Design and fabrication of drug-delivery systems toward adjustable release profiles for personalized treatment

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Abstract
Advanced polymeric controlled delivery systems are designed to effectively treat chronic diseases by adjusting the temporal profile of drug release. Most conventional controlled-release carriers provide a constant and sustained-release profile of therapeutics for an extended time. Although these systems have improved the patients’ compliance and adherence and have reduced the administration frequency, they cannot be used for optimal treatment of diseases that require variable patterns of drug release in the treatment regimen. These patterns and the specific rhythms of medical conditions determined by both the body’s internal biological clock cycles (i.e., circadian rhythm) and each patient’s characteristics call for patient-specific controlled drug-delivery systems that can provide adjustable drug release profiles. The importance of individualized therapy and the variety of biodegradable polymers with tunable physicochemical properties promote the design and manufacturing of polymeric delivery systems that release therapeutics at controllable rates. In the past two decades, novel biomaterials and fabrication methods have been utilized to improve the traditional drug-delivery design and manufacturing technologies. This review article provides a critical discussion of emerging polymeric controlled-release systems and the mechanisms through which they release their therapeutic agents. Advances and challenges in the design and the fabrication processes of polymeric drug-delivery systems, particularly solid oral dosage forms and implantable microchips, with controllable release profiles of drugs, are reviewed, focusing on the application of microtechnology and 3D printing techniques in their manufacturing.

KEYWORDS
3D printing, adjustable drug release, advanced drug-delivery systems, microfabrication, personalized treatment, polymeric controlled-release systems
Because of the prevalence of chronic diseases and the advent of advanced drug-delivery systems (DDSs), the pharmaceutical drug-delivery market is expected to rise from $1430 billion in 2020 to over $2015 billion by 2025 (https://www.marketsandmarkets.com/Market-Reports/drug-delivery-technologies-market-1085.html). Oral DDSs have been comprising more than 50% of this ever-rising market over the past decades. Despite the recent advances in other drug administration methods, oral drug-delivery remains the preferred route since it is cost-effective, non-invasive, and does not require administration expertise.1–3

In conventional oral DDSs, the entire drug is released immediately following administration to obtain rapid systemic drug absorption. Such immediate-release oral formulations result in an instantaneous increase in blood plasma drug concentration (to a possibly toxic level) and subsequently a rapid drop (to a subtherapeutic level), necessitating frequent administrations to maintain the drug concentration at the therapeutic level.4 The emergence of controlled-release systems (CRSs) has decreased the risk of drug toxicity and administration frequency, ultimately leading to enhanced patient compliance.5 Due to their tunable mechanical properties, biodegradable polymers have been extensively utilized in CRSs, particularly for the fabrication of oral dosage forms.6,7

To obtain the optimal therapeutic effect, it is crucial to ensure the timely release of drugs through controlled-release DDSs. Despite considerable advances in polymeric oral controlled-release DDSs, most of them merely offer a flat drug plasma concentration or extended-release profiles. Nevertheless, various clinical circumstances call for differential drug release rates with variable patterns for ideal treatment. Based on the close relationship between clock genes and diseases, the temporal drug release profile is mostly defined by the body’s endogenous biological cycles, aka, the circadian rhythm.8 Additionally, patient age, gender, and special conditions require patient-centric therapies via personalized medicine.9

The increased interest in patient-specific treatments and the variety of biodegradable polymers with tunable physicochemical properties promote the design and fabrication of advanced DDSs that release therapeutics at controllable rates. Fabricating advanced oral controlled-release formulations with desired drug release characteristics necessitates a high level of flexibility not met by the conventional manufacturing methods, such as compression tableting, currently adopted by pharmaceutical industries. Besides, the application of biodegradable polymers in controlled-release DDSs has increased the need for new tablet manufacturing methods.

