science, engineering and health studies

Review Article

Science, Engineering and Health Studies
https://lio1.tci-thaijo.org/index.php/sehs
ISSN (Online): 2630-0087

Recent advances in 3D printing for floating drug delivery platforms

Pornsak Sriamornsak[1,2], Kampanart Huanbutta[3] and Tanikan Sangnim[4]*

[1] Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand
[2] Academy of Science, The Royal Society of Thailand, Bangkok 10300, Thailand
[3] School of Pharmacy, Eastern Asia University, Pathum Thani 12110, Thailand
[4] Faculty of Pharmaceutical Sciences, Burapha University, Chonburi 20131, Thailand

ABSTRACT

Floating drug delivery is a gastro-retentive delivery system offering an advantage for poor-bioavailability drugs, which have low absorption in the upper gastrointestinal tract. This system can be administered effectively, increasing bioavailability and optimizing absorption. This technique can also prolong drug release, resulting in less frequent drug administration throughout the day. However, key restrictions of floating drug delivery are the ability to change drug dosage, drug release kinetics, buoyant force, and duration to suit each patient. With the constraints of the conventional manufacturing process, 3D printing has been developed to produce floating drug delivery devices with flexible dosage forms. This review summarizes studies that used different 3D printing techniques and materials to produce their own floating drug delivery systems and also discuss the limitation of this manufacturing technique.

Keywords: additive manufacturing; 3D printing; gastro-retentive drug delivery system; floating drug delivery system

***Corresponding author**:
Kampanart Huanbutta
kampanart@eau.ac.th

***Received**: 11 January 2022*
***Revised**: 4 February 2022*
***Accepted**: 21 February 2022*
***Published**: 19 August 2022*

***Citation**:
Sriamornsak, P., Huanbutta, K., and Sangnim, T. (2022). Recent advances in 3D printing for floating drug delivery platforms. Science, Engineering and Health Studies, 16, 22010001.

1. INTRODUCTION

Currently, 3D printing has been used in various fields, and its applications continue to expand. The concept of 3D printing has been initiated in 1970; 3D-printed products were fabricated using high-energy beam to solidify the powdered material layer by layer, and this process is called "selective laser sintering" (Babbar et al., 2020). Then, in the 1980s and 1990s, stereolithography (SLA) and fused deposition modeling (FDM) printing techniques were invented and introduced (Gupta et al., 2019). Initially, 3D printing has been utilized to accelerate prototyping in the motor vehicle and aircraft industries. Then, its application has been expanded to construction, education, medication, art, jewelry, and so on (Freedman, 2017).

The 3D printing technique increasingly gains interest in pharmaceutical and medical research and application because of its potential to prepare personalized medicine that can obtain maximum therapeutic outcomes with minimal side effects. Apart from personalized pharmaceutical dosage forms, several complex drug delivery systems, such as fixed dose combination (Khaled et al., 2015), extended drug release (Skowyra et al., 2015), and gastro-retentive platform (Zhang et al., 2020), have been developed using different 3D printing techniques.

Over the past few years, assorted novel designs of floating drug delivery systems prepared by 3D printing have been developed and published (Charoenying et al., 2020a; Singpanna et al., 2020; Zhang et al., 2020). This printing technology can overcome the limits of traditional floating drug delivery system preparation (tableting and coating), such as the difficulties in adjusting the dose (cannot break the tablet) and controlling drug release patterns. Furthermore, drug is released at different body parts in each patient because the stomach emptying period of each patient varies. Therefore, floating drug delivery systems necessitate individualized dose forms and preparation.

This review discusses how 3D printing techniques can be applied to construct gastro-retentive drug delivery systems. Traditional and novel preparation procedures for floating drug delivery systems are reviewed and updated. Advantages and points for improvement of the 3D-printed floating drug delivery systems are discussed and considered. Finally, the future and feasibility of 3D printing and the authors' opinions are discussed.

2. 3D PRINTING IN THE PHARMACEUTICAL FIELD

2.1 Types of 3D printing technologies used for pharmaceutical dosage form preparation

Although various 3D printing processes have been developed, only four techniques are commonly employed in the fabrication of pharmaceutical dosage forms: FDM, thermal inkjet (TIJ), liquid dispersion on powder, and light-introduced polymerization (Figure 1).

2.1.1 Fused deposition modeling

The procedure comprises selecting the suitable thermoplastic polymer, which is melted and extruded through a movable heated nozzle. The molten polymer is injected layer by layer. Then, it solidifies as the designed shape that was created using computer-aided design models. This method can be applied to various dosage forms that incorporate polymers, such as implants and constant-drug-release tablets (Katakam et al., 2015; Ventola, 2014). FDM 3D printing has many advantages. For example, FDM printers are inexpensive, and the materials used in these printers are inexpensive and readily available. Moreover, printing precision is sufficient to produce high-detail items in a short amount of time. Given their limitations in the complexity of the features they can produce, FDM printers are best suited for finer models or professional-quality prototypes. The printed object cannot be utilized as a mechanical part because of its insufficient robustness.

2.1.2 3D thermal inkjet

This technique entails heating the ink fluid with the aid of a micro-resistor, resulting in the formation of a vapor bubble that nucleates and expands, forcing the ink to drop out of the nozzle. This process is called drop-on-demand inkjet printing and pneumatic extrusion. Different from other printers, the 3D TIJ can print liquid with different properties. This technique has been used in dispensing extemporaneous medicinal preparation/solution (Buanz et al., 2011). Moreover, it can be used in the development of biopharmaceutical products.

