2019

Development of Controlled Release Oral Dosages by Density Gradient Modification Using 3D Printing Technologies

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Development of Controlled Release Oral Dosages by Density Gradient Modification Using 3D Printing Technologies

A Thesis

presented in partial fulfillment of requirements

for the degree of Master of Science

in the Department of Pharmaceutics and Drug Delivery

The University of Mississippi

by

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May 2019

ABSTRACT

Over the years, three-dimensional (3D) printing has gradually become more common in people's lives. Due to its quick development, it has attracted the attention of researchers in the pharmaceutical industry. The main purpose of this project was to couple fused deposition modelling (FDM) 3D printing with hot melt extrusion (HME) technology to manufacture tablets with different drug release profiles and to solve dose issues related to an individual's physiological differences and to enhance extended release properties. Ketoprofen was used as the model drug and different properties were added to the polymer to create a formulation suited to HME technology for the production of filaments used for printing.

This study also investigated polymer matrices and how 3D printing can affect a drug's release into the body.

DEDICATION

This paper will be dedicated to everyone I love; especially my parents and grandfather, Jianbo Hu, Li Sha and Yitang Hu, who have cared about me from the other side of the ocean.

Thank you so much to everyone who supported me in through the good times and bad.

ACKNOWLEDGMENTS

I would like to express my appreciation to all those who made this study possible and helped me writing this thesis. I gratefully acknowledge the help of my advisor, Dr. Michael A. Repka, who has offered me valuable suggestions in the academic studies.

Second, I would like to express my heartfelt gratitude to Dr. Walter G. Chambliss and Dr. Eman Ashour. It's my honor to have them be my committee member for the master thesis defense.

Special thanks should go to my seniors in the lab Pengchong Xu and Jiaxiang Zhang, who taught me a lot and always have instructive advice and useful suggestions on my project.

Last my thank would go to my family and friends for their loving consideration and great confidence in me these years.

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1. Introduction

The solid dispersion mainly means that the poorly soluble drug is dispersed in a water-soluble carrier in an amorphous state. For poorly water soluble drugs, solid dispersions have been shown to significantly improve their dissolution rate, solubility and oral bioavailability. It improves the wettability of the drug by minimizing the particle size, thereby improving the oral bioavailability. In this study solid dispersion was obtained through a method called Hot Melt Extrusion (HME) (Vasconcelos, Sarmento and Costa, 2007; Sareen, Joseph and Mathew, 2012). HME has been used in the manufacturing process of the plastics industry for a long time, but only recently has it begun to show great potential in pharmaceutical use. When using the HME process for the creation of a pharmaceutical dosage, a homogeneous mixture of active pharmaceutical ingredient (API) and other excipients are rapidly heated and softened in the extruder and then pressurized into filaments through the die. In addition to improving the oral bioavailability of API, HME can also be used to develop controlled release drug systems and the ability to mask API's bitter taste (Tiwari et al., 2016). HME is an effective technique for producing solid dispersions, which has great advantages over conventional processes for the high lipophilicity and poor solubility drugs. The use of HME technology to improve apparent solubility and dissolution of APIs and drug's oral bioavailability demonstrate the value of this

technology as an important drug delivery processing tool (Repka et al., 2007). In recent years, more and more researchers have attempted to combine HME with 3D printing, and their achievements have also proved that this novel technology has great potential for development (Goyanes et al., 2015).

In the traditional sense, three-dimensional printing(3DP) has changed the ink from the normal printer to thermoplastics. Now the most common 3D printing material is Polylactic Acid (PLA). PLA is an extremely common synthetic plastic with a low melting point and can be melt processed at 180°C. There are many factors that affect the use of filaments and 3D printing, but the most important parameters for evaluating whether a filament suits the production standards of a 3d printed medicine are the viscosity, stiffness and brittleness of the filament. These aspects are important during the printing process as filaments with the wrong attributes will often crack or detach from the 3d printer's baseplate in such a way that printing cannot be completed. Since most of the plastics manufacturing industry typically uses PLA in 3d printing, we can use PLA as a reference to evaluate whether or not our extruded filaments meet the industry standard (Zhang et al., 2017).

The principle of the fused deposition modelling (FDM) 3D printer is based on a digital model file, using an adhesive material such as plastic to construct an object by layer-by-layer printing. Until this layer is completely printed and cured that the next layer can be started. This covering surface and the curing process are repeated until the object is finished. The first step of 3D printing is to design the required 3D model by a computer aided design (CAD) program (eg, Autodesk®

Fusion 360™) and then convert it to a STL file (Standard Mosaic Language or STereo-lithography) (Gross et al., 2014). 3d printers have a chamber dedicated to feeding a solid filament into the extruder; and while it is best to be able to feed continuously, the material can also be fed as a liquid using a pump. The material should uniform in its preparation so that the chemicals are distributed evenly in the final tablet form (Gibson et al., 2015). Once in the feeding chamber, the filament is then heated up to a melting point in a 3D printer which is then pushed through the extruder and printed as the design designated by the STL file. (Fig. 1).

