*https://doi.org/10.31925/farmacia.2026.1.3* **REVIEW**

# A BREAKTHROUGH IN DESIGNING GASTRORETENTIVE DRUG DELIVERY SYSTEMS (GRDDS) *VIA* 3D PRINTING

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## Abstract

The oral delivery of certain drugs, due to their physiological limitations, such as instability at alkaline pH, high solubility in gastric media, short biological half-life and envisioned local gastric action, requires the design of gastroretentive drug delivery systems (GRDDS). GRDDS are intended for prolonged gastric retention that exhibits improved bioavailability and patient compliance. Various conventional approaches have been used to design GRDDS, which include low-density systems, mucoadhesive systems, superporous or expandable systems, high-density systems and so on. There exist certain limitations with these conventionally designed systems, such as interference with the normal physiological functioning of the stomach, delayed floating lag time, rapid gastric emptying, etc. In addition to this, material and manufacturing process complexity leads to a tedious and time-consuming process. Contrary to this, the 3D printing technique, due to its technical advancement and feasibility to design tuned and complex geometries with more precision and accuracy, could be utilized easily and efficiently to design GRDDS. Moreover, the design of customized GRDDS using 3D printing techniques also allows for dose adjustment and control over drug release patterns. Extrusion-based 3D printing techniques, such as pressure-assisted micro-syringes (PAM) and fused deposition modelling (FDM), are the most widely used methods for designing 3D-printed GRDDS among the various 3D printing techniques that have evolved so far. This review emphasizes the recent research in the design of GRDDS *via* 3D printing techniques, elaborating on the various polymers used for 3D printing, types of extruders and 3D printers employed for designing GRDDS.

## Rezumat

Administrarea orală a anumitor medicamente, în contextul unor limitări fiziologice precum instabilitatea la pH alcalin, solubilitatea ridicată în mediul gastric, timpul de înjumătățire biologic scurt și necesitatea unei acțiuni locale la nivel gastric, impune dezvoltarea unor sisteme de livrare gastroretentivă a medicamentelor (GRDDS). Aceste sisteme sunt concepute pentru a prelungi retenția gastrică, cu scopul de a îmbunătăți biodisponibilitatea și complianța pacientului. Pentru proiectarea GRDDS au fost utilizate multiple abordări convenționale, precum sisteme cu densitate scăzută, sisteme mucoadezive, sisteme superporoase sau expandabile, sisteme cu densitate crescută, *etc*. Totuși, aceste strategii prezintă limitări semnificative: interferența cu funcționarea fiziologică a stomacului, evacuarea gastrică rapidă și alte constrângeri similare. În contrast, tehnologia imprimării 3D, datorită progreselor tehnice și capacității de a genera geometrii complexe, optimizate și controlate cu precizie, reprezintă o alternativă eficientă pentru dezvoltarea GRDDS. Mai mult, utilizarea imprimării 3D permite personalizarea GRDDS, facilitând ajustarea dozei și controlul profilului de eliberare a substanței active. Dintre tehnicile de imprimare 3D, metodele bazate pe extrudare, precum extrudarea asistată de presiune prin microseringă și modelarea prin depunere de filament topit, sunt cele mai frecvent aplicate în fabricarea GRDDS.

**Keywords**: gastroretentive drug delivery system, 3D printing, pressure assisted microsyringes, fused deposition modelling, tuned geometries, customized dosing

## Introduction

3D printing is a digital manufacturing technique that involves the use of computer-aided designs to produce 3D objects in a layer-by-layer fashion by depositing, fusing, or solidifying a wide variety of materials (1-3). The application of 3D printing is expanding in biomedical (4) and drug delivery fields (5, 6). The biomedical application covers bioprinting of tissues and organ models (7), fabrication of the personalized prosthetics (8, 9) and patient-specific implants (10). The pharmaceutical application covers the design of customized drug products with tuned drug release characteristics with more ease and convenience compared to conventional manufacturing methods (11-13). More significantly, the 3D printing technique could design personalized products at low cost on a small scale with reduced material waste (14-16). The drug manufacturing field has been revolutionized since 2015, after the FDA approval of the first 3D-printed drug product, SPRITAM, an anti-epileptic drug, Levetiracetam, designed as an ODT (orally disintegrating tablet) using zip-dose technology by Aprecia Pharmaceuticals, USA (17).