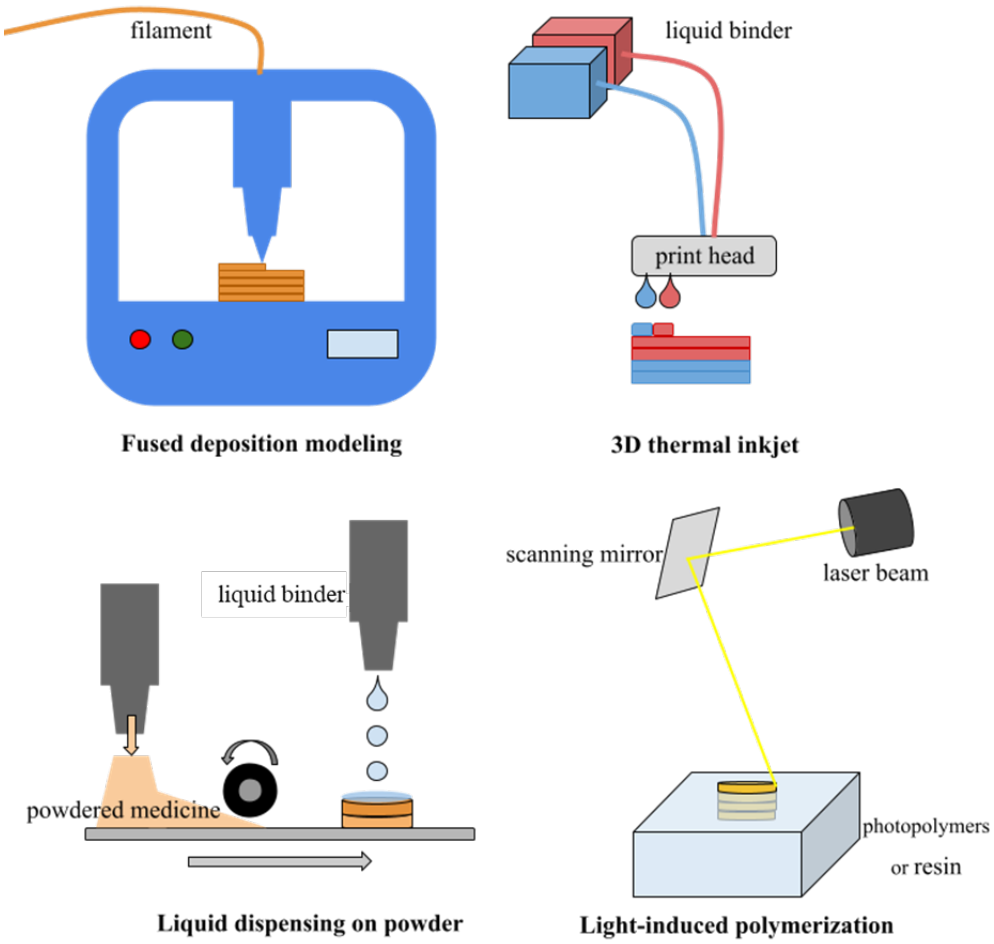

Figure 1. Common 3D printing processes used in pharmaceutical dosage form preparation

2.1.3 Liquid dispensing on powder

Liquid dispensing on powder is a powder-based 3D printing process in which various combinations of active chemicals and ink are sprayed or dropped in differing droplet sizes on a powder substrate before solidifying into a solid dosage form. The advantage of this technique is its ability to be expanded on a large scale. Furthermore, the product has a low density and is porous, making it ideal for the preparation of rapid-dissolving tablet dosage forms. ZipDose is an example of a commercial name that can create porous dosage forms for fast disintegrating purposes with high drug load (Bansal et al., 2018).

2.1.4 Light-induced polymerization

Light-induced polymerization is a 3D printing technique that uses light or UV radiation to solidify photopolymers or radiation-curable resins one layer at a time. Light-induced polymerization has been developed into several advanced 3D printing techniques, such as SLA, digital light processing, and continuous direct light processing. This technique has been applied to prepare prototypes or product molds (Méndez-Ramos et al., 2016). Light-induced polymerization printers can be used to create highly detailed and complex designs. The finished product surface is smooth; thus, sanding is often unnecessary. Light-induced polymerization models are built using resin, which can be damaged by continuous sun exposure. Furthermore, the printing time and cost are above average. Using 3D printers requires technical expertise because light-induced polymerization is sophisticated. It is unsuitable for inexperienced users.

2.2 Advantages of 3D printing in the pharmaceutical field

Several advantages of 3D printing over conventional manufacturing have been reported in the pharmaceutical field. First, 3D printing can improve productivity. The 3D printing is faster than traditional methods for fabricating pharmaceutical products, such as prostheses and implants, with the added benefit of improved resolution, repeatability, precision, and consistency (Schubert et al., 2014). Second, 3D printing is suitable for customized and personalized products and pharmaceutical dosage forms. Last, the objects created by 3D printing are inexpensive. With all materials practically affordable, 3D printing is advantageous for small-scale production units or enterprises that manufacture complicated products or parts (Mertz, 2013).

3. MECHANISM AND TYPE OF GASTRO-RETENTIVE DRUG DELIVERY SYSTEMS

As shown in Figure 2, different mechanisms of gastro-retentive drug delivery systems have been developed and published. Each mechanism has its own set of benefits and drawbacks, making it suitable for various applications.