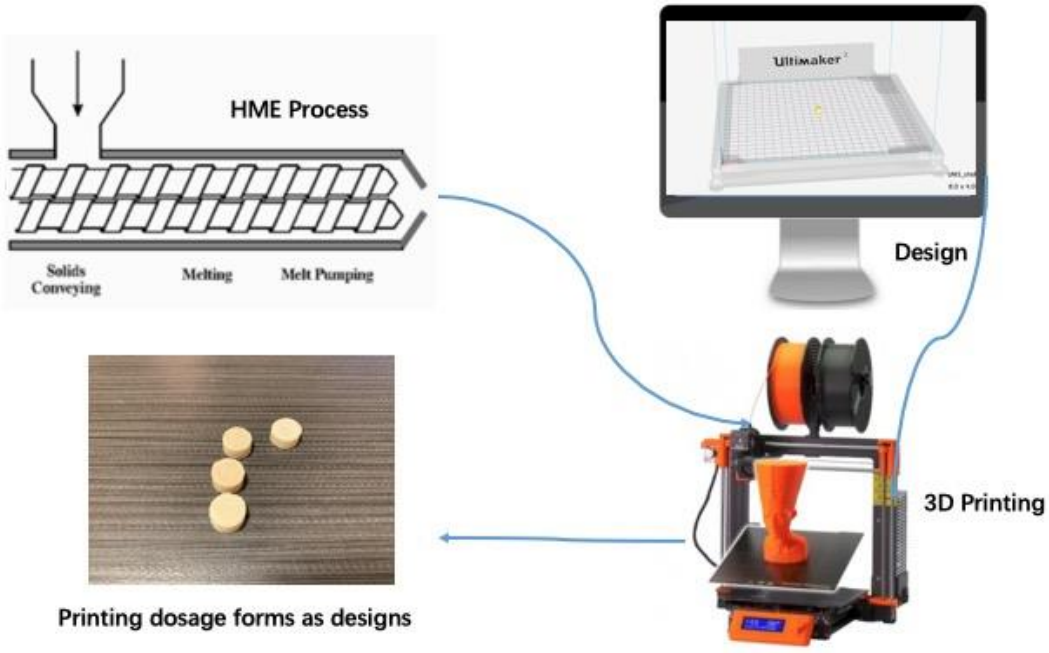


Figure 1. HME combined with 3D Printing process schematic diagram

Under the Biopharmaceutical Classification System (BCS), drugs that have unit does that result in low solubility in 250ml of aqueous over a range of pH are classified as Class II or Class IV (depending on permeability) so they emphasize dissolution as a rate-limiting step for oral

absorption of BCS Class II and Class IV drugs (Sareen et al., 2012). According to the existing guidelines, ketoprofen is a weak acid, belonging to the BCS Class II. Because of this, we needed to improve the solubility of Ketoprofen.

3D printing has many advantages over traditional dosage forms so more manufacturers are investing in research and development. The first 3D printed prescription drug has already been successfully marketed in the US. Called Spritam-Aprecia, it was approved by the FDA in 2015 for the treatment of partial epileptic seizures. This new dosage form requires only a little bit water to allow the tablet to dissolve quickly in the mouth, which also gives people who have difficulty swallowing more choices (Aprecia Pharmaceuticals, Langhorne, PA, USA).

The gastrointestinal tract is the main limiting factor when looking at the speed of oral controlled release formulations. And while it is difficult to optimize the formulation to deal with this factor, it can be done through the control the dissolution process and by guiding the development and quality of the final product by studying the rate of release of in vitro controlled release formulations and predicting the rate of release through mathematical models. Drug dissolution is a complex process and while it is difficult to use a fixed mathematical model for all the dissolution data, it is possible. Current researchers tend to use some classical mathematical model to forecast the release for example, zero-order kinetic release model, first-order kinetic release model, Higuchi model and Ritger - Peppas model. These classic mathematical models are a big help in analyzing the data.

In this research, the intent is to investigate the different types of pharmaceutical polymers to prepare filaments suitable for 3D printing. The main objectives of this study are as follows: 1) Using Autodesk® Fusion 360™ to design an original model of the tablet for print. 2) Based on the physical and chemical properties of the API and polymer, select the appropriate polymers suitable for 3d printing. 3) Couple HME and FDM 3D Printing to print controlled release tablets of different densities. 4) Studying the in vivo dissolution release profile of 3D printed tablets.

With the continuous development of the pharmaceutical field, the development of personalized doses of drugs has received increasing attention. 3D printing technology can meet the individual needs of people just as compared with traditional pharmaceutical dosage forms (Jonathan and Karim, 2016).

2. Materials and Methods

2.1 Materials

Ketoprofen (LGM Pharma, Jersey City, NJ, USA), the chemical used as the model API in this study, is an arylalkanoic acid compound. It has analgesic, anti-inflammatory and antipyretic effects, as well as a melting point of around 93-96 ° C. Other chemicals were also studied alongside the Ketoprofen. These include Benecel^{TM} Hydroxypropyl methylcellulose(HPMC) K4M, AquaSolve^{TM} Hydroxypropyl methylcellulose (HPMC) -AS HG, and Klucel^{TM} hydroxypropylcellulose (HPC) LF wich were all donated by Ashland Inc. which is located in Covington, KY, US.

a) Methods

2.2.1 Formulations

We created a filament made up of 30% (w/w) Ketoprofen, 50% (w/w) HPMC K4M and 20% (w/w) HPMC- AS HG; we also made another filament with 30% (w/w) Ketoprofen, 50% (w/w) HPMC K4M and 10% (w/w) HPMC- AS HG 10% HPC LF. Both types of filament were prepared using a Thermo Fisher Scientific 11 twin-screw co-rotating extruder. Two formulations and the extrusion conditions were listed in Table 1.

Table 1. Two different formulations for extrusion.

Formulations	Process Temperature (°C)	Ketoprofen w/w%	HPMC-K4M w/w%	HPMC-ASHG w/w%	HPC LF w/w%
F1	150	30	50	20	0
F2	150	30	50	10	10

2.2.2 HME Process

The two formulations were mixed as a powder to ensure an even distribution of chemicals before we applied the HME process. Then a Thermo Scientific™ Pharma 11-mm diameter Twin-screw Extruder (Thermo Fisher, Waltham, MA, US) was used in this study to prepare the filaments for printing. The formulations were extruded at 150℃ and the screw speed of 50 rpm in all zones with the standard configuration (Fig. 2). In addition, compared to the standard 3D Printing filament PLA and the 1.75mm diameter required of the 3D Printer; a 1.5mm round shape die was chosen to extrude filaments for the next 3D Printing step.

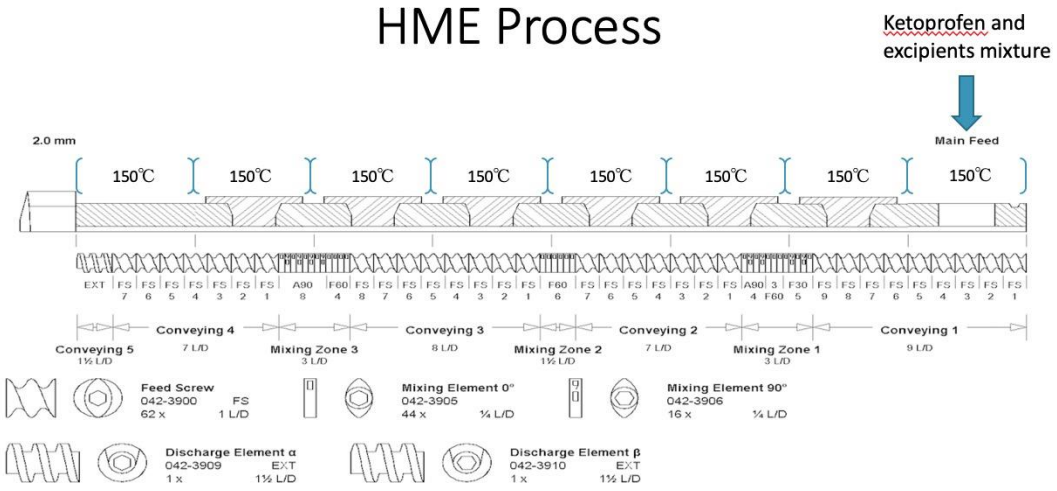


Figure 2. Standard screw configuration of Thermo Scientific™ Pharma 11-mm diameter Twin-screw Extruder.