More recently, Triastek's 3D-printed T22 gastric retention drug received Investigational New Drug (IND) approval from the US FDA. The T22 gastric retention prototype is designed for treating pulmonary arterial hypertension (PAH) and chronic thrombo-embolic pulmonary hypertension (CTEPH). This gastro-retentive 3D-printed product, after oral administration, expands in the stomach to a size bigger than the pylorus, leads to increased gastric retention time and releases the drug in a predetermined manner. This 3D-printed product was fabricated by using melt extrusion deposition (MED) and micro injection molding (MIM) processes (18). The 3D printing technique has been comprehensively utilized in designing oral (19-21), topical, transdermal (22), vaginal (23) and ocular (24) drug delivery products. Moreover, 3D printing also provides flexibility in designing paediatric formulations in different shapes, designs, colours and flavours, which attracts and provides patient compliance among children (25, 26). On-demand manufacturing for customized delivery at the point of care (hospitals and pharmacies) with flexibility in dose and design beside improved patient compliance are a few of the advancements of 3D printing techniques over conventional manufacturing techniques (1, 27). The various 3D printing methods include powder-based, inkjet-based, vat photo-polymerization and extrusion-based printing techniques (6, 28). The powder-based binding or fusion technique involves selective laser sintering (SLS) and binder jetting, *i.e.*, drop-on-solid deposition methods of particle binding to create the 3D objects (29). This powder-based binding 3D technique has been used to manufacture the FDA-approved Spritam® tablet. The inkjet-based 3D printing technique is comprised of drop-on-demand (DOD) printing and continuous inkjet printing (CIJ), which precisely deposits droplets of materials in a layer-by-layer pattern *via* an inkjet printhead (30). The vat photopolymerization involves exposure of photopolymeric materials to UV light followed by curing of materials by different methods such as stereolithography (SLA) and digital light processing (DLP) (31). The extrusion-based 3D printing techniques are comprised of pressure-assisted microsyringes (PAM), fused deposition modelling (FDM) and direct powder extrusion (DPE) methods (32-34). In these methods, the 3D objects were designed by extrusion of the polymeric materials in the form of paste, filament and powder from a syringe or extruder nozzle with the application of pressure or heat (35). Figure 1 provides a schematic illustration of various extrusion-based 3D printing techniques.

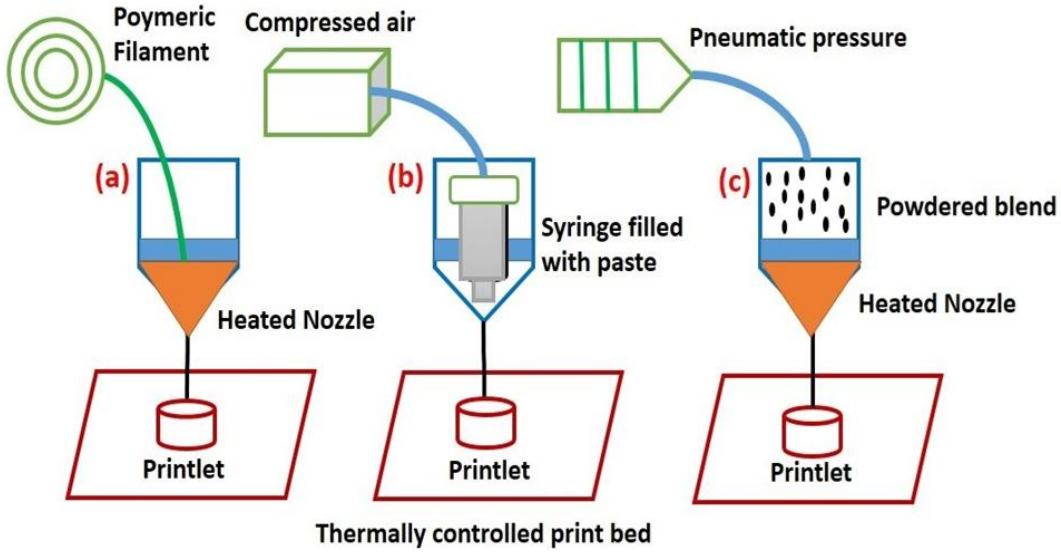


**Figure 1.**
Representing different types of extrusion-based 3D printing techniques, (a) FDM 3D printing technique, (b) PAM 3D printing technique, (c) DPE 3D printing technique

**3D Printing Advancement Over Conventional Approaches to Design GRDDS**

Though various conventional approaches have been explored to design GRDDS, they exhibit certain limitations, such as delayed floating lag time that may lead to the possibility of gastric emptying of the system before complete drug release, with material and manufacturing process complexity that leads to a tedious and time-consuming process. Moreover, the conventionally designed system may lose buoyancy due to erosion or dissolution of the polymeric material by losing the structural integrity of the designed system. Contrary to this, the 3D printing technique, due to its technical advancement and feasibility to design hollow structures with low density that float in the gastric media for prolonged periods with better

integrity and strength, can be used with more precision and accuracy to design floating GRDDS. Moreover, the conventionally designed floating systems also exhibit limitations, such as dose adjustment is not being possible in the case of a conventional tablet, as if the tablet is broken into two halves to adjust the dose, it loses its buoyancy. Secondly, control over drug release patterns is not possible with conventional floating tablets, and the conventional floating tablets could also lead to the release of drugs in different parts of the GIT due to the variability in gastric emptying time shown by every individual (36). These constraints might be addressed by designing customized GRDDS using 3D printing techniques.

The breakthrough of 3D printing has expedited the development of 4D printing techniques, where time acts as the fourth dimension. Thus, by using smart materials and smart design within the time frame, the 4D devices exhibit specific properties in response to stimuli, such as expandability, self-fitting, self-folding and unfolding. Various approaches have also been made by using the 4D printing technique to design GRDDS using smart materials and designs (37-40). Recently, there has been a significant increase in scientific publications, patents and copyrighted designs highlighting the promising potential of 3D-printed oral drug delivery systems. Among these contributions, approximately forty journal articles have specifically addressed gastroretentive drug delivery concepts. This review emphasizes the role of 3D printing techniques in the design of GRDDS, their advantages over conventional methods of manufacturing, various polymers used, types of extruders and 3D printers employed, system design and their outcomes.

