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3D Bioprinted Gastroretentive Drug Delivery Systems – A New Frontier

Choudari Tarun[1], R. Sandhya Jyothi[2], Sasubilli Akshaya[3]

[1,3] *Student, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, India*

[2] *Research Scholar, AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam, India*

[2] sandhyajyothi.rs@andhrauniversity.edu.in, [1] tarunlucky225@gmail.com , [3]sasubilliakshaya@gmail.com

Abstract:

Gastroretentive drug delivery systems (GRDDS) have long been recognized as a pragmatic solution to the pharmacokinetic challenges posed by drugs with narrow absorption windows, pH-dependent solubility, or localized gastric action. While conventional approaches such as floating tablets, mucoadhesive films, and in situ gels have been extensively explored, they remain constrained by the limitations of batch manufacturing: inability to tailor geometry, restricted drug loading options, and difficulty achieving truly personalized release profiles. The emergence of three-dimensional (3D) bioprinting as a pharmaceutical fabrication tool has opened a genuinely transformative chapter. By enabling precise spatial control over material deposition, layer by-layer construction of complex hollow or porous architectures, and patient-specific dose customization, 3D printing addresses many shortcomings of conventional predecessors. This review consolidates foundational and contemporary evidence to present a unified narrative on 3D bioprinted GRDDS, covering gastroretentive mechanisms, bioprinting technologies, key drug candidates, evaluation methodologies, and the regulatory pathway for these novel dosage forms.

Keywords—3D bioprinting, gastroretentive drug delivery, floating tablets, mucoadhesive systems, fused deposition modeling, personalized medicine, bioavailability enhancement.

I. INTRODUCTION

The gastrointestinal (GI) tract, despite being the most widely used route for drug administration, presents several formidable barriers to consistent drug absorption. Gastric emptying is not a fixed biological event – it is influenced by the nature of food consumed, postural position, underlying disease states, sex differences, and even genetic factors [1,2]. For a subset of drugs whose absorption is confined to the proximal gastrointestinal tract or whose efficacy depends on sustained action against gastric pathogens, this unpredictability translates directly into therapeutic failure.

Gastroretentive drug delivery systems were conceived precisely to arrest this variability. By engineering dosage forms that remain in the stomach for extended durations – through buoyancy, bioadhesion, swelling, or mechanical unfolding – GRDDS enable prolonged, controlled drug release at the site of maximum absorption [3,4]. Research has explored diverse formulation strategies: mucoadhesive films of antiretroviral agents like ritonavir [3], in situ gelling systems incorporating ivabradine [4], natural polymer-based floating tablets of cephalexin [5], and floating in situ gels of ciprofloxacin [6].

Three-dimensional printing entered the pharmaceutical mainstream when the US Food and Drug Administration (FDA) approved the first 3D-printed drug product – Spritam (levetiracetam) by Aprecia Pharmaceuticals – in August 2015 [7]. Since then, 3D printing's application to GRDDS has expanded rapidly: hollow floating devices, mucoadhesive matrix tablets, expandable gastric retention platforms, and polypills for co-administration of multiple agents have all been reported [2,8,9,10]. This review consolidates findings from seminal and emerging literature to provide a comprehensive picture of where 3D bioprinted GRDDS stands today.

II. GASTRORETENTIVE DRUG DELIVERY: FUNDAMENTALS AND CLASSIFICATION

A. Physiological Basis of Gastroretention

The stomach's role in drug absorption is often underestimated. Its highly acidic environment (pH 1.2–3.5 in the fasted state) is the principal site of dissolution for weakly basic drugs, and many molecules – metformin, levodopa, gabapentin, amoxicillin – are absorbed primarily in the upper small intestine, making prolonged gastric residence advantageous. The muscular contractions of the stomach, particularly the migrating motor complex (MMC) during the interdigestive phase, are the primary drivers of gastric emptying. Dosage forms that survive these contractions or exploit the fed-state inhibition of MMC can achieve extended gastric residence times [3,8].

B. Mechanisms of Gastric Retention

Seven distinct mechanisms have been described for GRDDS, of which floating, mucoadhesive, and swelling/expanding systems have received the greatest pharmaceutical attention [8].