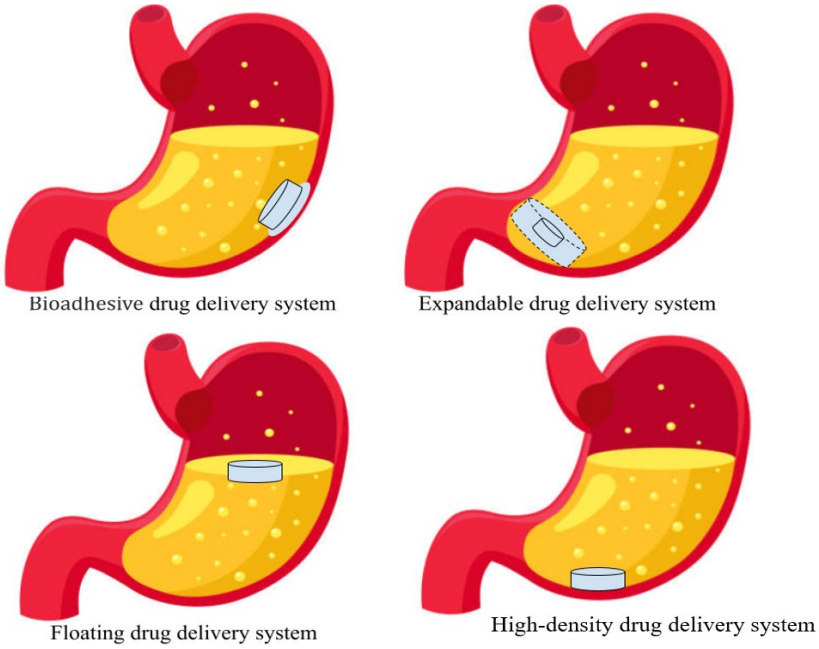

Figure 2. Mechanism and type of gastro-retentive drug delivery systems

3.1 Bioadhesive drug delivery system

A bioadhesive drug delivery platform is employed within the lumen as a delivery system to increase drug absorption in a site-specific way. Bioadhesive polymers, which may stick to the epithelial surface of the stomach, are used in this method (Chavanpatil et al., 2006). Polycarbophil, carbopol, lectins, chitosan, gliadin, and alginate are some of the promising pharmaceutical excipients frequently used in bioadhesive drug delivery systems.

3.2 Expandable drug delivery system

Expandable gastro-retentive delivery systems are easily swallowed and achieve a significantly larger size (approximately 12-18 mm) in the stomach because of swelling or unfolding. This phenomenon can extend their gastric retention period. Following drug release, the size of the system is reduced when it is expelled from the stomach (Melocchi et al., 2019).

3.3 Floating drug delivery system

Given its low density (less than 1.004 g/cm^3), the system floats in and above the gastric contents without impacting the gastric emptying rate (Whitehead et al., 1998). This property enables the system to float in the gastric fluid for an extended length of time while the drug releases at the desired rate. These systems can stay afloat in the stomach via one of two mechanisms, noneffervescent systems or effervescent systems, which are distinguished by gas generation.

3.4 High-density drug delivery system

The high density (more than 1.004 g/cm^3) of this system is used as a strategy to create a retention mechanism. This strategy allows it to sink to the stomach's bottom, where it remains. Given their retention in the antrum rugae or folds, high-density pellets could withstand stomach peristaltic motion, extending the gastrointestinal transit time from 5.8 h to 25 h, as reported by Garg and Gupta (2008).

4. FLOATING DRUG DELIVERY SYSTEM FABRICATED BY 3D PRINTING

In the last few years, 3D printing has been applied to fabricate floating drug delivery systems because of its several advantages as mentioned above. The most common 3D printing technique and gastro-retentive mechanism used in the studies are FDM and floating, respectively. As demonstrated in Table 1, several types of printing materials were used.

Table 1. Summary of the floating drug delivery systems fabricated by 3D printing

Article title	Printing technique	Printing material	Model drug	Research highlight	Reference
3D-printed gastroretentive sustained release drug delivery system by applying design of experiment approach	FDM	polylactic acid	baclofen	This method may be used to alter the release rates of other conventional formulations without requiring sophisticated formulation.	Jeong et al., 2020
Fabrication of floating capsule-in-3D-printed devices as gastro-retentive delivery systems of amoxicillin	FDM	polyvinyl alcohol	amoxicillin	The 3D-printed devices can be applied to other conventional solid dosage forms for prolonged drug release.	Charoenying et al., 2020a
Development of a zero-order kinetics drug release floating tablet with anti–flip-up design fabricated by 3D-printing technique	FDM	polylactic acid	metronidazole	The system provided good evidence for using this stable (anti-flip-up) floating tablet model in applications requiring constant drug release	Huanbutta et al., 2021
Design and development of zero-order drug release gastroretentive floating tablets fabricated by 3D printing technology	FDM	polyvinyl alcohol	metronidazole	Drug release pore sizes and air volumes of these tablets were pivotal to zero-order drug release kinetics and floating time	Huanbutta et al., 2019
Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing	FDM	hydroxypropyl cellulose and ethyl cellulose	theophylline	Floating pulsatile tablets with the desired lag time for pulse release of theophylline were successfully developed with the proposed HME coupled 3D printing technique.	Dumpa et al., 2020
Fabrication of intragastric floating, controlled release 3D printed theophylline tablets using hot-melt extrusion and fused deposition modeling	FDM	hydroxypropyl cellulose and stearic acid	theophylline	The model drug was loaded in the filament of hydroxypropyl cellulose and stearic acid. With zero-order drug release profiles, the 3D hollow tablets with varying infill percentages and shell thickness demonstrated appropriate buoyancy.	Giri et al., 2020
Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its in vivo pharmacokinetic evaluation in Beagle dogs	FDM	polylactic acid	acyclovir	The ability of a 3D printed gastro-floating device paired with a traditional acyclovir sustained release tablet to reduce dose frequency and increase acyclovir oral bioavailability.	Shin et al., 2019

Table 1. (continued)

Article title	Printing technique	Printing material	Model drug	Research highlight	Reference
Hot-melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine	FDM	hydroxypropyl cellulose and polyvinylpyrrolidone	cinnarizine	High drug-loaded filaments, from the proper polymer composition.	Vo et al., 2020
Three-dimensional printing of gastro-floating tablets using polyethylene glycol diacrylate-based photocurable printing material	light-induced polymeriza-tion	polyethylene glycol diacrylate	metoprolol tartrate	Extrusion 3D printing using photocurable materials has been shown to be a simple and effective method of producing bespoke oral floating tablets with complex interior structures and variable characteristics.	Lin et al., 2021
Structure-based gastro-retentive and controlled-release drug delivery with novel 3D printing	pressure-assisted microsyringe	hydroxypropyl methylcellulose, microcrystal-line cellulose, lactose, and polyvinylpyrrolidone	Ginkgolide	To accomplish longer and steady gastro-retention and controlled-release of pharmaceuticals, pressure-assisted microsyringe 3D printing was utilized to construct gastro-retentive drug delivery systems (focused on inner structure innovation).	Wen et al., 2019
Preparation of clarithromycin floating core-shell systems (CSS) using multi-nozzle semi-solid extrusion-based 3D printing	multi-nozzle semi-solid extrusion	hydroxypropyl methylcellulose and polyvinylpyrrolidone	clarithromycin	The micro-airbag structure and CO_2 generation further increased the buoyancy of core-shell system extending floating time.	Chen et al., 2021a
Three-dimensional (3D)-printed devices composed of hydrophilic cap and hydrophobic body for improving buoyancy and gastric retention of domperidone tablets	fused deposition modeling	polyvinyl alcohol and polylactic acid	domperidone	Capsule-shaped floating device (CFD) using FDM 3D-printer with 2 polymer combination.	Charoenying et al., 2020b
Preparation of high-drug-loaded clarithromycin gastric-floating sustained-release tablets using 3D printing	semisolid extrusion	hydroxypropyl methylcellulose and polyvinylpyrrolidone	clarithromycin	Semisolid extrusion-based 3D printing provided potential for achieving a high drug loading gastric-floating sustained-release tablets.	Chen et al., 2021a