2.2.3 Filaments Texture Analysis

A TA-XT2i analyzer (Texture Technologies, Hamilton, MA, USA) was used to test the filament stiffness in this study. Smooth and even filaments were selected for texture analysis and each segment was cut 5cm long. In order to better optimize the formulation, we performed a stiffness test and 3-point bend test. When performing stiffness tests, we set the conditions to a speed of 2 mm/s and a trigger force of 5.0 g. For the 3-point bending test, we easily found the breaking force, breaking distance, stiffness and other parameters for each filament. Each of the filaments was placed on a test bench with a size of 25 mm. The test speed was 10 mm/s with a trigger force of 5.0 g; this was done at distances of 10.00 mm. Fifteen filaments for each formulation were tested and data collection and analysis were performed using Exponent software version 6.1.5.0 (Stable Micro Systems, God-alming, UK).

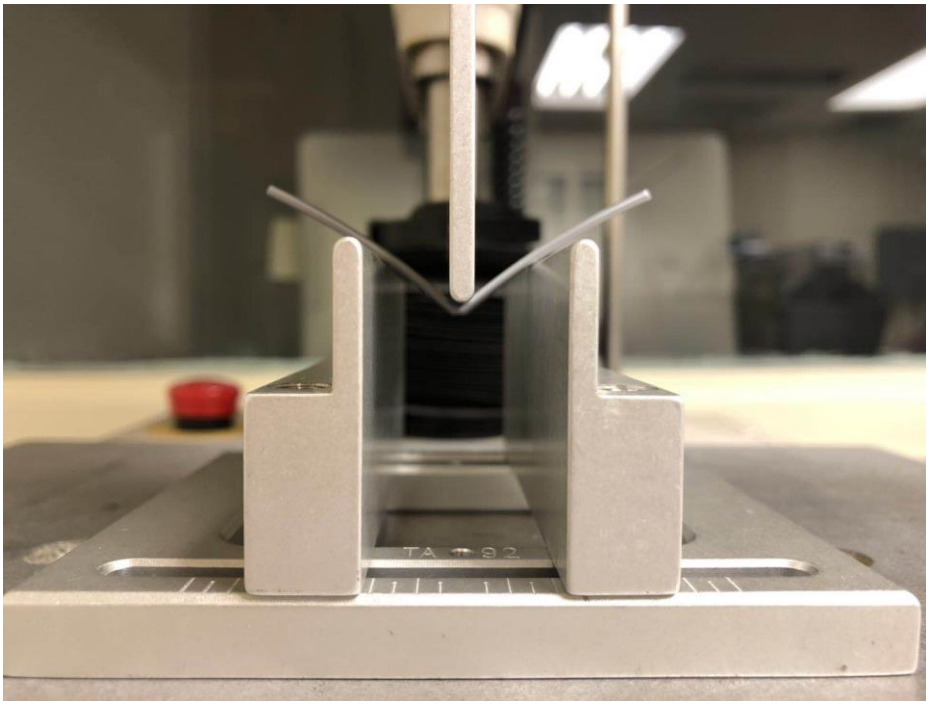


Figure 3. PLA 3-point bending test

2.2.4 Model Design for 3D Printing

Autodesk® Fusion 360TM (Autodesk Inc., USA) was used to design the tablet model we used in this study. The geometry of the selected dosage form is a tablet consisting of a cylindrical housing with a similarly shaped core (Figure 4). It was then exported as an STL file to be used with our printer, an Original Prusa i3 MK3S kit (PRUSA RESEARCH S.R.O. ,Prague, Czech Republic).

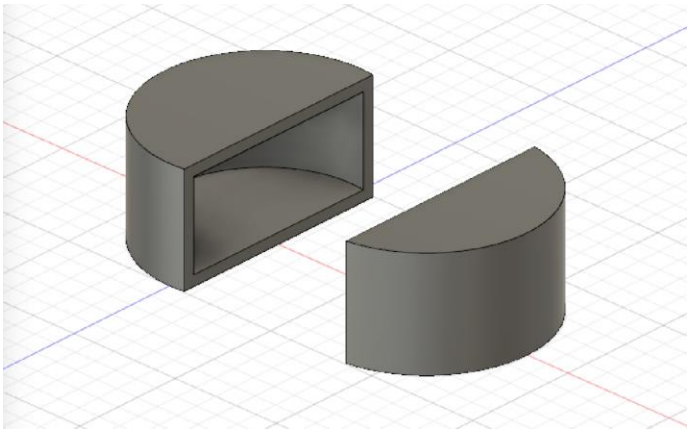


Figure 4. 3D printing design of shell

2.2.5 Thermogravimetric Analysis (TGA)

Thermogravimetric analysis (TGA) is a thermal analysis method that measures the mass of a sample as its temperature changes over time. For this study, the samples were tested by using a PerkinElmer Pyris 1 TGA Thermogravimetric Analyzer (PerkinElmer Inc, Waltham, MA, USA). By heated the samples from room temperature to 350 ℃ at 10℃/min in an open aluminum pan and applied ultra-purified nitrogen as a purge gas at a rate of 35 ml /min, data was collected then analyzed using Pyris software (TA Instruments, LLC, Water, USA).

2.2.6 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) is a thermal analysis technique. It can measure a variety of thermodynamic parameters. The mixing powder, filaments, and printed tablets were all analyzed using DSC. The Diamond DSC system (PerkinElmer, Waltham, MA, US) was used to

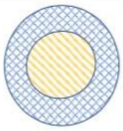
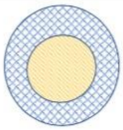
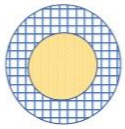
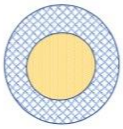
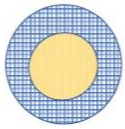
measure and analyze the sample by heating the temperature from 10° C to 200 ° C at 25 ° C / min with a 5-15 mg sample inside a Tzero Hermetic Aluminum plate. Ultra-purified nitrogen was used as a purge gas at a rate of 50 mL/min. We collected the data using Pyris software (PerkinElmer) and analyzed the temperature and the amount of heat transferred per unit time.

