly after the 3D printing and monitored every hour until either tablet sink or dissolved. The vial's resulting floating profile showed that tablets on M10 and M11 floated for about 9 hours while M17 floated for about 8 hours. The floating profile results were confirmed within the dissolution apparatus at the drug release experiment day. The observed results between the vial and dissolution was consistent in the floating time for the formulations M10, M11, and M17 despite the presence of paddle in the dissolution apparatus, yet the floating matched the vial floating time.

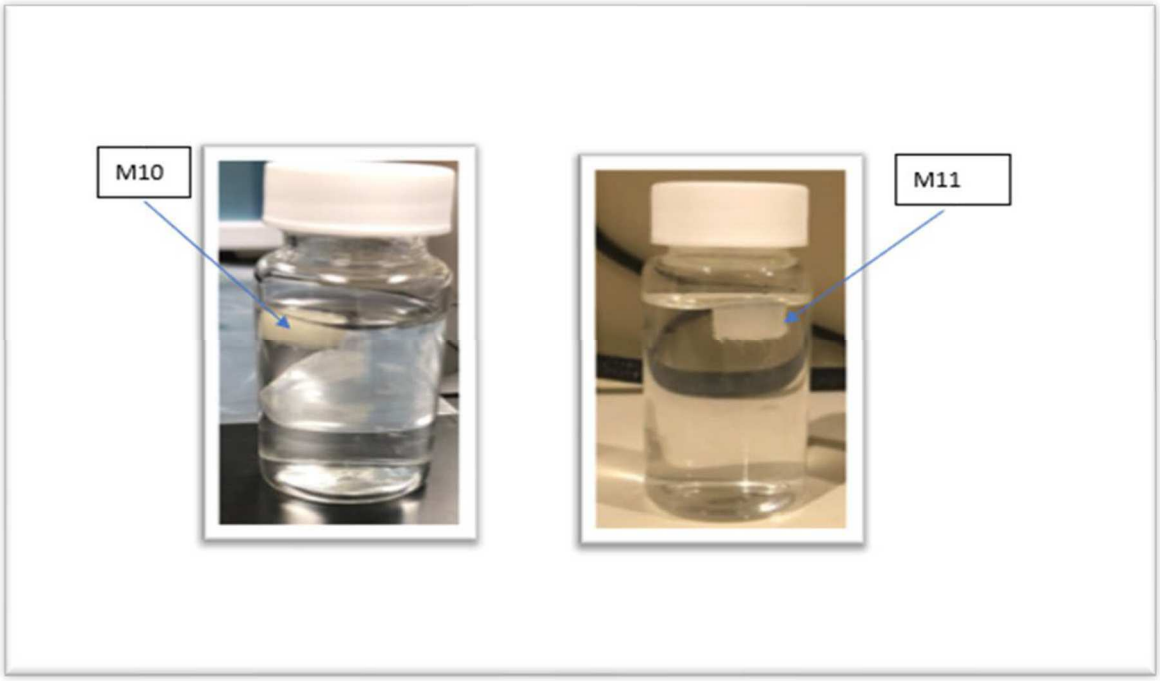


Figure 10. Floating test on M10 and M11 after 3D printing

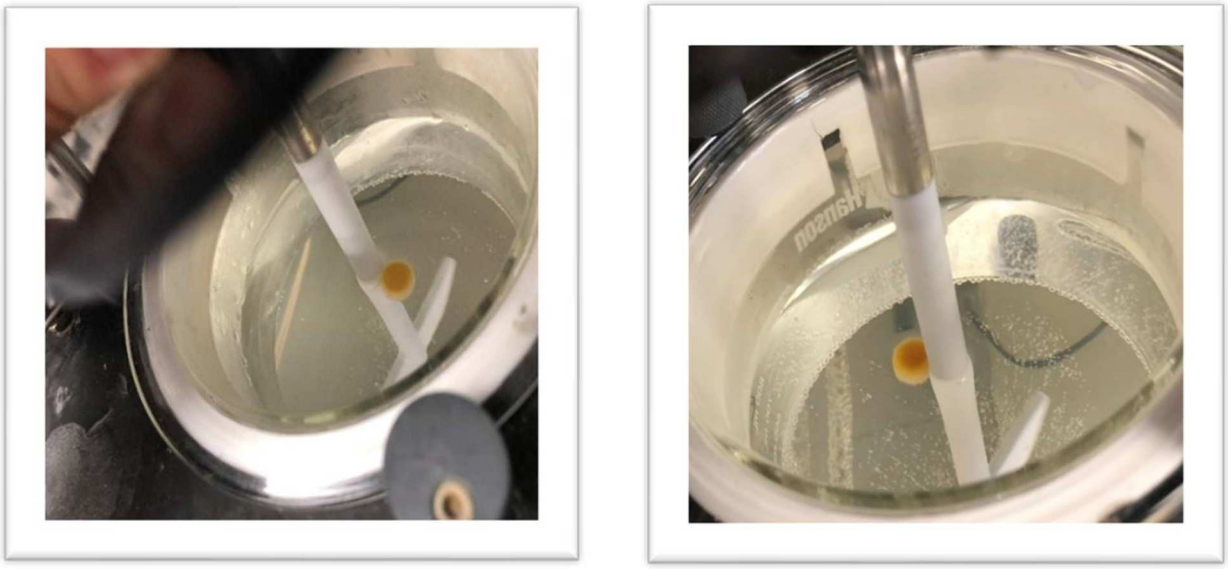


Figure 11. Dissolution of M17 to assess the drug release and the floating profile.

CHAPTER IV
CONCLUSION

Famotidine formulation development for floating tablets using hot-melt extrusion with FDM 3D-printing technology was examined and produced. The HME process was shown to have the ability to develop some suitable filaments regarding the mechanical properties for FDM-3D printing of floating tablets of famotidine through the printer for some successful formulations. The Finding in the formulations with both HPC (different grades) and HPMC E5 is hard to print because of the soft filament properties. Assumption of EC-containing formulations may need to add anti-oxidation due to the oxidation of EC in high temperatures. Five filaments (M10, M11, M15, M16, M17) out of seventeen were printable based on printing trials. M10, M11, and M17 showed a good floating profile in both 20 ml vials and confirmed in the dissolution apparatus. Drug release observations for floating tablets for both M10 and M17 were examined for 9 hours and 8 hours, respectively, until fully dissolved. Drug release and floating were maintained for both M10 and M17. Finally, formulation optimization for floating famotidine tablet needs to be performed.

BIBLIOGRAPHY

BIBLOGRAPHY