4.1 3D-printed external device for floating purposes

This approach applies 3D printing to prepare external devices to elevate the systems. The 3D-printed devices must make the whole drug delivery system density less than the gastric medium. As a result, several 3D-printed device structures and forms were devised and manufactured. Using the 3D-printed capsular device (Figure 3), Jeong et al. (2020) created a new oral drug delivery system for gastro-retentive sustained drug release. A FDM 3D printer was used to fabricate and print the capsule that can manage drug release rates from an inner commercial immediate-release tablet while floating in the gastric medium.

As depicted in Figure 4a, Charoenying et al. (2020a) also designed a floating 3D-printed capsular device for combining with commercial amoxicillin capsules. The designed 3D-printed devices had a floating time of more than 10 h in an *in vivo* floating trial in rabbits and the drug release kinetics from the commercial amoxicillin in the 3D-printed device obeyed the Higuchi model (Charoenying et al., 2020a). Shin et al. (2019) also created a gastro-retentive system in a capsular device format by utilizing 3D printing (Figure 4b) and tested its *in vivo* pharmacokinetics after oral delivery in beagle dogs. The acyclovir sustained-release tablet was introduced to the floating device to facilitate the extended release of the medicine in the stomach. X-ray images showed that the 3D-printed floating system remained in the beagle dog's stomach for longer than 12 h. When compared with the

resultsobtained after the administration of immediate-release and floating SR tablets, the time to reach the highest concentration (T_{max}) of acyclovir from the floating SR tablet was significantly delayed, whereas the maximum concentration (C_{max}) decreased and the area under the curve increased in the *in vivo* pharmacokinetic study. The *in vivo* dissolution profiles of the floating system were also predicted using a population pharmacokinetic model based on *in vivo* pharmacokinetic data. Dumpa et al. (2020) used a hot-melt extrusion-paired FDM 3D printing and direct compression approach to create a new core–shell gastro-retentive floating pulsatile drug delivery system in the shape of a tablet, as illustrated in Figure 4c. Hot-melt extrusion has been used to produce hydroxypropyl cellulose and ethyl cellulose-based filaments for the printing of shells to cover theophylline core tablets. Changes in 3D printing infill density alter the porosity of the dosage form, potentially elevating the system (Dumpa et al., 2020).

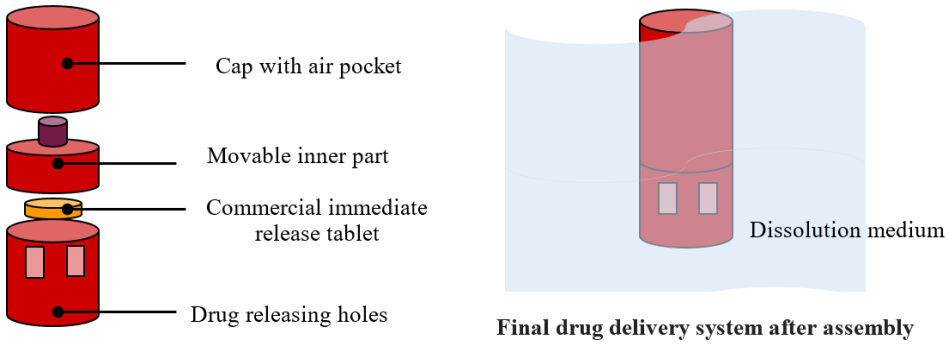

Figure 3. 3D-printed capsular device for gastro-retentive drug delivery systems designed by Jeong et al. (2020)