2.2.7 Filaments and 3D Printing

We used the prepared filaments to print tablets through a fused deposition modeling (FDM) 3D printer called the Original Prusa i3 MK3S kit (PRUSA RESEARCH S.R.O. ,Prague, Czech Republic). The tablet core was made using F1(30% (w/w) Ketoprofen, 50% (w/w) HPMC K4M and 20% (w/w) HPMC- AS HG) and the outside shell was made up of F2(30% (w/w) Ketoprofen, 50% (w/w) HPMC K4M and 10% (w/w) HPMC- AS HG 10% HPC LF). We then imported the design into Ultimaker CURA software (version 3.4.1; Ultimaker, Geldermalsen, The Netherlands) to prepare it for printing.

The printing setting were as follows: printing temperature: 220℃; build plate temperature: 45℃; layer height: 0.06mm; wall thickness: 0.8mm; wall line count: 2; top/bottom thickness: 0.6mm; top/bottom layers: 10; horizontal expansion: 0mm; print speed: 60mm/s; build plate adhesion type: brim.

Table 2. Density gradient modification 3D Printing tablets design

Core Density \ Shell Density	20%	30%	40%
40%	T1 	T2 	T3 
50%	T4 	T5 	T6 
60%	T7 	T8 	T9 

2.2.8 Scanning Electron Microscopy (SEM)

The cross sections and surfaces of the shell and core of the printed tablet were analyzed using a JSM-7200 FLV Field-Emission Scanning Electron Microscope (SEM) (JEOL, Peabody, MA, U.S.). All samples are covered by a gold layer by a gold sputtering system for 30 s at ~ 70 mTorr pressure for visualization. Pictures were then taken by a Canon 60D camera (Canon, Tokyo, Japan). SEM is critical to our understanding of the internal structure of microscopic drugs, so we can also get more information about the potential release mechanism of drugs (Siepmann and Göpferich, 2001).

2.2.9 Tablet Morphology Test

In this study, VWR® Digital Calipers (VWR®, PA, U.S.) were used to get the precise diameter and height of every tablets, checking each different density combination 5 times. The

standard tablet hardness tester (VK200; Agilent Technologies, Santa Clara, CA, USA) was used to determine the hardness of tablets, and each group was also be measured five times.

2.2.10 In Vitro Drug Release Study

A drug dissolution profile was obtained by the United States Pharmacopoeia (USP)-II Dissolution Apparatus (Hanson SR8-plusTM; Hansen Research, Chatsworth, Calif., USA) for 3D Printing tablets. The dissolution test was performed according to the United States Pharmacopoeia standards using a Phosphate Buffer (pH 6.8). Each experiment was performed in triplicate using 900 mL of the dissolution medium for 24 hours at 37℃ with the paddle speed set to 50 rpm peddle speed and samples were taken at 0.25, 0.5, 0.75, 1, 2, 4, 6, 8, 12, 24 hours and analyzed. The amount of Ketoprofen released was determined by HPLC (Waters Corp., Milford, MA, USA) at 246nm using methanol: water as 7:3 as the moving phase and the sample analysis was performed using Empower software (version 2, Waters Corp.).

2.2.11 Dissolution Mathematical Model Study

An OriginPro 2019 64bit (OriginLab, Northampton, MA, U.S.) was used to analyze and create the dissolution curve in this study. The previous data from the in vitro drug release was imported to OriginPro 2019 64bit and choose the non-linear fitting and drawing and analyzing its relative curve carried out. In this experiment, we investigated the relationship between solubility and common mathematical release models of dissolution: zero-order kinetic release model, first-order kinetic release model, Higuchi model and Ritger - Peppas model. By comparing its

compatibility with various models, the most suitable mathematical dissolution model for ketoprofen-3D Printing tablets was selected to provide more accurate prediction of dissolution for future production. Correlation coefficient(R^2) was an important parameter in this study to judge the degree of fit of the model.

3. Results and Discussion

3.1 Thermal Analysis

From the TGA result (Fig.5), ketoprofen was been observed start to degrade after 290℃ and other polymers start degrade around 350℃, so that also means the samples would stay stable during the HME 150℃ and 3D printing 220℃.

The DSC curves for homogeneous F1 and F2 mixtures without HME process are for the Core and Shell curves respectively in Figure 6 below. Their DSC curve peaked at about 93℃. The curves of F1 and F2 after the HME process are the core and shell print shown in the Figure6. It can be clearly seen that after the heating process, there is no peak in F1 and F2, which shows that ketoprofen successfully formed homogeneous solid dispersion and achieved the amorphous state with polymer during the HME process.