[1] J. Norman, R. D. Madurawe, C. M. V. Moore, M. A. Khan, and A. Khairuzzaman, "A new chapter in pharmaceutical manufacturing: 3D-printed drug products," *Advanced Drug Delivery Reviews*, vol. 108. Elsevier B.V., pp. 39–50, Jan. 01, 2017. doi: 10.1016/j.addr.2016.03.001.

[2] "Stereolithography (SLA) 3D Printing Guide." https://formlabs.com/blog/ultimate-guide-to-stereolithography-sla-3d-printing/ (accessed Mar. 15, 2022).

[3] "The 3D Inkjet Printing Process Explained." https://www.nano-di.com/blog/2019-the-3d-inkjet-printing-process-explained (accessed Mar. 15, 2022).

[4] unknown, "Nanodimension, The 3D printing process explained," *Nanodimension. (n.d.). The 3D inkjet printing process explained. Https://Www.Nano-Di.Com/Blog/2019-the-3d-Inkjet-Printing-Process-Explained. Retrieved February 22, 2022, from https://www.nano-di.com/blog/2019-the-3d-inkjet-printing-process-explained*.

[5] S. J. Trenfield, A. Awad, A. Goyanes, S. Gaisford, and A. W. Basit, "3D Printing Pharmaceuticals: Drug Development to Frontline Care," *Trends in Pharmacological Sciences*, vol. 39, no. 5. Elsevier Ltd, pp. 440–451, May 01, 2018. doi: 10.1016/j.tips.2018.02.006.

[6] E. Lepowsky and S. Tasoglu, "3D printing for drug manufacturing: A perspective on the future of pharmaceuticals," *International Journal of Bioprinting*, vol. 4, no. 1, 2018, doi: 10.18063/IJB.v4i1.119.

[7] O. A. Mohamed, S. H. Masood, and J. L. Bhowmik, "Optimization of fused deposition modeling process parameters: a review of current research and future prospects," *Advances in Manufacturing*, vol. 3, no. 1, pp. 42–53, Mar. 2015, doi: 10.1007/s40436-014-0097-7.

[8] M. Maniruzzaman *et al.*, "A Review of Hot-Melt Extrusion: Process Technology to Pharmaceutical Products," *International Scholarly Research Network ISRN Pharmaceutics*, vol. 2012, 2012, doi: 10.5402/2012/436763.

[9] H. Patil, R. v. Tiwari, and M. A. Repka, "Hot-Melt Extrusion: from Theory to Application in Pharmaceutical Formulation," *AAPS PharmSciTech*, vol. 17, no. 1, pp. 20–42, Feb. 2016, doi: 10.1208/s12249-015-0360-7.