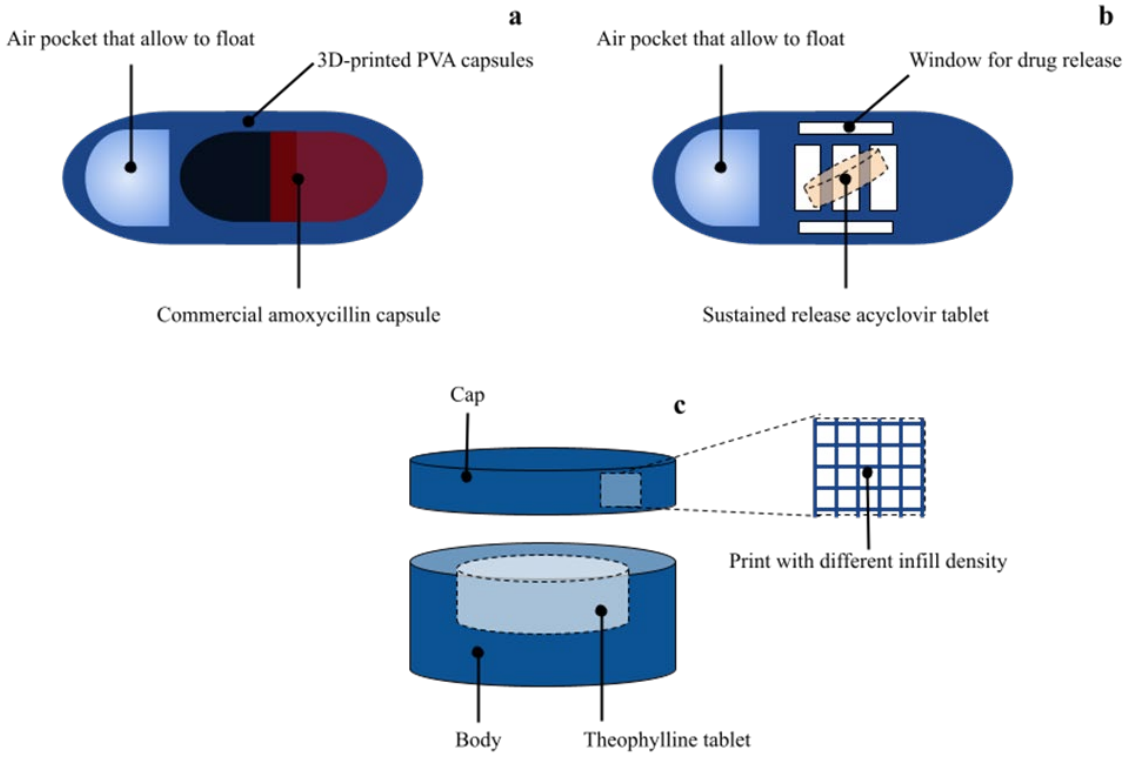

Figure 4. Schematic of the 3D-printed external device for the gastro-retentive system from the studies of (a) Charoenying et al. (2020a), (b) Shin et al. (2019), and (c) Dumpa et al. (2020)

4.2 Drug-incorporated polymer-based floating system

Another strategy to develop a floating system is to incorporate the drug with the printing material and then print them into the designed shape and structure. The drug is dispersed in a printing material or polymer, leading to the establishment of a matrix in this approach (Table 2). A constantly extended drug release profile is possible with proper dosage form design and formulation. Various printing materials and printing processes can be used to obtain a lengthy floating period of the dosage form with zero-order kinetic drug release. By combining hot-melt extrusion with FDM 3D printing, Giri et al. (2020) have developed a specific methodology for manufacturing

gastro-retentive floating tablets. Hot-melt extrusion was applied to produce theophylline-containing filaments inside a hydroxypropyl cellulose matrix. As shown in Figure 5a, the hollow structure on the interior of the tablet provided buoyant force and influenced the drug release profile. All of the gastro-retentive floating tablets produced were able to float for 10 h and had zero-order release kinetics. Vo et al. (2020) employed a hot-melt extrusion method to combine hydroxypropyl cellulose and vinylpyrrolidone vinyl acetate copolymer with the model drug (cinnarizine), as depicted in Figure 5b. The tablet was prepared in the form of a cylindrical hollow tablet model to lift the system. The drug release from floating tablets followed pseudo-zero-order kinetics and could be regulated for up to 12 h. In addition to the FDM printing method, Lin and colleagues used a photocurable polymer (polyethylene glycol diacrylate (PEGDA)) in conjunction with HPMC K100M to manufacture customized oral preparations with complex internal structures and changeable features (Figure 5c). HPMC K100 was optimized as an additive to boost the printability of materials having a high amount of PEGDA to achieve suitable mechanical strength and sustained-release behavior. Wen et al. (2019) developed a technique for integrating 3D printing and floating drug delivery system (with a focus on inner structure innovation) to achieve long and consistent floating and controlled drug release. As shown in Figure 5d, a pressure-assisted micro-syringe 3D printer was used to develop and materialize three digital models of varying structures. The optimized formulation could retain the system in the *in vitro* test for 10–12 h and in the *in vivo* test for 8–10 h with sustained drug release. Not only one printing material can be printed at a time, but two substances can also be printed simultaneously. Chen et al. (2021a) used multi-nozzle semi-solid extrusion 3D printing to create a core–shell structure with a floating core and a low-density drug-loaded shell. As presented in Figure 5e, many micro-airbags inflated when the solution reached the floating core and produced carbon dioxide. The micro-airbag structure and carbon dioxide production could elevate the system. This structure and floating core bring a new approach to developing a stable floating drug delivery system in the gastrointestinal tract (Chen et al., 2021a).

Table 2. List of polymers and their properties applied to produce a 3D printing model for floating drug delivery systems

Printing technique	Printing material	Printing material properties and preparation	Reference
FDM	hydroxypropyl methylcellulose (HPMC)	HPMC is a nonionic thermoplastic polymer. HPMC, together with the drug, can be melted and prepared as filament before being used in the 3D printing process.	Giri et al., 2020; Lin et al., 2021
FDM	hydroxypropyl cellulose (HPC) and polyvinylpyrrolidone vinyl acetate (PVA/VA) copolymer	HPC is a nonionic thermoplastic cellulose derivative. PVP/VA are also thermoplastic copolymers. They can be melted with the drug and treated as filament before being employed in the 3D printing process.	Vo et al., 2020
Pressure-assisted microsyringe	hydroxypropyl cellulose (HPMC), microcrystalline cellulose (MCC), and lactose	All of these ingredients including drug can be combined to make a slurry. Then they were printed and dried in the position specified by the 3D model.	Wen et al., 2019
FDM	polylactic acid (PLA)	PLA is a synthetic biodegradable polymer that is insoluble. It's a thermoplastic polymer with a high strength and modulus. PLA may persist up to 3h in acid, making it ideal for drugs that need to be released slowly.	Fu et al., 2018
FDM	Soluplus®	Soluplus® is a polymeric solubilizer with an amphiphilic chemical structure. It is a graft copolymer composed of polyethylene glycol, polyvinyl acetate, and polyvinyl caprolactam. It is suitable for hot-melt extrusion because of its T_g of about 70°C and low hygroscopicity.	Hardung et al., 2010

4.3 3D-printed floating drug delivery system with a specific mechanism

For various objectives, many mechanisms have been introduced to floating drug delivery systems. As illustrated in Figure 6a, the 3D-printed floating drug delivery model, which features a pore at the bottom to regulate the drug release rate, was developed by Huanbutta et al. (2019). According to the Noyes–Whitney equation, if the drug release region (bottom pore) is fixed, the drug will release constantly:

$$dC/dt = A*(D/h)*(Cs - C) \quad (1)$$

where dC/dt is the dissolution rate of the drug, A is the surface area available for dissolution, D is diffusivity, h is apparent thickness, and C_s and C are the solubility concentration of the drug and the concentration of the dissolved drug at time t, respectively (Hattori et al., 2013). The drug release obeyed zero-order kinetics, and the system could float for more than 4 h. However, the developed model might flip up in the patient's stomach, causing obstruction of drug release. Therefore, the floating drug delivery model inspired by a buoy was developed. From the developed model shown in Figure 6b, the drug was constantly released from the tablet housing during 8-9 h with stable floating. These findings support the use of the floating tablet concept in applications that need consistent drug release and customized therapy (Huanbutta et al., 2021).