Microfabrication techniques have been utilized for manufacturing oral DDSs with delicate features since it allows more precise control over the fabricated geometry.10 Some microfabrication methods, including photolithography, have been combined with replica molding steps to reduce manufacturing costs, increase fabrication resolution, and accelerate the fabrication process.11,12 For instance, these methods have been utilized for manufacturing CRSs in the form of microchips designed for achieving long-term pulsatile release.13 Despite the microchips’ ability to provide highly controllable release profiles brought about by the resolution and scalability of microfabrication techniques, limitations accompanying these implantable microchips leave the oral CRSs the preferred delivery option.14 Recently, 3D printing technology has been widely adopted for manufacturing polymeric oral tablets.15 Most of the 3D-printed tablets simply offer sustained release profiles of drugs, while some studies reported achieving more complex release rates. Although intricate tablet designs and specialized manufacturing processes have allowed for more complicated release patterns, there exist limitations that have impeded their widespread application. To address some of these limitations, improved tablet designs and alternative strategies of fabrication methods have been proposed.

In this review, the emergence of the polymeric controlled-release systems alongside their most common mechanisms is explored. Subsequently, the need for adjustable release profiles of drugs based on circadian rhythm is discussed. Developments in fabrication methods and designs of polymeric DDSs with controllable release profiles of drugs, focusing on using the microtechnology and 3D printing techniques for implantable microchips and solid oral dosage forms, are also reviewed.
and subsequently, a fast decrease in the bloodstream drug concentration. In such settings, the plasma concentration duration in both effective and nontoxic ranges is short, rendering the conventional release systems suboptimal. Figure 1B shows the importance of keeping the drug concentration level in the therapeutic window (below the toxic and above the subtherapeutic level). This figure also displays multiple administrations required for drug capsules to maintain their concentration within the therapeutic range. Multiple administration processes reduce patient compliance and cause plasma concentration fluctuations. As shown in Figure 1A, the blue curve (DR formulations) follow the same pattern as the IR forms but only releases the entire drug after a lag time to deliver it in specific locations or at a certain time through the GI tract, and still cannot address the safety issues involved in IR systems. Recently ER or controlled-release oral tablets were introduced to tackle the aforementioned problems.16

CRSs have emerged to improve health by enhancing drug efficacy, reducing dose-dependent drug toxicity, and improving patient compliance and convenience. Thus, controlled-release drug delivery allows the tunable release of therapeutic substances in response to time or different stimuli (temperature, pH, enzymes, etc.) while maintaining the dose at the effective level. Maintaining the level of biologically active agents in the therapeutic zone decreases drug toxicity and hence the side effects. CRSs are designed to sustain the required drug plasma concentration for an extended time and consequently eliminate the need for
frequent administrations.\textsuperscript{17} Figure 1B schematically compares drug burst release through the conventional means of delivery (black curve) with a typical drug release from a CRS (brown curve).

CRSs often utilize synthetic biodegradable polymers to act as carriers for delivering their cargos. Based on the site of action and the desired temporal release profile, numerous synthetic polymers with specific physicochemical properties have been widely used to create CRSs.

Biodegradable polymers have been widely used in drug-delivery applications because of their advantages over other biomaterials, specifically their tunable mechanical properties as an essential factor for achieving more efficient DDSs. In the past 50 years, synthetic biodegradable polymers have been preferred over the naturally occurring ones for use in advanced DDSs due to their availability and their easily adjustable physicochemical properties.\textsuperscript{18} In the 1960s, polyesters such as poly(D, L-lactic acid) (PLA), poly(glycolic acid) (PGA), and their copolymer poly(D, L-lactic-coglycolic acid) (PLGA) were developed as synthetic biodegradable polymeric sutures.\textsuperscript{19,20} Since then, synthetic biodegradable polymers have been extensively used as biocompatible delivery systems easily eliminated after the therapeutics are released in the human body. Aliphatic polyesters such as PLA, PGA, and poly-caprolactone (PCL), among biodegradable polymers, are the most frequently used materials in biomedical applications owing to their availability, biocompatibility, and flexible degradability. These polyesters, as well as other synthetic biodegradable polymers, including polyphosphazenes, polyurethanes, polyanhydrides, polyorthoesters, and different types of hydrogels, have been extensively studied over the past 20 years for controlled-release drug-delivery applications.\textsuperscript{21,22}

2.2 | Mechanisms of controlled drug release from polymeric systems

The variety of available drugs in the market for treating different diseases increases the importance of using CRSs to enhance drug efficacy. A significant number of CRSs have been developed for various clinical conditions. In particular, polymeric controlled-release solid dosage forms avoid the immediate release of therapeutics by modifying the drug pharmacokinetics. Choosing the most suitable delivery system for a specific clinical condition requires knowledge about different mechanisms of CRSs and their design factors.