[10] D. Khong Tan, M. Maniruzzaman, and A. Nokhodchi, "pharmaceutics Advanced Pharmaceutical Applications of Hot-Melt Extrusion Coupled with Fused Deposition Modelling (FDM) 3D Printing for Personalised Drug Delivery", doi:

10.3390/pharmaceutics10040203.

[11] D. M. Smith, Y. Kapoor, G. R. Klinzing, and A. T. Procopio, "Pharmaceutical 3D printing: Design and qualification of a single step print and fill capsule," *Int J Pharm*, vol. 544, no. 1, pp. 21–30, Jun. 2018, doi: 10.1016/J.IJPHARM.2018.03.056.

[12] A. Melocchi, F. Parietti, A. Maroni, A. Foppoli, A. Gazzaniga, and L. Zema, "Hot- melt extruded filaments based on pharmaceutical grade polymers for 3D printing by fused deposition modeling," *Int J Pharm*, vol. 509, no. 1–2, pp. 255–263, Jul. 2016, doi: 10.1016/J.IJPHARM.2016.05.036.

[13] A. Awad, S. J. Trenfield, S. Gaisford, and A. W. Basit, "3D printed medicines: A new branch of digital healthcare," *Int J Pharm*, vol. 548, no. 1, pp. 586–596, Sep. 2018, doi: 10.1016/J.IJPHARM.2018.07.024.

[14] P. O. Talke and D. R. Solanki, "Dose-response study of oral famotidine for reduction of gastric acidity and volume in outpatients and inpatients," *Anesth Analg*, vol. 77, no. 6, pp. 1143–1148, 1993, doi: 10.1213/00000539-199312000-00011.

[15] R. G. Berlin, B. v. Clineschmidt, and J. A. Majka, "Famotidine: an appraisal of its mode of action and safety," *Am J Med*, vol. 81, no. 4B, pp. 8–12, Oct. 1986, doi: 10.1016/0002-9343(86)90594-2.

[16] K. Miyata, T. Kamato, A. Nishida, and K. Honda, "Studies on the mechanism for the gastric mucosal protection by famotidine in rats," *Jpn J Pharmacol*, vol. 55, no. 2, pp. 211–222, 1991, doi: 10.1254/JJP.55.211.

[17] S. Budavari, M. O'Neil, A. Smith, P. Heckelman, and J. Obenchain, *The Merck index : an encyclopedia of chemicals, drugs, and biologicals*, 12th ed. Whitehouse Station NJ: Merck, 1996.

[18] Z. Fedorowicz, E. J. van Zuuren, and N. Hu, "Histamine H2-receptor antagonists for urticaria," *Cochrane Database of Systematic Reviews*, vol. 2012, no. 3, Mar. 2012, doi: 10.1002/14651858.CD008596.pub2.

[19] M. Darwish, M. Bond, E. Hellriegel, P. Robertson, and J. P. Chovan, "Pharmacokinetic and pharmacodynamic profile of bendamustine and its metabolites," *Cancer Chemotherapy and Pharmacology*, vol. 75, no. 6, pp. 1143–1154, Jun. 2015, doi: 10.1007/S00280-015-2727-6.

[20] H. Echizen and T. Ishizaki, "Clinical Pharmacokinetics of Famotidine," *Clinical Pharmacokinetics*, vol. 21, no. 3, pp. 178–194, 1991, doi: 10.2165/00003088-199121030-00003.

[21] A. N. Chremos, “Clinical pharmacology of famotidine: A summary,” *Journal of Clinical Gastroenterology*, vol. 9, pp. 7–12, 1987, doi: 10.1097/00004836-198707002-00003.

[22] "Famotidine: Uses, Interactions, Mechanism of Action | DrugBank Online." https://go.drugbank.com/drugs/DB00927 (accessed Mar. 15, 2022).

[23] "Pepcid AC, Zantac 360 (famotidine) dosing, indications, interactions, adverse effects, and more." https://reference.medscape.com/drug/pepcid-ac-zantac-360-famotidine-341989 (accessed Apr. 23, 2022).

[24] S. S. Davis, "Formulation strategies for absorption windows," *Drug Discov Today*, vol. 10, no. 4, pp. 249–257, Feb. 2005, doi: 10.1016/S1359-6446(04)03351-3.

[25] A. Streubel, J. Siepmann, and R. Bodmeier, "Drug delivery to the upper small intestine window using gastroretentive technologies," *Curr Opin Pharmacol*, vol. 6, no. 5, pp. 501–508, Oct. 2006, doi: 10.1016/J.COPH.2006.04.007.