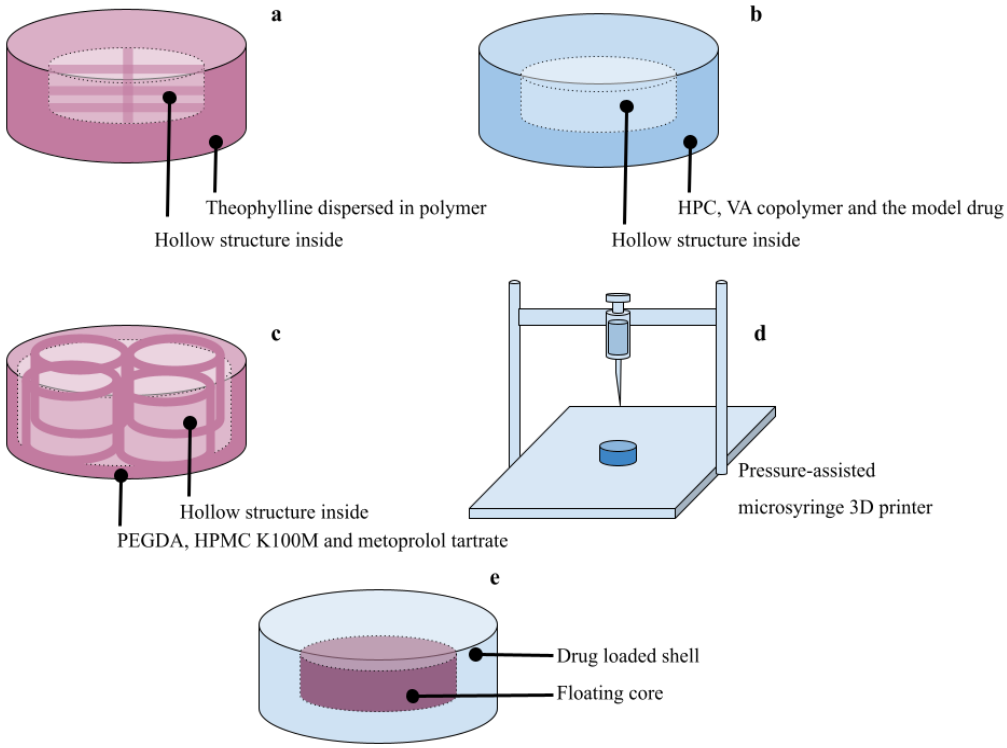

Figure 5. Schematic of the drug-incorporated polymer 3D-printed floating systems from the studies of (a) Giri et al. (2020), (b) Vo et al. (2020), (c) Lin et al. (2021), (d) Wen et al. (2019) and (e) Chen et al. (2021a)

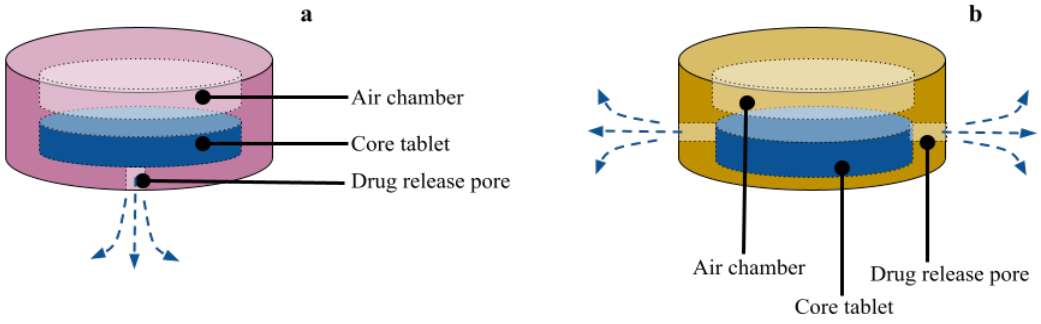

Figure 6. Schematic of 3D-printed floating drug delivery system with (a) zero-order kinetic drug release and (b) antiflip-up mechanism

5. LIMITATION OF 3D-PRINTED FLOATING DRUG DELIVERY SYSTEMS

For the past 3 years, 3D-printed floating drug delivery systems have been widely developed. Several factors must be considered when determining whether or not a technology is feasible to utilize.

5.1 Size and shape of the tablet or capsule

Several variables contribute to the 3D-printed floating tablet or capsule being larger than a conventional tablet, which is usually between 15 and 22 mm in diameter. The flotation mechanisms of the tablets and capsules usually require an air chamber sufficiently large to elevate the system and drug from buoyant force. Furthermore, high-resolution printing may be required for floating mechanisms or structures, necessitating a larger print size than usual.

5.2 Drug loading efficiency and stability

In the drug loading polymer prepared for FDM 3D printing, the drug must cooperate with the polymer in the form of the filament. The prepared filament must be sufficiently flexible for the printing process. Therefore, the polymer cannot hold a large amount of the drug, and a large tablet size is required to achieve a therapeutic dose. Furthermore, drug stability after the printing process is critical because the 3D printer uses high temperature to melt polymers or printing materials.