Floating systems rely on achieving a bulk density lower than that of gastric fluid (~1.004 g/mL), accomplished through gas generation (effervescent approach) or low-density porous matrices [5,6]. 3D printing elevates this concept by enabling the precise engineering of air-filled chambers, obviating the need for gas-generating excipients.

Mucoadhesive systems exploit the interaction between polymer functional groups and mucin glycoproteins lining the

gastric mucosa. When combined with 3D printing, mucoadhesive GRDDS can be fabricated with precisely defined surface areas and spatially controlled polymer concentrations [3,8].

Expandable systems undergo a dimensional increase after ingestion, adopting a configuration large enough to exceed the pyloric orifice (~13 mm). This mechanical strategy is particularly attractive for 3D printing because geometry of expansion can be digitally specified with precision unattainable by traditional molding or compression.

C. Advantages of 3D Bioprinted GRDDS over Conventional Systems

The most clinically significant advantage of 3D bioprinted GRDDS is the capacity for patient-specific dose customization. In contrast to the fixed-dose paradigm of mass-manufactured tablets, 3D printing enables real-time modification of drug content, geometry, and release rate simply by altering the digital design file, without any change to equipment or tooling [1,8,13]. This is particularly relevant for drugs such as metformin, levodopa, and gabapentin, where the therapeutic dose varies substantially between patients.

Geometric design freedom constitutes a second major advantage. Conventional tablet compression produces forms limited to cylinders and ovals; 3D printing can fabricate hollow chambers for effervescent-free buoyancy, internal lattice scaffolds, multi-compartment architectures, and surface topographies optimized for mucoadhesion – all in a single manufacturing step [2,8,15]. The polypill capability represents an advantage with no meaningful conventional parallel, enabling multi-drug GRDDS with tailored release profiles for each active pharmaceutical ingredient [2,16,17].

III. THREE-DIMENSIONAL BIOPRINTING TECHNOLOGIES IN GRDDS

A. Fused Deposition Modeling (FDM)

FDM is arguably the most widely studied 3D printing technology in pharmaceutical GRDDS research. A thermoplastic polymer filament is heated above its glass transition temperature and extruded through a nozzle to build the dosage form layer by layer. Hot-melt extrusion (HME) is typically coupled with FDM: the drug is first incorporated into a polymer matrix to form a printable filament [9,10].

Chai and colleagues provided an early demonstration of FDM's potential for gastroretentive floating delivery by printing hydroxypropyl cellulose (HPC)-domperidone filaments into hollow-structured tablets. By varying shell count and infill percentage, they achieved dosage forms that floated for approximately ten hours in vitro and demonstrated 222% relative bioavailability relative to commercial tablets in rabbit pharmacokinetic studies [10].

Subsequent work developed gastroretentive floating devices for propranolol HCl from dual-compartment PVA and PLA shells using FDM [9], and FDM was applied to famotidine using HPC and HPMC-based drug-loaded filaments, achieving prolonged gastric flotation and extended drug release [13]. For thermolabile drugs, core-shell floating pulsatile systems were designed where the shell was FDM-printed while the drug-loaded core was a directly compressed tablet, shielding the active from thermal exposure [2].

B. Stereolithography (SLA) and Digital Light Processing (DLP)

SLA and DLP technologies construct objects by selectively photopolymerizing liquid resin formulations. These techniques offer exceptional resolution – down to 25–50 micro meters – enabling micro-scale structural features that FDM cannot reliably achieve [15]. For GRDDS, this resolution enables intricate internal channel networks or microporous scaffolds that finely tune both buoyancy and drug release. The primary obstacle remains the limited number of biocompatible, pharmaceutical-grade photopolymerizable excipients.

C. Inkjet and Semi-Solid Extrusion Printing

Inkjet-based 3D printing deposits drug solution droplets onto a substrate in a binder-jetting configuration – the technology underlying the ZipDose platform used in Spritam [7]. Semi-solid extrusion (pressure-assisted microsyringe or direct ink writing) extrudes paste-like materials without heat, and is particularly suited to thermosensitive biologics and hydrogels. Given prior successes with floating in situ gels of ciprofloxacin [6] and ivabradine [4], semi-solid extrusion presents a logical 3D printing bridge for converting gel-based formulations into reproducible dosage forms with defined three-dimensional architectures.