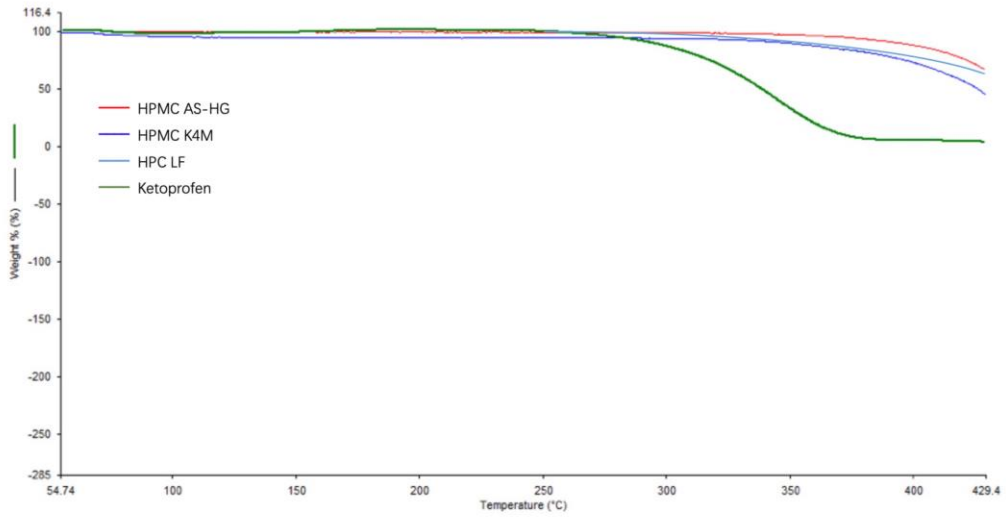


Figure 5. TGA thermogram for ketoprofen, HPMC- K4M, HPMCAS-HG and HPC-LF

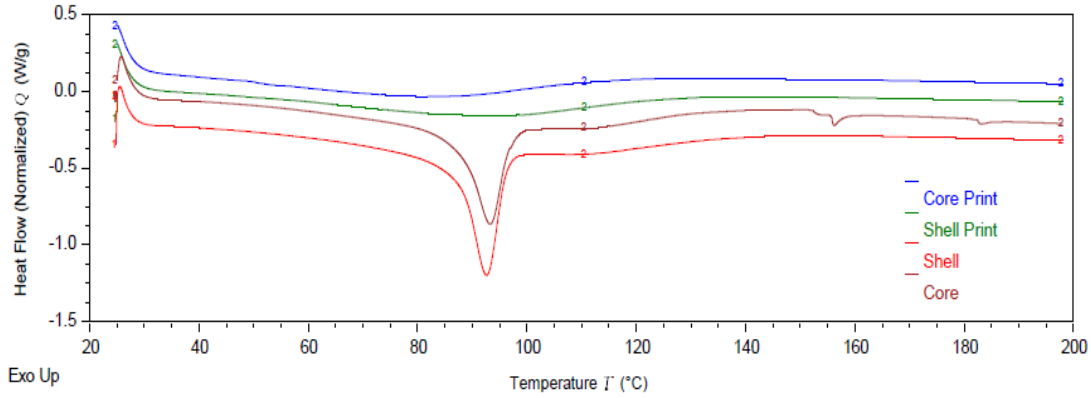


Figure 6. DSC thermogram for F1 and F2 homogeneous mixture and the printed core and shell grinded powder

Klucel™ HPC LF can be an immediate release- tablet binder, and AquaSolve™ HPMC-AS HG can be a controlled release tablet binder. So when we add AquaSolve™ HPMC-AS HG into shell's formulation, which has not been included in core formulation, we find some interesting

effects. The different formulation design, combined with the difference between internal and external densities, can make the drugs in the shell release at a different rate, reaching the minimum effective concentration more quickly. Alongside that, a modified core can help to maintain a high blood concentration longer. This cascade makes the duration of action of the drug longer and maintain blood levels within the therapeutic window for a longer period of time.

Two formulations of ketoprofen- loaded filaments were successfully produced through the HME process. Compared to conventional methods, HME produces filaments which cause the API and polymer to form an amorphous condition in the molten state, and it squeezes more air out so that they can be intimately mixed. The lower porosity facilitates the of controlled release drug, which provides better control of its release curve. HME's extrusion process increases the hardness of the filaments and reduces the elastic deformation, which can better meet the requirements of 3D Printing.

3.2 Filament Texture Analysis

During 3D Printing, the filament is wound by a rotatable axle and fed automatically at a constant speed through a rigid feeding gear. Because of this, the filaments must have certain properties to work in the feeding system. If the filaments are not hard enough or too brittle or the viscosity is too low, they will be easily be broken during the feeding process and the printing cannot be continued. 3D Printing technology is still mainly used in the plastics industry rather

than pharmaceutical area, so we can compare the filaments we made with standard PLA to judge whether they are suitable for printing. Viscosity; hardness and brittleness are the most important parameters to look at when evaluating the compliance of filaments. The ability to deform a material when it is stressed is called ductility. The properties of the material itself that are hard and difficult to bend are defined as stiffness, which is when the ductility is low (Rösler et al., 2007). The stiffness is the key to determining whether the filaments can be successfully fed into the 3D Printer's feeder, because the filaments are easily broken during this process. According to physics, the brittleness should be calculated like this formula:

$$\text{Stiffness} = F/\delta$$

Here, the applied force is F, and deformation is δ. In this study, we think that the breaking force is applied force, and the breaking distance represents deformation. In 3-point bending test, the breaking force means the magnitude of the force let filaments break. The breaking distance is the distance from the filaments start deformation till fracture. Then using these two parameters we can calculate the stiffness of the filaments. In this study, each group of filaments was tested and printed ten times. Successful printing for more than six times would be defined as adequate properties for 3D Printing. According to the previous study, we already chose the filaments good for printing in this study. As such, both F1 and F2 show good mechanical properties and have been printed successfully ten times each.

Table 3. Filaments 3-point bending test and stiffness test results

Formulation	Force (g)	Distance (mm)	Stress (g/mm^2)	Stiffness (g/mm)	Property
PLA	1189±12.62	3.75±0.21	10825.054±366.197	317.6±14.71	adequate
F1	628.78±25.49	8.57±0.96	6933.691±974.492	73.36±28.01	adequate
F2	431.5±9.44	6.8±0.45	7006.152±434.166	63.46±11.23	adequate

Compared with PLA, F1 and F2 require a relatively larger breaking force, and the breaking distance and stiffness are relatively smaller. This is because F1 and F2 are relatively soft, and the ductility is not easy to be broken. F1's breaking force and breaking distance are larger than F2 which has added extra HPC LF. It can also be concluded that HPC LF will soften the properties of the filaments, and HPMC AS-HG has higher stiffness than HPC LF. So HPC LF can only be added in a small amount to moderate the drug release. If there is too much, the filament cannot meet the requirements of 3D Printing.

3.3 Tablets Morphology Analysis

As shown in Figure 6, 3D Printing drug can maintain the stability of the print to produce tablets with specifications. Figure 7 shows the shells from 20% to 30% 40% from left to right. It can be clearly seen that the outer surface of the lower density shell is more rough, because the

lower density of the tablet is less precise. Figure 7b is 40% 50% 60% core from left to right, because the smaller the outer surface is smoother and less rough, but compared to Figure 7a, the difference in density can be clearly compared. Figure 7c shows a printed shell on the left and a core on the right.