CRSs utilizing polymers as carriers can be divided into six main categories: diffusion, dissolution, solvent-activated (swelling and osmotic-controlled), ion-exchange, stimuli-responsive, and chemically mediated (erosion- and degradation-controlled) systems\textsuperscript{23–25} (Figure 2).

2.2.1 | Diffusion and dissolution CRSs

Diffusion is the most common mechanism of releasing drugs from polymers caused by a nonequilibrium concentration gradient.\textsuperscript{26} Diffusion-based CRSs are designed as the reservoir or polymeric matrix systems, depending on their morphological construction. Reservoir systems typically consist of a water-insoluble polymeric membrane through which the drug diffuses out, while in polymeric matrix systems, the drug is released by passing through the matrix itself.

As shown in Figure 2A, in both reservoir systems and polymeric matrices, the drug can be dissolved in an aqueous solution either above the saturation concentrations or below its saturation level. In the former case, the drug’s concentration inside the polymer decreases over time by releasing the dissolved drug. Therefore, undissolved drug aggregates will be dissolved to replace the released drug molecules, leading to a controlled release rate (almost zero-order release). When the drug aggregates have fully dissolved, the concentration of the drug in the polymer goes under the saturation level. From this step onward, both systems behave similarly where the amount of the drug released from the polymer decreases over time until the completion of the drug release, as shown in Figure 2A. This is the reason for most of the controlled-release polymeric tablets to release a constant at best, and typically, a decreasing amount of drugs over time. Even though this can minimize concentration-related adverse effects, it may not necessarily improve the treatment efficacy.

Dissolution CRSs can also be designed as reservoirs or matrix systems using slowly dissolving polymers whereby dissolution rate defines the release rate of drugs. In dissolution-controlled matrix systems, drugs are encapsulated within a polymer and are released while the matrix is dissolving (Figure 2B). Therefore, one of the essential factors for selecting a suitable polymer for a dissolution CRS is polymer solubility. Most CRSs are a combination of the diffusion and dissolution systems in which drugs are trapped in polymeric membranes or matrices. Due to polymer dissolution, some pores will be created that allow water penetration to the polymer. As a result of the water flow inside the polymeric structure, the drug diffuses out of the polymeric matrices or membranes. Sometimes one of these mechanisms dominates the other, which results in dissolution-limited or diffusion-limited CRSs.\textsuperscript{27}
FIGURE 2  Polymeric controlled-release mechanisms. Schematic illustration of (A) Diffusion-based CRSs. Drugs are trapped in systems and diffuse out through the reservoir membranes or polymeric matrices over time. In general, the drug release can be controlled for a prolonged time by initially loading drugs above the saturation level. (B) Dissolution CRSs. In the reservoir systems, the thickness of the membrane determines the drug release rate by controlling the polymer dissolution rate. In matrix systems, dissolution of the boundary layer determines the release rate of the drug. (C) Solvent-activated and stimuli-responsive systems. (i) The swelling-controlled system shows drug diffusion through the expandable hydrogel. (ii) The designed orifice in an osmotic-controlled system lets drug molecules release out with an adjustable release rate. (iii) External physical stimuli to activate the responsive polymeric carriers to release their cargo in a controllable manner. (D) Chemically mediated CRSs. (i) Detachment of drug molecules from pendant side-chain polymeric systems. (ii) Surface versus (iii) bulk erosion mechanisms through erodible systems.
2.2.2 Solvent-activated CRSs

Penetration of water or body fluids into some polymeric systems can cause the controlled release of drugs. Depending on their mechanism of action, solvent-activated systems can be divided into osmotic pressure-controlled and swelling-controlled systems.