5.3 Industrial manufacturing

At this time, only one 3D-printed drug, namely, Spritam® (levetiracetam) from Aprecia Pharmaceutical, has been approved by the US FDA (Dubin, 2018). Spritam® is formulated with ZipDose technology, which combines additive manufacturing and formulation science to produce

rapidly disintegrating formulations of medications. Personalized medicine is too complex for industrial manufacturing. As a result, in the hospital setting, the concept of a customized drug dose has been implemented (Öblom et al., 2019). Öblom and team compared 2D and 3D printing techniques to the current method for producing patient-tailored warfarin doses at hospital unit setting pharmacies in Finland. The potential of the printing technology to fabricate on-demand patient-specific dosages is demonstrated in this research (Öblom et al., 2019).

5.4 Registration and quality control

Devices manufactured using 3D printing, similar to those made with conventional manufacturing methods, are subject to regulatory guidelines. In 2016, the FDA released draft guidelines for manufacturers that use 3D printing about the technical considerations for additively manufactured devices. The draft recommendation provides manufacturer options for device design, manufacturing, and testing considerations for designing 3D-printed devices (FDA, 2017). United States Pharmacopeia (USP) and British Pharmacopoeia have not released any criteria or monograph about the quality control of drugs manufactured by 3D printing yet. Nevertheless, USP recognizes the significance of innovative technologies in the pharmaceutical sector. As a result, USP organizes workshops and meetings to obtain information and comments on 3D printing processes for pharmaceutical manufacturers (USP, 2020). Another issue to be concerned about is the quality control approach for personalized medication printing in hospitals and at home. Pharmacists or regulators must ensure that the custom-printed medication items meet pharmaceutical quality requirements.

6. CONCLUSION

The 3D printing is a relatively new technique that allows complex structures and adjustable dosage forms to be manufactured, producing a sophisticated drug release profile for each patient and ailment. This technology meets several needs, including a customizable retention period, buoyant force, and drug release profile, for floating drug delivery systems. These advantages can assist clients with illnesses that need floating drug delivery systems to achieve the best possible results. A stable and feasible model, formulation, and printing process will be available and developed in the near future for application in actual clinical settings.

REFERENCES

Babbar, A., Jain, V., Gupta, D., Prakash, C., Singh, S., and Sharma, A. (2020). 3D Bioprinting in pharmaceuticals, medicine, and tissue engineering applications. In *Advanced Manufacturing and Processing Technology* (Prakash, C., Singh, S., and Davim, J. P., eds.), 1st ed., pp. 147-161. Boca Raton, Florida: CRC Press.

Bansal, M., Sharma, V., Singh, G., and Harikumar, S. L. (2018). 3D printing for the future of pharmaceuticals dosages forms. *International Journal of Applied Pharmaceutics*, 10(3), 1-7.

Buanz, A. B. M., Saunders, M. H., Basit, A. W., and Gaisford, S. (2011). Preparation of personalized-dose salbutamol sulphate oral films with thermal ink-jet printing. *Pharmaceutical Research*, 28(10), 2386-2392.

Charoenying, T., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Akkaramongkolporn, P., and Opanasopit, P. (2020a). Fabrication of floating capsule-in-3D-printed devices as gastro-retentive delivery systems of amoxicillin. *Journal of Drug Delivery Science and Technology*, 55, 101393.

Charoenying, T., Patrojanasophon, P., Ngawhirunpat, T., Rojanarata, T., Akkaramongkolporn, P., and Opanasopit, P. (2020b). Three-dimensional (3D)-printed devices composed of hydrophilic cap and hydrophobic body for improving buoyancy and gastric retention of domperidone tablets. *European Journal of Pharmaceutical Sciences*, 155, 105555.

Chavanpatil, M. D., Jain, P., Chaudhari, S., Shear, R., and Vavia, P. R. (2006). Novel sustained release, swellable and bioadhesive gastroretentive drug delivery system for ofloxacin. *International Journal of Pharmaceutics*, 316(1-2), 86-92.

Chen, P., Liu, J., Zhang, K., Huang, D., Huang, S., Xie, Q., Yang, F., Huang, J., Fang, D., Huang, Z., Lu, Z., and Chen, Y. Z. (2021a). Preparation of clarithromycin floating core-shell systems (CSS) using multi-nozzle semi-solid extrusion-based 3D printing. *International Journal of Pharmaceutics*, 605, 120837.

Chen, P., Luo, H., Huang, S., Liu, J., Lin, M., Yang, F., Ban, J., Huang, Z., Lu, Z., Xie, Q., and Chen, Y. Z. (2021b). Preparation of high-drug-loaded clarithromycin gastric-floating sustained-release tablets using 3D printing. *AAPS PharmSciTech*, 22(3), 131.

Dubin, C. H. (2018). 3D printing – 3D printed drugs hold great potential for personalized medicine. *Drug Development & Delivery*, 18(2), 50-55.

Dumpa, N. R. Bandari, S., and Repka, M. A. (2020). Novel gastroretentive floating pulsatile drug delivery system produced via hot-melt extrusion and fused deposition modeling 3D printing. *Pharmaceutics*, 12(1), 52.

FDA, US. (2017). FDA's role in 3D printing. *Food and Drug Administration*. [Online URL: https://www.fda.gov/medical-devices/3d-printing-medical-devices/fdas-role-3d-printing] accessed on October 22, 2021.

Freedman, J. (2017). *Future Uses and Possibilities of 3D Printing*, New York: Cavendish Square Publishing, LLC., pp. 5-25.

Fu, J., Yin, H., Yu, X., Xie, C., Jiang, H., Jin, Y., and Sheng, F. (2018). Combination of 3D printing technologies and compressed tablets for preparation of riboflavin floating tablet-in-device (TiD) systems. *International Journal of Pharmaceutics*, 549(1-2), 370-379.

Garg, R., and Gupta, G. D. (2008). Progress in controlled gastroretentive delivery systems. *Tropical Journal of Pharmaceutical Research*, 7(3), 1055-1066.