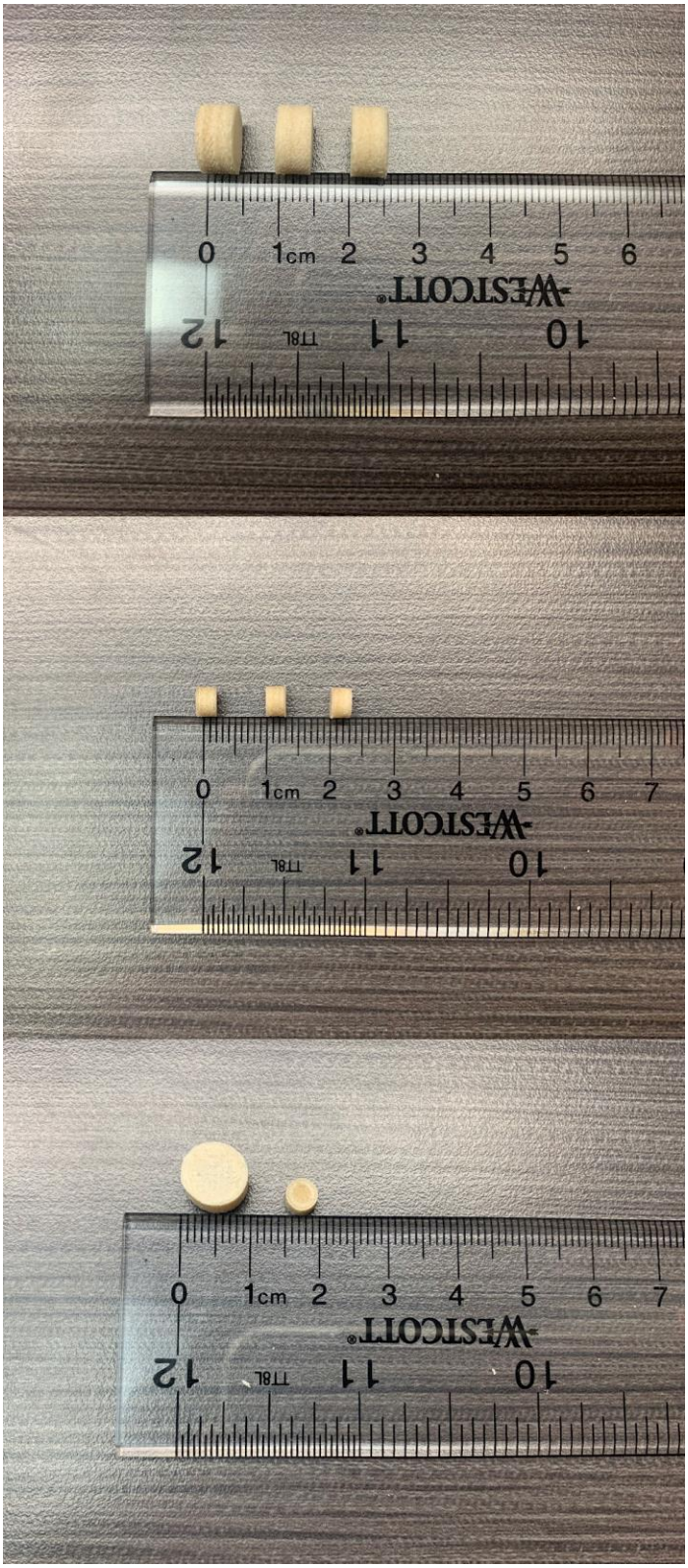


Figure 7. Difference in size and texture between shell and core

The SEM pictures of core and shell cross-section of 3D printed tablets show that the tablets are smooth and have excellent performance. Figure 8 also proved the difference of the 3D printing densities microscopically. For the outside shell it looked really porous and loose and for the inside core was much tighter. It can also be seen the layer by layer printing style form the bottom left one (Fig 8).

It can be seen from Figure 8 that 3D printing has demonstrated the advantages of stable quality of printed tablets in the pharmaceutical area, which laid the foundation for research consistency.

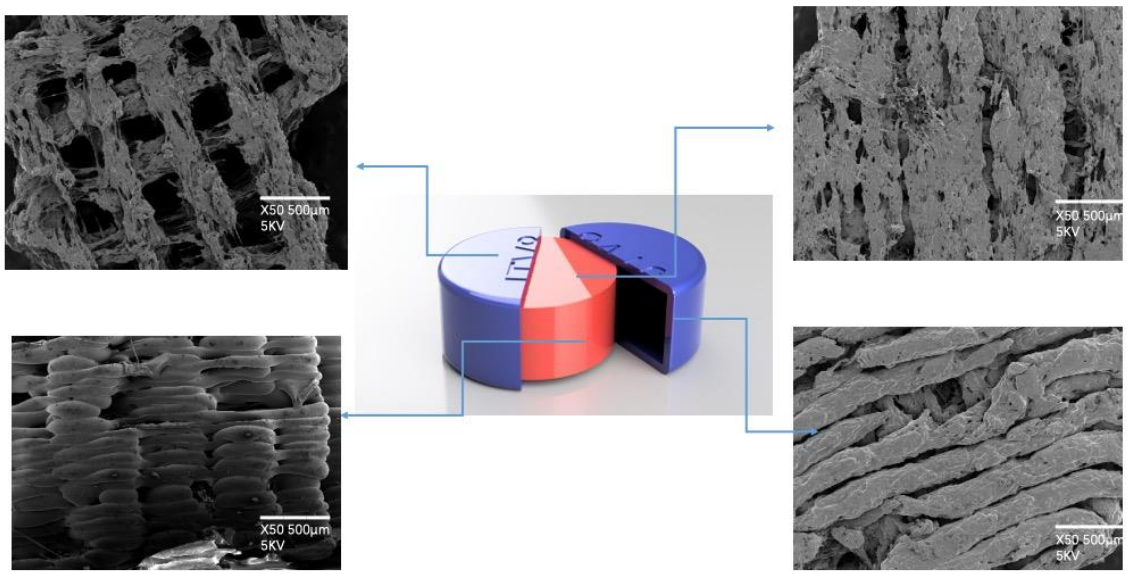


Figure 8. SEM 3D structure of T5, with a 30% shell fill and 50% core fill

The geometric characteristics for 3D printed tablets data (Table 4) shows pretty consistent, it means the printed tablets had really good stability at size. It can be seen from the data (Table 4) that due to the special structure of the shell core of the tablet, its hardness mainly depends on the density of the shell and is independent of the core, hardness would increase with the density increase. It can be seen from Table 4 that 3D printing has demonstrated the advantages of stable quality of printed tablets in the pharmaceutical area, which laid the foundation for research consistency.