**Design of GRDDS by Using 3D Printing Techniques**

Amongst the various types of 3D printing techniques, extrusion-based 3D printing technique was extensively utilized for the design of GRDDS. Two types of extrusion-based 3D printing techniques were mostly used: PAM and FDM techniques (41).

**PAM-based GRDDS**

PAM-based GRDDS were fabricated by semisolid extrusion of drug-loaded polymer paste through micro-syringes. This technique could be the future of pharmaceutical drug manufacturing, as it involves the use of similar pharmaceutical-grade excipients that are used in conventional tablet manufacturing. Numerous GRDDS have been designed by using this technique. More recently, a gastroretentive pulsatile-release multiunit 3D-printed tablet loaded with artesunate was designed by using an extrusion-based 3D printing technique. This gastroretentive tablet design consisted of three units: immediate release, delayed release and a block unit. The designed tablet exhibited an immediate release phase for 1 hour, followed by a block phase of 7 hours, then the second drug release phase exhibited delayed release, which lasted for 14 hours. The orally administered gastro-retentive tablets showed 20 hours of gastric floating in rabbits (42). In another instance, gastroretentive 3D-printed tablets (printlets) loaded with nanocrystals of niclosamide were fabricated by using the melt solidification, an extrusion-based printing process. In this study, oblong-shaped printlets with 30% infill loaded with 25% niclosamide nanocrystals were designed. The nanometrization of niclosamide resulted in enhanced solubility and drug dissolution. The designed 3D printlets exhibited enhanced gastroretention in dogs (180 mins) and achieved total disintegration of the printlet by complete erosion and thus exhibited a sustained drug release profile (43). In a similar study, ionotropic gelation of sodium alginate was demonstrated to design a floating drug delivery system of propranolol HCl by exploiting co-axial semisolid extrusion 3D printing. The hollow drug delivery system with varying number of layers was designed with varying concentrations of sodium alginate matrix (4% and 6%) and crosslinking agent (calcium chloride 0.25, 0.5 and 0.1 M). The result of this study revealed that all the printed hollow drug delivery systems exhibited low density values (0.39 to 0.57 g/cm$^3$) and a total floating time of 5 ± 1 hours with no floating lag time. The complete drug release was accomplished in 6 hours, and all the systems followed Peppas-Korsmeyer release kinetics, indicating a non-Fickian transport mechanism involving matrix swelling. Thus, this approach provides a successful duo with high reproducibility in developing floating drug delivery systems (44). In a similar study, a high-drug-loaded sustained-release gastric floating tablet of clarithromycin was designed by using the semisolid extrusion 3D printing technique. The sustained- release tablet was formulated by using HPMC K15 MCR, which forms a matrix gel, PVPk30 and poloxamer 188 as a drug release modifier. The results of this study demonstrated high drug loading of 81.7% with instant and prolonged floating (> 10 hours) with no burst drug release. A sustained drug release was achieved (up to 8 hours and 12 hours by 125 mg and 250 mg tablets, respectively), and the 3D-printed tablets followed the Korsmeyer-Peppas release kinetic model (45). Figure 2 represents different geometrical approaches used to design GRDDS in literature.