D. Selecting the Right Technology

The choice of 3D printing technology for GRDDS depends on thermal stability of the drug, desired porosity and density, required printing resolution, polymer compatibility, and process scalability. FDM remains dominant because of its material versatility, cost-effectiveness, and maturity of HME-filament preparation techniques [2,8]. Hybrid approaches – combining FDM scaffolds with compressed drug cores, or marrying SLA geometries with inkjet drug loading – are likely to offer the most sophisticated and therapeutically optimized outcomes.

IV. MUCOADHESIVE 3D BIOPRINTED SYSTEMS

Mucoadhesive GRDDS represent one of the most promising application areas for 3D bioprinting because of the multi-parameter optimization challenge they pose. Effective mucoadhesion requires not only the right polymer chemistry but also the appropriate surface area available for mucin interaction, the rheological behavior of the polymer at the gastric surface, and the mechanical strength of the adhesive bond against gastric peristalsis.

The versatility of 3D printing in designing mucoadhesive matrices was illustrated in a study by Khizer and colleagues, who developed personalized 3D-printed mucoadhesive gastroretentive hydrophilic matrices for the management of overactive bladder (OAB) using gabapentin via FDM coupled with HME [8,16]. Mucoadhesive polymers commonly incorporated include HPMC, carbopol 934P, sodium carboxymethylcellulose (NaCMC), PVP, and chitosan. The key advance that printing adds is reproducibility: the same complex geometry can be printed repeatedly without operator-dependent variation – addressing a chronic limitation of conventional film-casting and gel-forming approaches [3].

V. FLOATING 3D BIOPRINTED SYSTEMS

Floating GRDDS have been the most extensively explored category within the 3D bioprinting literature, primarily because

the physical principle of buoyancy maps so naturally onto the structural capabilities of additive manufacturing.

Mora-Castaño and colleagues systematically advanced this space through studies on high drug-loaded 3D printed gastroretentive floating tablets using HPMC-based filaments (Affinisol 15LV) with metformin as a model drug. Their work demonstrated that FDM-printed tablets achieved immediate and sustained buoyancy without any gas-generating excipients, with robust release kinetics across multiple printing geometries [9].

Huanbutta and colleagues applied a design of experiment (DoE) methodology to the development of 3D-printed gastroretentive sustained-release tablets, using systematic variation of formulation and printing parameters to identify the optimal combination of polymer concentration, layer height, and infill pattern for maximizing floating duration and controlling drug release rate [18].

Mini floating polypills represent a particularly forward-looking application. Windolf and colleagues developed 3D-printed mini floating polypills for Parkinson's disease incorporating levodopa, benserazide, and pramipexole in customizable doses, demonstrating the capacity of 3D bioprinting to address complex pharmacokinetic management needs of chronic neurological disease [2,16].

VI. DRUG CANDIDATES FOR 3D BIOPRINTED GRDDS

The selection of drug candidates for 3D bioprinted GRDDS is guided by three principal criteria: the presence of a narrow absorption window in the upper GI tract, a short biological half-life necessitating frequent dosing, or a requirement for local action within the stomach [2,8].

Metformin is most frequently cited in the floating 3D printing literature because of its exclusive absorption in the proximal intestine and documented clinical benefit of sustained gastric release [9]. Domperidone, studied in early FDM floating tablet reports [10], has a limited gastric absorption and short half-life that benefits from extended local presence. Famotidine, as an H2-receptor antagonist acting locally on the gastric mucosa, benefits from prolonged gastric residence, and the 3D printing approach using HME-FDM resolved its solubility challenges simultaneously [13].

Propranolol HCl exemplifies the class of drugs with a narrow absorption window and significant first-pass metabolism that benefits from controlled gastric release [9,16]. The applicability to antiretroviral drugs such as ritonavir is compelling given pH-dependent solubility and clinical need for sustained plasma levels [3]. Similarly, ciprofloxacin and fluoroquinolones used for H. pylori eradication stand to benefit from gastric site-specific precision that 3D printing offers [6].

VII. EVALUATION OF 3D BIOPRINTED GASTRORETENTIVE SYSTEMS

In vitro floating performance is typically evaluated in simulated gastric fluid (SGF, pH 1.2) at 37°C under gentle agitation. The floating lag time and total floating duration are key parameters. For FDM-printed hollow devices, these are largely a function of the ratio of air-filled chamber volume to total device volume – directly programmable through CAD software [8,9].