Table 4. Geometric characteristics of the 3D printed tablets

Tablets	Diameter(mm)	Height(mm)	Weight(mg)	Hardness(kp)
20%Shell 40%Core	10.04±0.17	5.07±0.08	337±24	14.4±0.1
20%Shell 50%Core	10.14±0.32	5.05±0.09	339±30	14.4±0.1
20%Shell 60%Core	10.08±0.28	5.02±0.05	347±12	14.4±0.1
30%Shell 40%Core	10.09±0.31	5.11±0.21	332±17	15.3±0.1

30%Shell 50%Core	9.98±0.23	5.02±0.06	340±12	15.1±0.2
30%Shell 60%Core	10.17±0.29	5.17±0.08	351±10	15.1±0.2
40%Shell 40%Core	10.01±0.09	5.04±0.19	343±18	15.3±0.3
40%Shell 50%Core	10.05±0.13	5.12±0.25	357±21	15.4±0.2
40%Shell 60%Core	10.05±0.17	5.15±0.03	347±19	15.4±0.2

3.4 In vitro drug release study

3D printed tablets of different densities were evaluated by their drug release rates curve. The 3D printed drugs all show good properties in controlled release rates because they have higher hardness, toughness and stiffness. It can be seen from Figure 9 that the release rate of a 3D printed drug is significantly slower as the density of the shell and core increases. This shows that we have successfully used a density gradient difference to produce 3D printed tablets that control the dissolution rate. The core and shell density is different through a maximum of 20% shell and

40% core, which makes the dissolution profile optimal. In the previous research, due to the special nature of 3D printing, the printed structure is very hard and compact, so it is recommended to try not to let the core have too high density under the condition of model design, which is not conducive to dissolution.

It is also clear from the dissolution curve that the density is one of the important factors when determining the dissolution rate of 3D Printing tablets. 3D printing requires only the change of the parameters in the software to make the operation more simple, fast and intuitive, and make the process more controllable, which is more conducive to manufacturing more personalized designs.

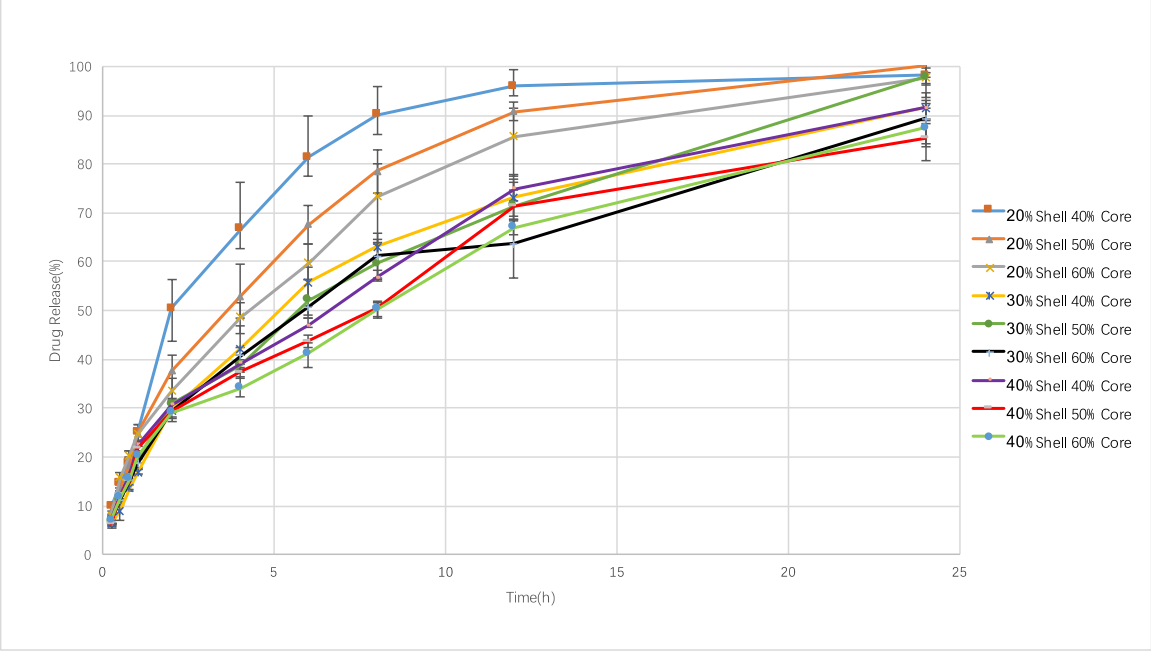


Figure 9. In vitro drug release profiles of tablets T1-T9, 100mg ketoprofen released from the HPMC and HPC matrix

3.5 Dissolution Kinetic Studies

The in vitro dissolution rate of a drug is an important parameter for determining formulation. When the dissolution rate of a certain dosage is expressed by a special mathematical function, it is easier to make a quantitative analysis of the dissolution prediction. Here a model of kinetics is used, where the drug release (Q(t)) over time is a function of time (t). To better analyze the dissolution of the drug, the following function is used here for analysis (Costa and Lobo, 2003).

3.5.1 Zero-order Kinetic Release Model

The formula here is: $Q(t)=Q_0+K_0t$. Where Q(t) is the release amount of the drug at time t, K_0 is the zero-order dissolution rate and it is a constant value, and M_0 is the initial amount of the drug in the solution at the initial state, that is, when t=0 (Vareles et al., 1995).

3.5.2 First-order Kinetic Release Model

This model uses the formula, $\ln Q(t)=\ln Q_0+K_1*t$. It's equal to $Q(t)= Q_0*(1-e^{-K1t})$, where Q(t) is the release amount of the drug at time t, K_1 is the first-order dissolution rate and. In this circumstances, the percentage of drugs eliminated per unit time in the body remains constant (Sweeney and Burnham, 1990).

3.5.3 Higuchi Model

This formula is: $Q(t)= Q_0 + K_H*t^{1/2}$. Where Q(t) is the release amount of the drug at time t, K_H is the drug release rate of Higuchi model and this model is the most common model to describe the controlled release drug (Gohel et al., 2000; Petropoulos et al., 2012).

3.5.4 Ritger - Peppas Model

The Ritger – Peppas model follows the formula, $Q(t) /Q(\infty) = kt^n$. Where Q(t) is the release amount of the drug at time t, Q is the release amount of drug at time ∞,

K and n are coefficients (Ritger and Peppas ., 1987).

3.5.5 Analysis of the Drug Using Mathematical Models

In this research, the parameters of the relevant fitting equations and other calculations can be easily calculated by using OriginPro 2019 64bit for the different kinetic release models, zero-order kinetic release model, first-order kinetic release model, Higuchi model and Ritger -Peppas model. OriginPro 2019 64bit software can perform a variety of complex data simulation and numerical analysis and drawing operations. Since the original software directly obtains an intuitive release curve from the initial data, it can directly observe the data with large dispersion and better eliminate the experimental error.

OriginPro 2019 64bit was used for data linear and nonlinear fitting, and input of the function worked successively. Table 5 shows the zero-order kinetic release model(a), first-order kinetic

release model(b), Higuchi model (c), Ritger - Peppas model(d) and Peppas- Sahlin model, which were used in OriginPro 2019 64bit for the linear and nonlinear curve fitting. Studying these can also help us to understand the release of drugs more closely. The release of the drug can be divided into Fickian and non-Fickian diffusion. When the drug only has Fickian diffusion, the release rate of the drug is independent of the concentration of the drug, and the diffusion concentration is only time-dependent with distance. It can be seen from the figure that the first-order kinetic release model; Ritger-Peppas model fits the curve better than the other 3 models (Dash et al., 2010; Costa and Lobo, 2001).