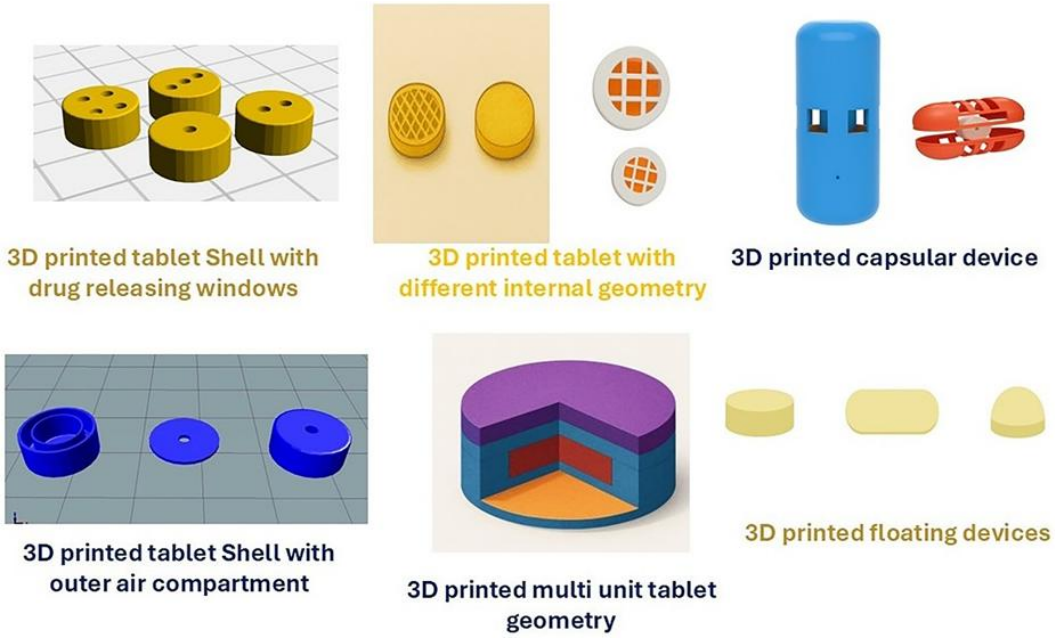


**Figure 2.**
Different geometrical approaches used to design GRDDS in literature (42, 43, 46-51)

Moreover, a few studies have made use of plant-based natural materials in designing gastric floating tablets by using semisolid extrusion-based 3D printing. In one instance, puerarin, a natural isoflavonoid, was used to fabricate gastric floating tablets to study the impact of design and composition modification. A concentric annular ring pattern tablet with varying outer line width was printed by using varied formulation design and composition. The results of this study revealed improved floating properties and sustained drug release profiles. In *in vitro* floating studies, the 3D-printed puerarin tablets showed 12 hours of gastric floating, and the *in vivo* studies exhibited 6 hours of gastric floating. The drug release rate was influenced by tablet design, formulation design and composition. An increase in polymer amount decreased the release rate. The different proportions of fillers do not influence the drug release rates. The drug release rate was also influenced by the geometrical changes in the design. An increase in the outer line width of the tablet accelerated the drug release rate (52). In another study, ginkgolides-based 3D-printed gastric floating tablets with structural modifications were designed *via* a semisolid extrusion-based 3D printing technique. Three digital models with different internal structures (intersecting angles and full filling gaps) were fabricated and evaluated for gastric buoyancy and drug release characteristics. The designed tablets showed 10 - 12 hours of *in vitro* floating and 8 - 10 hours of *in vivo* floating duration. All the tablets exhibited 10 - 12 hours of controlled drug release profile based on internal geometry. Model 1 exhibited 10 hours of controlled drug release compared to models 2 and 3, which exhibited 12 hours of controlled drug release. This difference is due to wide filling gaps in model 1, providing more space for drug dissolution. The drug release kinetics adhered to zero-order release with polymer erosion as the drug release mechanism (53). The types of polymers used and the floating behaviour of various PAM-based GRDDS are shown in Table I.

**Table I**
Represents types of polymers used and the floating behaviour of various PAM based GRDDS

| Drug used | Polymers used | Floating behaviour | | Reference |
|---|---|---|---|---|
| | | TFT | FLT | |
| **Artesunate** | PVP K30, croscarmellose sodium, octadecanol, HPMC K15M and Poloxamer F68 | About 20 h | 0 min | (42) |
| **Niclosamide** | Gelucire 50/13, Poloxamer 188, | Up to 12 h | - | (43) |
| **Famotidine** | HPMC 2208, MCC, PVP K30 and lactose monohydrate | > 10 h | 0 sec | (54) |
| **Ricobendazole** | Sodium alginate matrix, calcium chloride crosslinking ink, hydroxyethyl cellulose | 5 - 14 h | 0 - 30 min | (55) |
| **Propranolol HCl** | Sodium alginate, tween 85, calcium chloride and hydroxyethyl cellulose | 5 ± 1 h | 0 sec | (44) |
| **Clarithromycin** | HPMC K15M CR, Povidone (PVP k30), ethyl cellulose (EC 20), Carbomer 934P, Poloxamer (P188) and nano-$CaCO_3$. | > 10 h | immediate | (56) |
| **Clarithromycin** | HPMC K15MCR, PVP k30, Poloxamer (P188) | > 7 - 10 h | instant | (45) |

| Drug used | Polymers used | Floating behaviour | | Reference |
|---|---|---|---|---|
| | | TFT | FLT | |
| **Dipyridamole** | HPMC K4M, HPMC E15, PVP k30, MCC PH101 and lactose | 30% and 50% infill- > 12 h; 70% infill- 8 h; 100% infill- no floating | No floating lag time | (57) |
| **Puerarin** | HPC-M, HPMC (METHOCEL™ E50LV), MCC PH101 and lactose | *In vitro* 12 h, *In vivo* 6 h | No floating lag period | (52) |
| **Ginkgolides** | HPMC K4M, HPMC E5LV, MCC, lactose and PVP K30 | *In vitro* 10 - 12 h, *In vivo* 8 - 10 h | Up to 2.5 seconds | (53) |

TFT – Total floating time; FLT – Floating lag time

## FDM-based GRDDS

FDM-based GRDDS were fabricated by extrusion of filaments (drug-loaded or without drug) through micronozzles. The filament, which is used as a feed-stock, is made up of various types of pharmaceutical-grade excipients developed by using the hot melt extrusion (HME) process. The FDM-based GRDDS were designed in two ways: one by directly extruding the drug-loaded filament and another by extruding non-drug-loaded filament, enclosed with a conventional tablet or drug core.

## FDM-based GRDDS Designed *via* Drug-loaded Polymeric Filaments

In the drug-loaded polymeric filament approach, the initial step is to develop a filament by hot melt extrusion (HME) subsequent to FDM 3D printing to design a GRDDS. Recently, extended-release famotidine floating tablets were developed by fabricating a drug-loaded polymeric filament using hydroxypropyl cellulose (HPC LF) and hydroxy-propyl methylcellulose (HPMC E5) to enhance the drug solubility and extend gastric retention and drug release. 3D-printed hollow tablets were designed and characterized by differential scanning calorimetry (DSC) and FTIR spectroscopy. The results indicated drug amorphization and stabilization of solid dispersion. The optimized formulation achieved a gastric retention of about nine hours and showed an extended drug release profile (58).