Drug release characterization employs USP apparatus II (paddle) or apparatus III (reciprocating cylinder) in SGF, with sampling at regular intervals. Mucoadhesive force measurement is conducted using texture analysis, measuring work of adhesion required to detach the dosage form from a mucin-coated surface or ex vivo gastric tissue preparation [8].

In vivo evaluation employs gamma scintigraphy, radiographic imaging with radiopaque markers ($BaSO_4$), and pharmacokinetic studies in animal models. Chai and colleagues demonstrated by radiographic imaging that $BaSO_4$-labelled FDM floating tablets were retained in rabbit stomachs for over eight hours, with pharmacokinetic comparisons confirming 222% relative bioavailability for the 3D-printed floating domperidone tablets versus commercial reference [10].

VIII. REGULATORY LANDSCAPE

The regulatory framework governing 3D-printed pharmaceuticals is still being shaped, and the unique attributes of these dosage forms present specific challenges [1]. The FDA's approval of Spritam in 2015 established that digitally fabricated dosage forms could meet regulatory expectations, but was followed by the important observation that 3D printing technology does not change the regulatory expectations for drug product quality [7].

In 2017, the FDA published Technical Considerations for Additive Manufactured Medical Devices guidance; subsequently, Triastek's 3D-printed drug applications received IND approval, signalling increasing regulatory comfort [1,7]. The European Medicines Agency (EMA) has published reflection papers on 3D printing for pharmaceutical applications, acknowledging both the promise of personalized medicine and the challenges of validating highly flexible manufacturing systems [1,15].

For GRDDS specifically, the regulatory evaluation must address additional dimensions: the buoyancy mechanism must be validated as reliable across the physiological range of gastric conditions; the gastric retention claim must be supported by imaging data; and the release mechanism must be shown to be robust against variations in gastric pH, enzyme activity, and food effect [1,8].

IX. CHALLENGES AND FUTURE PERSPECTIVES

Material limitations constitute the most immediate technical challenge. FDM requires thermoplastic filaments, limiting the range of excipients to those with suitable melt rheology and thermal stability. The development of novel pharmaceutical-grade filament materials, potentially through co-extrusion with plasticizing excipients, is an active area requiring sustained investment [2,8].

Drug loading constraints represent another concern. FDM filaments with high drug content (above 30–40%) often display brittleness that compromises printing fidelity [2,8]. Scale-up and cost remain genuine barriers to commercial translation; bench-top 3D printers used in research are slow relative to conventional tablet presses. Hybrid manufacturing approaches – where 3D printing is used only for the gastroretentive shell while the drug-loaded core is conventionally compressed – may offer a pragmatic middle ground [14,19].

Looking ahead, the integration of artificial intelligence (AI) and machine learning with 3D bioprinting holds significant

promise for GRDDS optimization. AI-assisted design could predict optimal printing architecture for a target release profile, reducing iterative experimental cycles. Combined with real-time process monitoring through PAT tools, this creates a framework for adaptive manufacturing of personalized GRDDS [14,20].

X. CONCLUSION

Three-dimensional bioprinting has evolved from a conceptual novelty to a scientifically validated and regulatory-recognized pharmaceutical manufacturing paradigm. For gastroretentive drug delivery systems, 3D printing introduces a new design vocabulary: digital architectures, programmable porosity, patient-specific geometries, and multi-drug layering.

Contemporary evidence from FDM-printed floating tablets of metformin, domperidone, propranolol, and famotidine, alongside mucoadhesive printed systems for gabapentin and Parkinson's disease polypills, confirms that 3D bioprinting not only matches the performance of conventional GRDDS but extends it – in terms of dose flexibility, geometric precision, multi-drug capability, and manufacturability of complex architectures. The regulatory framework is maturing, and the approval of Spritam has established a viable precedent for digital pharmaceutical manufacturing.

Challenges in material development, drug loading, scale-up, and cost remain, but they are engineering challenges rather than fundamental scientific barriers. As formulation science, printing technology, regulatory science, and computational design continue to converge, 3D bioprinted GRDDS are well positioned to become a clinical reality.

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