When considering the results of Ritger-Peppas equation, it can be seen that the fitting error at the last moment of cumulative drug release is large, but this can also be explained by the fact that the standard deviation of the raw data at the last moment is inherently large. The R^2 of the Ritger-Peppas equation also shows a good fit. When $n \leq 0.45$, it means that there is only Fickian diffusion (drug diffusion); when $n \geq 0.89$, there is only Case II transport (skeletal erosion) and when $0.45 < n < 0.89$, the drug release mechanism called non-Fick diffusion(anomalous transport). So n is the most important parameter in this equation and we printed 9 groups at different densities. The fitting results of the tablets all conformed to $0.45<n<0.89$, which indicates that the dissolution process of this drug has both Fickian diffusion and Case II transport. The tablet release is the result of drug diffusion and skeleton dissolution (Ritger & Peppas, 1987).

In order to better judge which diffusion dominates in the Ketoprofen-based 3D Printing tablets, the correction formula of the Ritger-Peppas formula, Peppas-Sahlin model is introduced here for further calculation. $Q(t)/Q(\infty) = k_1t^{n1} + k_2t_2^{n1}$, which involves the analysis of several variables. The model considers both Fickian diffusion (the first term of the equation) and the Case II relaxation (the second term of the equation) contribution. If the release of the drug only has a Fickian diffusion and the Case II relaxation can be completely ignored, the n_1 in the formula is equal to the n in the Rigter- Peppas formula. Therefore, the difference between n and n1 also proves that the release mechanism of the drug is the result of Fickian diffusion and Case II relaxation coupling. The percentage of drug F released by Fickian diffusion can be calculated by the following formula: $F=1/(1+k_2/k_1*t\text{^}n_1)$.

The ratio of Case II relaxation R to F can be calculated by the following formula (Peppas and Sahlim, 1989; Unagolla and Jayasuriya, 2017): $R/F= k_2/k_1*t\text{^}n_1$.

Table 5. Dissolution kinetic parameters of 3D printing tablets

	Zero-order		First-order		Ritger- Peppas		Higuchi		Peppas-sahlin			
	K_0	R^2	K_1	R^2	n	R^2	K_H	R^2	K1	K2	N1	R^2
T1	4.22	0.83	0.31	1.00	0.47	0.94	23.23	0.94	0.19	0.07	0.85	1.00
T2	4.54	0.87	0.29	0.99	0.52	0.97	23.97	0.97	0.18	0.05	0.72	1.00
T3	5.21	0.69	0.42	0.95	0.56	0.93	25.18	0.96	0.11	0.04	0.80	0.99

T4	5.38	0.71	0.26	0.96	0.59	0.96	22.79	0.98	0.12	0.05	0.67	1.00
T5	10.30	0.87	0.51	0.98	0.66	0.98	25.24	1.00	0.11	0.02	0.67	1.00
T6	4.69	0.81	0.32	0.95	0.54	0.98	21.30	0.99	0.13	0.02	0.59	1.00
T7	4.91	0.87	0.19	0.94	0.50	0.99	20.03	0.99	0.12	0.06	0.53	1.00
T8	5.68	0.78	0.50	0.95	0.59	0.94	21.39	0.97	0.10	0.04	0.52	0.99
T9	5.69	0.78	0.49	0.95	0.58	0.94	21.42	0.97	0.09	0.04	0.52	0.99

Because the degradation of drugs is a very complex process as they are affected by not only physical factors but also chemical factors. Any mathematical modeling method must consider these processes. Although the Higuchi model is the most frequently used model in controlled release drug mathematical model fitting, researchers have pointed out that the classical equation using the Higuchi model is premised and more suitable for ideal conditions. The release of the drug needs to meet the following conditions (Siepmann & Göpferich, 2001; Zhang et al., 2017):

i. The initial drug concentration should be much higher than the solubility of the drug.

ii. Drug spread is one-dimensional.

iii. Drug release under pure diffusion control.

iv. The swelling or dissolution of the iv polymer carrier is negligible.

Table 5 shows the different mathematical models fitting results, and after compared with the correction coefficient (R^2) we can see the Ritger –peppas , higuchi and peppas –sahlin fits the drug release more than others. And in all of these 3 model, Peppas-sahlin fits best. Because Peppas- sahlin is the correction formula of the Ritger-Peppas formula, so we will also get the diffusion method from it. We can use this equation to accurately predict the dissolution and release rate of the drug in future, which is of great significance for production.

Based on these prerequisites, the Higuchi model is not suitable for in vitro release of 3D printing in this study. Since the diffusion of the 3D printed tablet is not one-dimensional but three-dimensional, the initial drug concentration is not much higher than the solubility of the drug, and the swell happened during HPMCAS-HG skeleton erosion. Though Higuchi model fits good in here, it won't be applicable to describe this release profile.

Table 6. R/F parameters for T1-T9

	T1	T2	T3	T4	T5	T6	T7	T8	T9
R/F	1.69	1.52	1.50	1.29	1.21	1.13	1.38	1.20	1.07

The table shows R/F of all 9 group tablets are greater than 1, so Case II relaxation dominates the dissolution part compared to Fickian diffusion. It can also be concluded that as the density increases, its dominant position will gradually weaken.

4. Conclusion

In this study we successfully produced ketoprofen-loaded filaments and printed them into designed tablets. At the same time, we successfully used the single-punch method to compress the tablets and performed a comparison of the in vitro dissolution experiments. Experiments have shown that the same material has significantly improved the dissolution rate after HME and 3D Printing process, and the therapeutic window of the drug is larger and better. We also confirmed that the printing density has a great influence on the dissolution rate of 3D printed tablets by the dissolution of 3D printed tablets of different density gradients. When the density is greater, the dissolution is slower; and when the density is lower, and the dissolution can be faster in the body. The effects of different printing densities on a drug's rate of release were successfully summarized by using the mathematical model, which provided data for the rational prediction of drug's rate of release in the future.

This research successfully combined 3D printing and HME to produced controlled release tablets with different densities. This research provides a foundation for the development of controlled release tablets using combined 3D printing and HME technology thus expanding the use of this emerging technology for development of more complex pharmaceutical in the future.

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