[26] B. N. Singh and K. H. Kim, "Floating drug delivery systems: an approach to oral controlled drug delivery via gastric retention," *J Control Release*, vol. 63, no. 3, pp. 235–259, Feb. 2000, doi: 10.1016/S0168-3659(99)00204-7.

[27] V. K. Pawar, S. Kansal, G. Garg, R. Awasthi, D. Singodia, and G. T. Kulkarni, "Gastroretentive dosage forms: A review with special emphasis on floating drug delivery systems," *https://doi.org/10.3109/10717544.2010.520354*, vol. 18, no. 2, pp. 97–110, Feb. 2010, doi: 10.3109/10717544.2010.520354.

[28] "FLOATING DRUG DELIVERY SYSTEM: A REVIEW | INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH." http://ijpsr.com/bft-article/floating-drug-delivery-system-a-review-2/?view=fulltext (accessed Mar. 29, 2022).

[29] V. Bhardwaj and S. Harikumar, "FLOATING DRUG DELIVERY SYSTEM: A REVIEW," *An International Research Journal*, vol. 4, no. 1, pp. 26–38, 2013, Accessed: Mar. 15, 2022. [Online]. Available: http://www.pharmacophorejournal.com/

[30] J. Fu *et al.*, "Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems," *Int J Pharm*, vol. 549, no. 1–2, pp. 370–379, Oct. 2018, doi: 10.1016/J.IJPHARM.2018.08.011.

[31] N. R. Dumpa, S. Bandari, and M. A. Repka, "Novel Gastroretentive Floating Pulsatile Drug Delivery System Produced via Hot-Melt Extrusion and Fused Deposition Modeling 3D Printing," *Pharmaceutics*, vol. 12, no. 1, 2020, doi: 10.3390/PHARMACEUTICS12010052.

[32] X. Chai *et al.*, "Fused Deposition Modeling (FDM) 3D Printed Tablets for Intragastric Floating Delivery of Domperidone," *Sci Rep*, vol. 7, no. 1, Dec. 2017, doi: 10.1038/S41598-017-03097-X.

[33] B. R. Giri, E. S. Song, J. Kwon, J. H. Lee, J. B. Park, and D. W. Kim, "Fabrication of intragastric floating, controlled release 3D printed theophylline tablets using hot-melt extrusion and fused deposition modeling," *Pharmaceutics*, vol. 12, no. 1, Jan. 2020, doi: 10.3390/PHARMACEUTICS12010077.

[34] X. Chai *et al.*, "Fused Deposition Modeling (FDM) 3D Printed Tablets for Intragastric Floating Delivery of Domperidone," *Sci Rep*, vol. 7, no. 1, Dec. 2017, doi: 10.1038/S41598-017-03097-X.

[35] A. Q. Vo, J. Zhang, D. Nyavanandi, S. Bandari, and M. A. Repka, "Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine," *Carbohydrate Polymers*, vol. 246, p. 116519, Oct. 2020, doi: 10.1016/J.CARBPOL.2020.116519.

[36] M. Jaimini, A. Rana, and Y. Tanwar, "Formulation and evaluation of famotidine floating tablets," *Curr Drug Deliv*, vol. 4, no. 1, pp. 51–55, Dec. 2007, doi: 10.2174/156720107779314730.

[37] A. Zarghi, A. Shafaati, S. M. Foroutan, and A. Khoddam, "Development of a rapid HPLC method for determination of famotidine in human plasma using a monolithic column," *J Pharm Biomed Anal*, vol. 39, no. 3–4, pp. 677–680, Sep. 2005, doi: 10.1016/J.JPBA.2005.03.029.

[38] "POLYOX™ WSR N80 - Industrial Cellulosics by DuPont." https://www.industrialcellulosics.com/products/polyox/polyox-wsr-n80 (accessed Apr. 23, 2022).

[39] P. Solutions, "ETHOCEL™ One of the few water-insoluble polymers approved for global pharmaceutical applications".

[40] "Ashland | Klucel™ hydroxypropylcellulose." https://www.ashland.com/industries/pharmaceutical/oral-solid-dose/klucel-hydroxypropylcellulose (accessed Apr. 10, 2022).

[41] H. N. Joshi and T. D. Wilson, "Calorimetric Studies of Dissolution of Hydroxypropyl Methylcellulose E5 (HPMC E5) in Water," *American Pharmaceutical Association Journal of Pharmaceutical Sciences*, vol. 1, no. 10, p. 1033, 1993.

[42] "Poly(ethylene glycol)." https://polymerdatabase.com/polymers/polyethyleneglycol.html (accessed Apr. 10, 2022).

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