With a similar approach, a high-drug-loaded hydrophilic gastroretentive floating tablet was fabricated by using metformin HCl. Cylindrical-shaped 3D-printed tablets with different internal mesh sizes were fabricated using different drug loads and auxiliary excipient loads. The effect of three parameters (*i.e.*, different drug loads, auxiliary excipient loads and internal mesh sizes) on drug release was studied. The result of this investigation demonstrated that all the 3D-printed tablets exhibited a floating duration of > 8 hours with no floating lag time. The 3D-printed tablets with low drug loads (10% and 20%) exhibited 70% drug release in 8 hours, whereas the tablets with high drug loads (30% and 40%) exhibited 90% drug release in 8 hours. There was no significant impact of auxiliary excipient load and internal mesh size on drug release from the 3D-printed tablets. The drug release kinetics showed Higuchi's release model, and based on n values, diffusion was the drug release mechanism (59). In another approach, high-drug-loaded mucoadhesive gastroretentive floating tablets were designed for gabapentin by fabricating a high-drug-loaded PEO filament (98% drug loading) without using plasticizer. The 3D-printed tablets with varying numbers of shells (1, 2, 3 and 4) and with varying infill densities (0%, 10%, 20% and 30%) were fabricated to study their influence on buoyancy and drug release. The tablet density increased, and thus the floating time decreased with an increase in the number of shells and infill density. Similarly, the drug release rate decreased with an increase in the number of shells and infill density. The pharmacokinetic studies revealed an enhanced absorption of gabapentin compared to oral solution (60). Another study demonstrated the fabrication of gastroretentive floating tablets of Verapamil HCl in different contours (cylinder, capsule and hemisphere) and with different infill percentages (0 and 15%). The impact of geometry and infill percentage on floating and drug release was evaluated. The results revealed that all the 3D-printed floating tablets exhibited prolonged floating and sustained drug release profiles. The floating duration of cylinder-shaped tablets was more than that of capsule- and hemisphere-shaped tablets. This was due to the flat surface of the cylinder-shaped tablet that causes slow fluid penetration or rupture of the tablets compared to the curved surface of the hemisphere and capsule-shaped tablets that allow faster rupture due to less connective area between filament layers. With respect to drug release, the capsule-shaped tablet with high infill percentage exhibited the slowest drug release (80% drug release in 16 hours). Moreover, the drug release is affected by the weight of the formulation rather than the shape, as the surface area of all three-shaped tablets was close to each other to ensure similar fluid penetration (50). In another study, an intragastric floating sustained-release 3D-printed tablet of venlafaxine hydrochloride was designed by fabricating an insoluble PLA shell with an air chamber at the top and a drug-releasing window at the bottom of varied sizes (1.5, 2.5, 3, 3.5

and 4.5 mm) to facilitate floating and sustained drug release. The drug-loaded filament is used to print the core inside the shell by using a dual-extruder FDM 3D printer. The result of this investigation revealed that the presence of an air chamber in the tablet kept the tablet floating throughout the course of drug release. The 3D-printed floating tablets revealed sustained drug release for up to 24 hours, compared to shell-less tablets, which showed drug release for up to 5 hours. Among the various drug-releasing window sizes, the floating tablet with a 4.5 mm drug-releasing window size reached 100% drug release steadily in 24 hours. The drug release kinetics for the shell-less tablet was best fitted to Ritger-Peppas, with an n value between 0.45 and 0.89 signifying a drug release mechanism by erosion and diffusion. This is in comparison to an intragastric floating tablet with a 4.5 mm drug-releasing window that showed a zero-order sustained drug release profile (61).

In another instance, a floating mini polypill was designed for personalized therapy for Parkinson's disease by using a combination of levodopa, benserazide and pramipexole. Two filaments were prepared, one by using PVA for immediate release of pramipexole and the other by using ethylene-vinyl acetate copolymer (EVA) and polyvinylpyrrolidone-vinyl acetate copolymer (PVP-VA) for sustained release of levodopa/benserazide in a fixed combination dose (4:1). Polypills of different geometries were designed with comparable SA/V ratios in variable doses. In addition to this, mini dosage forms were also printed to adjust the daily dose requirement for personalized therapy. The designed floating mini polypills exhibited prolonged gastric residence time due to low density and revealed a tuned drug release profile due to the geometrical modification and thus provided different dosage regimes for personalized therapy (62). In another approach, 3D-printed gastroretentive floating tablets of theophylline were fabricated by using the FDM printing technique coupled with HME. In this approach, the drug-loaded filament was fabricated by using hydroxypropyl cellulose (HPC). The 3D-printed cylindrical hollow tablets were designed with varying shell thicknesses (0.4, 0.8 and 1.2 mm) and infill densities (0, 10, 20 and 30%). The designed tablets exhibited prolonged floating and controlled drug release characteristics based on infill % and shell thickness. The released drug from the 3D-printed tablets showed zero-order release kinetics with swelling and a Fickian diffusion drug release mechanism (63). In another study, novel pregabalin 3D-printed controlled-release tablets were designed using the FDM 3D printing technique. In this study, cylindrical tablets with different infill percentages (25%, 50% and 75%) having open and closed tops and bottoms were designed. The tablet with open top and bottom showed no buoyancy and sank immediately due to open channels at the top and bottom that allow water flow through the internal channels. The drug release was faster in open systems with a low infill percentage. Whereas the closed system showed a relationship between drug release and internal structure. The tablets with high infill percentage showed a significantly low and incomplete drug release. Thus, based on geometry, an optimized system with low infill and closed at the bottom and partially open at the top showed maximum buoyancy (> 24 hours) and achieved complete and controlled drug release. The optimized system followed zero-order release kinetics regulated by polymer erosion and drug diffusion (64).