Semipermeable polymeric membranes, which are permeable to water and impermeable to drug molecules, produce osmotic pressure in such systems. There are small holes (orifices) on these membranes, acting as pathways for drugs to be released (Figure 2C-ii). The osmotic pressure caused by the water permeation into the polymeric membrane through the orifices is the driving force of the drug release process. Permeability of the polymeric membrane, the size of orifices, and the level of osmotic pressure control the release of the biologically activated agents.27,28

In swelling-controlled systems, polymers such as natural or synthetic hydrogels are used that can absorb a considerable amount of water after being immersed in an aqueous media. When these polymers swell in the presence of water or body fluids, their volume increases (Figure 2C-i). In such systems, the diffusion of the drug through the expandable polymer and the polymer swelling characteristic control the drug release rate.29

2.2.3 Stimuli-responsive and ion-exchange CRSs

Some polymeric carriers can be activated to release their cargo by external stimuli, including physical, chemical, magnetic, electrical, or mechanical stimuli that create cues for polymers with specific properties to be activated.30 These structures can be used for both targeted and temporal drug-delivery CRSs. Several studies have been conducted on thermoresponsive,31 light-responsive,32 redox-responsive,33 pH-responsive,34 and enzyme-responsive35 controlled-release DDSs. As an example, Figure 2C-iii displays some physical stimuli that can activate responsive polymers to release their therapeutics.

Ion-exchange CRSs typically consist of resins made of crosslinked polymers with a considerable number of anionic and cationic functional groups. Body fluids can flow into their structure because of the crosslinked backbone of the polymer. Simultaneously, the ionic part of the network enables the ionic groups to exchange their mobile ions with another cation or anion.34 Therefore, there are two types of ionic-exchange DDSs: the release of cationic drugs using anionic resins or the release of anionic drugs using cationic resins. In these systems, the pH of the human body environment, the ionic strength, and the resin crosslink density can control the drug release rate.

2.2.4 Chemically mediated CRSs

Chemical reactions play an integral role in controlling the drug release from polymeric systems. Chemically controlled systems are generally divided into two groups, the pendant chain and erosion-controlled systems. In pendant chain polymeric systems, drugs are covalently bonded to the polymer backbone, with the polymers degrading once exposed to body fluids. The targeted site for delivering the drug has its own characteristics, leading to hydrolytic or enzymatic degradation of the drug–polymer bonds (Figure 2D-i). These systems can be used mostly for targeted drug delivery. The hydrolysis and the enzymatic degradation rates of the drug–polymer conjugation determine the rate by which the drugs detach from the polymer backbone.

In erodible polymeric CRSs, drugs are dispersed in a matrix that will be released upon degradation and subsequent erosion (Figure 2D-ii, iii). If the drug diffusion rate from the polymer is much faster than the erosion rate of the polymeric matrix, the release kinetic is diffusion-controlled, as described in the previous section. In contrast, if the polymer undergoes an erosion-controlled drug release mechanism, the drug-loaded matrix erodes before the occurrence of the drug diffusion.36,37 There are two types of erosion mechanisms, namely bulk and surface erosion. Bulk-eroding polymers are degraded from their inside and outside simultaneously in contact with water. In surface-erodible systems, polymer moieties are degraded from the surface such that the size of the polymer decreases while preserving the initial geometry of the polymer,38 as shown in Figure 2D-iii.

Although a combination of both mechanisms (surface and bulk erosion) occurs, the majority of the biodegradable polymers used for CRSs (e.g., polyesters) undergo bulk erosion due to their backbone chemical structure.39 Since water penetrates to the bulk of these polymers, the drug is not sufficiently protected, and hence the drug release kinetic is not accurately predictable. On the other hand, surface eroding systems protect water labile drugs as they have highly labile functional groups leading to fast hydrolysis on the surface, and because of the hydrophobic backbone, water cannot quickly pass through the polymer. Another exciting characteristic of surface eroding polymers is their mechanical properties, which do not change during erosion. Besides, the high predictability
FIGURE 3  Human circadian time chart and personalized medicine. The graph shows peaks of some biological features during 24 hours of the day in a person with regular daytime activity. It indicates the severity of various medical conditions’ time varies between individuals, for which personalized treatment is required. Besides, it also shows that most biological hormones have their specific timely release patterns. The thyroid-stimulating hormone (TSH), as well as the growth hormone and melatonin peak at bedtime while the concentration of the adrenocortical hormone (ACTH), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) is at the highest level at the start of the daytime. “Doctor with Patient Cartoon.svg from Wikimedia Commons by Videoplasty.com, CC-BY-SA 4.0”