Giri, B. R., Song, E. S., Kwon, J., Lee, J. H., Park, J. B., and Kim, D. W. (2020). Fabrication of intragastric floating, controlled release 3D printed theophylline tablets using hot-melt extrusion and fused deposition modeling. *Pharmaceutics*, 12(1), 77.

Gupta, V., Nesterenko, P., and Paull, B. (2019). *3D Printing in Chemical Sciences*, London: Royal Society of Chemistry Publishing, pp. 1-21.

Hardung, H., Djuric, D., and Ali, S. (2010). Combining HME & solubilization: Soluplus®—the solid solution. *Drug Delivery Technology*, 10(3), 20-27.

Hattori, Y., Haruna, Y., and Otsuka, M. (2013). Dissolution

process analysis using model-free Noyes-Whitney integral equation. *Colloids and Surfaces B: Biointerfaces*, 102, 227-231.

Huanbutta, K., and Sangnim, T. (2019). Design and development of zero-order drug release gastroretentive floating tablets fabricated by 3D printing technology. *Journal of Drug Delivery Science and Technology*, 52, 831-837.

Huanbutta, K., Sriamornsak, P., Kittanaphon, T., Suwanpitak, K., Klinkesorn, N., and Sangnim, T. (2021). Development of a zero-order kinetics drug release floating tablet with anti–flip-up design fabricated by 3D-printing technique. *Journal of Pharmaceutical Investigation*, 51(3), 213-222.

Jeong, H. M., Weon, K. Y., Shin, B. S., and Shin, S. (2020). 3D-printed gastroretentive sustained release drug delivery system by applying design of experiment approach. *Molecules*, 25(10), 2330.

Katakam, P., Dey, B., Assaleh, F. H., Hwisa, N. T., Adiki, S. K., Chandu, B. R., and Mitra, A. (2015). Top-down and bottom-up approaches in 3D printing technologies for drug delivery challenges. *Critical Reviews™ in Therapeutic Drug Carrier Systems*, 32(1), 61-87.

Khaled, S. A., Burley, J. C., Alexander, M. R., Yang, J., and Roberts, C. J. (2015). 3D printing of tablets containing multiple drugs with defined release profiles. *International Journal of Pharmaceutics*, 494(2), 643-650.

Lin, X., Fu, H., Hou, Z., Si, Y., Shan, W., and Yang, Y. (2021). Three-dimensional printing of gastro-floating tablets using polyethylene glycol diacrylate-based photocurable printing material. *International Journal of Pharmaceutics*, 603, 120674.

Melocchi, A., Uboldi, M., Inverardi, N., Briatico-Vangosa, F., Baldi, F., Pandini, S., Scalet, G., Auricchio, F., Cerea, M. Foppoli, A., Maroni, A., Zema, L., and Gazzaniga, A. (2019). Expandable drug delivery system for gastric retention based on shape memory polymers: Development via 4D printing and extrusion. *International Journal of Pharmaceutics*, 571, 118700.

Méndez-Ramos, J., Ruiz-Morales, J. C., Acosta-Mora, P., and Khaidukov, N. M. (2016). Infrared-light induced curing of photosensitive resins through photon up-conversion for novel cost-effective luminescent 3D-printing technology. *Journal of Materials Chemistry C*, 4(4), 801-806.

Mertz, L. (2013). Dream it, design it, print it in 3-D: What can 3-D printing do for you? *IEEE Pulse*, 4(6), 15-21.

Öblom, H., Sjöholm, E., Rautamo, M., and Sandler, N. (2019). Towards printed pediatric medicines in hospital pharmacies: Comparison of 2D and 3D-printed orodispersible warfarin films with conventional oral powders in unit dose sachets. *Pharmaceutics*, 11(7), 334.

Schubert, C., Van Langeveld, M. C., and Donoso, L. A. (2014). Innovations in 3D printing: A 3D overview from optics to organs. *British Journal of Ophthalmology*, 98(2), 159-161.

Shin, S., Kim, T. H., Jeong, S. W., Chung, S. E., Lee, D. Y., Kim, D. H., and Shin, B. S. (2019). Development of a gastroretentive delivery system for acyclovir by 3D printing technology and its in vivo pharmacokinetic evaluation in Beagle dogs. *PLoS One*, 14(5), e0216875.

Singpanna, K., Chareonying, T., Patrojanasophon, P., Rojanarata, T., Sukma, M., and Opanasopit, P. (2020). Fabrication of a floating device of domperidone tablets using 3D-printing technologies. *Key Engineering Materials*, 859, 289-294.

Skowyra, J., Pietrzak, K., and Alhnan, M. A. (2015). Fabrication of extended-release patient-tailored prednisolone tablets via fused deposition modelling (FDM) 3D printing. *European Journal of Pharmaceutical Sciences*, 68, 11-17.

USP. (2020). *Quality of 3D printing of medicines and supplements*. The United States Pharmacopeial Convention. [Online URL: https://www.usp.org/news/3d-printing-workshop] accessed on November 16, 2021.

Ventola, C. L. (2014). Medical applications for 3D printing: Current and projected uses. *Pharmacy and Therapeutics*, 39(10), 704-711.

Vo, A. Q., Zhang, J., Nyavanandi, D., Bandari, S., and Repka, M. A. (2020). Hot melt extrusion paired fused deposition modeling 3D printing to develop hydroxypropyl cellulose based floating tablets of cinnarizine. *Carbohydrate Polymers*, 246, 116519.

Wen, H., He, B., Wang, H., Chen, F., Li, P., Cui, M., Li, Q., Pan, W., and Yang, X. (2019). Structure-based gastro-retentive and controlled-release drug delivery with novel 3D printing. *AAPS PharmSciTech*, 20(2), 68.

Whitehead, L., Fell, J. T., Collett, J. H., Sharma, H. L., and Smith, A. M. (1998). Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. *Journal of Controlled Release*, 55(1), 3-12.

Zhang, P., Shadambikar, G., Almutairi, M., Bandari, S., and Repka, M. A. (2020). Approaches for developing acyclovir gastro-retentive formulations using hot melt extrusion technology. *Journal of Drug Delivery Science and Technology*, 60, 102002.