Similarly, to achieve prolonged gastric retention and to sustain the release characteristics of the APIs, fabrication of drug-loaded polymeric filament-based GRDDS or devices was also reported in the literature for allupurinol (65), felodipine (66), domperidone (67) and curcumin (68). Table II represents the filament composition, extrusion parameters and printing parameters used to design FDM-based drug-loaded 3D-printed GRDDS.

**Table II**

Filament composition, extrusion parameters and printing parameters used to design FDM based drug loaded 3D printed GRDDS

| Drug | Filament composition | Extruder used for filament making | Extrusion conditions | Printer used | Printing parameters | Ref. |
|---|---|---|---|---|---|---|
| **Famotidine** | HPC LF, HPMC E5 and EC | Co-rotating, twin-screw extruder | ET – 150ºC<br>RPM – 100ºC<br>ND – 1.5 mm | – | PT – 180ºC<br>BT – 60ºC | (58) |
| **Metformin HCl** | HPMC Affinisol™ HME 15 LV, magnesium stearate and PEG 6000 | Noztek Pro Desktop Filament Extruder | ET – 150ºC<br>RPM – 33ºC<br>ND – 1.75 mm | REGE MAT 3D V1 printer | PT – 200ºC<br>BT – 80ºC | (59) |
| **Gabapentin** | PEO | Noztek® Pro pellet and powder extruder | ET – 105ºC<br>ND – 1.75 mm | MakerBot replicator mini | PT – 115ºC | (60) |
| **Verapamil hydrochloride** | HPMC, Soluplus, PEG 400 | FilaBot® FOV1 Single crew Hot melt extruder | ET – 115ºC<br>ND – 1.7 ± 0.1 mm | MakerBot Replicator 2X 3D printer | PT – 195ºC<br>BT – 90ºC | (50) |
| **Venlafaxine hydrochloride** | PLA, HPMC HME 15LV, PVP VA64, Eudragit EPO, Eudragit RS PO and TEC | Hot melt extruder (Aoluode Machinery Co., Ltd.) | ET – 160ºC<br>RPM – 30ºC<br>ND – 1.75 ± 0.10 mm | FDM 3D printer (Raise 3D Pro2) | PT – 185 - 210ºC<br>BT – 60ºC | (61) |

| Drug | Filament composition | Extruder used for filament making | Extrusion conditions | Printer used | Printing parameters | Ref. |
|---|---|---|---|---|---|---|
| **Levodopa, benserazide and pramipexole** | PVA, mannitol, fumed silica, PVP-VA copolymer 60:40, EVA copolymer 82:18. | Twin-screw extruder (Pharmalab HME 16) | ET – 100ºC and 195ºC<br>RPM – 20ºC<br>ND – 1.85 mm | Prusa 3D printer | PT – 185ºC and 220ºC<br>BT – 70ºC | (62) |
| **Théophylline** | HPC, Stearic acid | Twin-screw extruder (Process 11) | ET – 150ºC<br>RPM – 50ºC<br>ND – 1.2 mm | FDM 3D printer (ANET-A8) | PT – 210ºC<br>BT – --- | (63) |
| **Propranolol HCl** | PVA | Single screw hot melt extruder (FilaBot® FOV1) | ET – 142ºC<br>RPM – 35ºC<br>ND – 1.75 mm | MakerBot Replicator 2X Desktop 3D printer | PT – 185ºC<br>BT – 110ºC | (69) |
| **Cinnarizine** | HPC, Kollidon VA64 | twin-screw co-rotating extruder (Process 11) | ET – 130ºC<br>RPM – ---<br>ND – 1.7 ± 0.5 mm | Prusa i3 FDM-3D printer | PT – 165ºC<br>BT – 40ºC | (70) |
| **Pregabalin** | HPMCAS, PEG 400 | Process 11 twin screw Hot Melt Extruder | ET – 125ºC<br>RPM – 10 - 20ºC<br>ND – 1.5 mm | Good bot 4025-MP FDM printer | PT – 180ºC<br>BT – 50ºC | (64) |

PT – Printing temperature; BT – Bed temperature; ET – Extrusion temperature; ND – nozzle diameter

**FDM-based GRDDS Designed *via* Non-drug-loaded Polymeric Filaments**

In the non-drug-loaded polymeric filament approach, commercial filaments (readymade) were used directly for 3D printing to design a hollow shell structure in which the drug core or commercial tablets were placed. The main objective in the design of GRDDS is to enhance the gastric retention time and obtain a sustained drug release profile for the dosage form. With this aim, a dual-compartment gastroretentive floating device was designed by using PLA and PVA filament. The outer compartment of the floating device is designed as a hollow compartment, which imparts floating, and the inner compartment is designed with a drug-releasing window and enclosed with an immediate-release commercial propranolol HCl tablet to modify its release characteristics. This investigation has successfully demonstrated enhanced buoyancy (over 24 hours) and a sustained drug release profile (up to 10 hours) for the enclosed immediate-release commercial tablet. The filament type (hydrophilic or hydrophobic) and the drug-releasing window opening size in the device have governed the floating duration and drug release time from the device (47). In another instance, 3D-printed floating tablets of three different configurations (cube, cylinder and sphere) with two different levels of wall thickness (0.4 and 0.8 mm) were fabricated by using PLA filament. Co-crystals of mosapride citrate were developed to enhance its solubility and filled as 3D printable gel in the designed floating tablets. The 3D-printed floating tablets exhibited prolonged floating duration (> 12 hours) with no floating lag time. All the 3D-printed floating tablets exhibited variable extended drug release depending upon the configuration and wall thickness. The drug release from the 3D-printed floating tablets of different configurations was in the order of cylinder > cube > sphere. The floating tablets with a wall thickness of 0.4 mm showed a lag time of 1 hour for drug release, whereas the floating tablets with 0.8 mm of wall thickness showed a lag time of 3 hours for drug release. The kinetic studies revealed a zero-order release with a diffusional mechanism indicated by Korsmeyer-Peppas exponent values (71). In a similar study, a 3D-printed floating device with an anti-flip mechanism was designed to enclose a metronidazole core tablet by using PLA filament. In this study, the floating device was designed as a tablet housing with a drug release orifice on the sides, and the core tablet was made by direct compression. The three factors, *i.e.*, the drug release orifice, air volume (altered by varying the device height) and compression force used to prepare the core tablet, were studied to optimize the device by using a Box-Behnken design. The result of this study revealed that the assembled tablet floated for a period of 12 hours without getting flipped. The optimized device exhibited constant drug release for 8 hours, provided with a drug release orifice of 23.10 $mm^2$, a device height of 2 mm and 3.63 tons of compression force to prepare the core tablet. The drug release kinetics followed a zero-order release rate, thus providing a constant drug release for about 8 - 9 hours (72). In another approach, a novel capsular device was designed by using FDM 3D printing to control the drug release from an enclosed commercial immediate-release baclofen tablet. The capsular device was designed with a cap having an air pocket to keep the device in an upright position during floating, and a magnet is attached at the cap bottom. The body is designed with windows for water influx at the top and to enclose an immediate release tablet provided with varying numbers, sizes and heights of drug-releasing holes to control the drug release from the enclosed tablet. Along with the cap and body, there exists a cylinder-shaped hollow

inner part with a magnet embedded at the top to control the movement of this inner part during floating. The capsular device was assembled by placing an immediate release (IR) tablet inside the body; on this, the inner part was placed, and then, a rapid disintegrating tablet (RDT) was placed on top of this inner part, followed by cap placement over the inner part. After the device assembly, the RDT exists at open windows, which allows water influx. The magnets at the cap bottom and at the top of the inner part control the movement of the inner part and cap. Once the device is placed in the dissolution medium, the RDT disintegrates in 1 minute, and then, the inner part heads towards the cap due to magnetic attraction and closes the windows. The IR tablet dissolves by water influx that occurs through the open windows, and the drug release was controlled by the number, size and height of drug-releasing holes in the body. The result of this study revealed that the capsular devices floated for a prolonged duration (> 24 hours) in an upright position (due to the air pocket inside at the top of the cap). All the capsular devices exhibited controlled drug release from 1.7 to 6.7 hours to reach 80% dissolution (T80) depending upon the size, height and number of drug-releasing holes in the device (51). Similarly, a gastroretentive capsule-shaped device was designed by using PVA filament and thermal crosslinking was carried out to prolong the gastric buoyancy and drug release from the enclosed conventional immediate-release amoxicillin capsules. The thermal crosslinking of the device at an elevated temperature and for prolonged time resulted in the decreased water insolubilization and decreased water uptake, which consecutively resulted in decreased swelling and dissolution rate. Thus, the 3D-printed capsule devices exhibited prolonged gastric buoyancy and sustained drug release profiles compared to conventional amoxicillin capsules. The result of in vivo studies in rabbits showed > 10 hours of gastric floating, and the drug release kinetics followed the Higuchi model. The drug release from the device was governed by the degree of thermal crosslinking of the device, which consecutively controls the swelling and erosion of the device (73). Similarly, to achieve prolonged gastric retention and to modify the drug release characteristics of the core, the design of non-drug-loaded polymeric filament-based gastro-retentive drug delivery shells was also reported in the literature for metronidazole (74), domperidone (75, 76), riboflavin (49) and captopril (46).

**Table III**

The type of filament used, the printer used and the printing parameters of FDM-based GRDDS designed via non-drug-loaded polymeric filaments

| Drug | Filament used | Printer used | Printing parameters | Ref. |
|---|---|---|---|---|
| **Captopril** | PVA | EASYTHREED X1 3D printer | PT – 190 - 210ºC<br>BT – 60ºC | (46) |
| **Propranolol HCl** | PVA and PLA | EASYTHREED X1 3D printer | PT – 200 - 210ºC<br>BT – 40 - 50ºC | (47) |
| **Mosapride citrate** | PLA | REGEMAT 3D V1 printer | PT – -----<br>BT – 60ºC | (71) |
| **Carvedilol** | PLA | Prusa i3 MK3® FDM 3D printer | PT – 190ºC<br>BT – 60ºC | (77) |
| **Metronidazole** | PLA | UP Mini 2 3D printer | PT – 210 - 220ºC<br>BT – 60ºC | (72) |
| **Domperidone** | PVA | Prusa i3 MK3 | PT – 195ºC<br>BT – 60ºC | (78) |
| **Baclofen** | PLA | Raise3D N2, Raise3D | PT – -----<br>BT – ----- | (51) |
| **Amoxicillin** | PVA | Prusa i3 MK3 | PT – 195ºC<br>BT – ------- | (73) |
| **Theophylline** | Hydroxypropyl cellulose (HPC) and ethyl cellulose (EC) | Prusa i3 | PT – 190ºC<br>BT – 60ºC | (79) |
| **Acyclovir** | PLA | Raise3D N2 | PT – 210ºC<br>BT – 65ºC | (48) |

PT – Printing temperature; BT – Bed temperature

## Scope and Future Direction

This review highlights the recent progress in GRDDS, specifically focusing on methods used for filament extrusion, 3D printing and use of different polymeric materials. Future research should focus on several critical aspects to transform 3D-printed GRDDS approaches into practical, real-world drug delivery applications. One of these aspects is clinical translation, which is progressing with implementation of 3D printing processes in hospital setups. Various researchers have adopted a proactive approach to conduct clinical studies in hospital settings, comparing the bioavailability of 3D-printed products with that

of conventional commercial products. Patient perception, preference and acceptability of 3D-printed products designed in different colours and shapes, including patient-self-designed ones, were evaluated among polypharmacy patients. In further support of this, 3D-printed products were clinically tested and evaluated for patient acceptability, pharmacokinetic profiles, precision, clinical accuracy and efficacy and have received a positive response among patients from compounding pharmacies and hospitals in China and Spain. In progression, a real-time 3D printer was established in a polypharmacy setup in Spain for automated compounding that has successfully resulted in precise and efficient compounding compared to manual filling of a product. These instances provide a pathway for further progress in practical implementation of 3D printing and bringing it closer to practical, real-world drug delivery application. Another aspect that should be focused on is instrumentation development. The currently available extruders and 3D printers should be further improved and developed with artificial intelligence (AI) and machine learning (ML). Integrating artificial intelligence (AI) and machine learning (ML) into extruders and 3D printers offers significant benefits by enhancing their capabilities and improving their performances. AI and ML can make extruders and 3D printers work better and faster and make it possible to regulate and optimize the printing process, which can lead to better quality output and possibly faster production times. The progression of 4D printing to design and develop GRDDS has led to the use of smart polymers that respond to the physiological stimuli to trigger drug release, thus providing better therapeutic control over the system. The integration of 4D printed GRDDS with biosensors enables real-time monitoring of drug release, gastric emptying data and patient adherence, thereby paving the way for an advanced personalized medicine approach. The U.S. Food and Drug Administration (FDA) approval, Investigational New Drug (IND) clearance and European Medicines Agency (EMA) initiation of early-stage regulatory deliberations evidenced the regulatory harmonization to advance 3D-printed GRDDS toward significant and real-world drug delivery applications.

## Conclusions

In the design of GRDDS, significant research has progressed over the last 7 - 8 years through the use of 3D printing techniques. 3D printing, due to its flexibility in product design, can print 3D products in any form, such as hollow systems, air-filled chambers and products with drug-releasing windows, thus providing a solution to conventional method difficulties faced during the design of GRDDS. Primarily, extrusion-based 3D printing techniques were employed, which demonstrated potential advantages over conventional methods for designing GRDDS with thermoplastic materials that inherently provide buoyancy to the system. By using the 3D printing technique, only low-density-based floating GRDDS were designed. Other approaches, like high-density systems and expandable systems, have not been designed so far by using 3D printing techniques. 3D printing is an inexpensive and practical approach that does not require any specialized materials to design GRDDS compared to conventional methods that require specific materials such as gas-generating agents, swelling agents, mucoadhesive polymers, etc. 3D printing is an emerging technique that has the potential to transform the drug manufacturing industries. 3D printing allows manufacturers to create customized drug products on demand, achieving designs that would otherwise be impossible with traditional production techniques. 3D printing reduces the new drug development cost for the pharmaceutical industry by enabling small-scale production at the product development stage. In the near future, the concept of personalized medicine at the point of care could succeed more commonly by implementing 3D printing in hospitals and pharmacies. The regulatory authorities should make progress in providing quality control guidelines for the on-demand production and use of 3D-printed drug products. A monograph should be included in the pharmacopeia for quality control testing of 3D-printed products. In conclusion, the 3D-printing technique has made a breakthrough in designing GRDDS.

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## Conflict of interest

The authors declare no conflict of interest.

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