and reproducibility of the surface eroding systems’ release kinetics render them more favorable for CRSs. This study focuses on advanced polymeric DDSs that mostly release their active pharmaceutical ingredient (API) through diffusion, dissolution, and chemically mediated mechanisms.

3  CIRCADIAN RHYTHM AND PERSONALIZED MEDICINE

The study of the biological rhythm (i.e., chronobiology) and the consequence of several natural rhythms is the temporal organization of human bodies. Suprachiasmatic nuclei, located in the hypothalamus, control the human circadian rhythm. This circadian rhythm governs the cells- to organs-level activities of our body, affecting the occurrence and even severity of medical conditions throughout the day. Figure 3 illustrates the importance of the circadian time structure, demonstrating the urgent need to develop personalized medicine delivery systems. In this figure, sleep time is considered from 10 p.m. to 6 a.m., and the rest of the time during the 24 hours of the day is considered activity time for a person with regular activity.

These patterns of symptom severity show the necessity of precise treatments in which the exact amount of therapeutics is released in the body during certain times of the
day, for specific durations. For instance, the gonadotropin-releasing hormone (GnRH) necessitates pulsatile drug release for therapeutic effectiveness. Peptic ulcer attacks and gallbladder occur mostly at night, while myocardial infarction (MI) or stroke occurs two to three times more frequently in the morning. The graph in Figure 3 also displays the peak of the basal gastric acid secretion and white blood cell count (WBC) at late night while the concentration of the hemoglobin and insulin is at the highest level at noon.

Decreasing release rates of the drugs over the 24 hours of the day, assuming that the medication starts in the early morning, are beneficial for diseases that are worse in the morning, including rheumatoid arthritis, asthma, and angina pectoris. Patients with osteoarthritis suffer from more severe pain in the afternoon. They should benefit from therapeutics with an increased release profile. Moreover, some agents or drugs require a particular administration profile during a specific period of time. For instance, patients with attention deficit hyperactivity disorder (ADHD) require a bimodal release profile of Ritalin-LA. In addition to the temporal profile, for some drugs (e.g., anticoagulants, antihypertensives, and antiepileptics), achieving an accurate plasma concentration throughout medication is very important due to the narrow therapeutic range and severe side effects.

Personalized medicine in drug-delivery systems has emerged as an approach to enhance treatments’ efficacy by designing customized therapy that follows the individual patient’s needs. To be more specific, a release profile that mimics the patient’s circadian rhythm is considered advantageous for insulin dosing and enables innovative methods in cancer treatment, highlighting the importance of developing CRSs that can adjust the drug release rate for different circumstances.

4 | DESIGN AND FABRICATION METHODS OF POLYMERIC DELIVERY SYSTEMS TO ACHIEVE ADJUSTABLE DRUG RELEASE

Several fabrication methods have been used for advanced DDSs. Although the pharmaceutical industry is still using compression tableting methods, increased interest in individualized therapy and the variety of biodegradable polymers with adjustable physicochemical properties promote new methods for fabricating advanced controlled DDSs. The focus of this section is on microfabrication and 3D printing technologies that recently have attracted attention for the manufacturing of advanced delivery systems with controllable drug release.

4.1 | Microtechnology for tunable drug release

Microfabrication was originally adopted from the microelectronics industry and has been used for manufacturing advanced DDSs. Recently, microfabrication technologies have been employed to manufacture high-throughput assays in various fields, including but not limited to drug discovery, tissue engineering, and drug delivery. Moreover, some issues of oral drug delivery can be addressed when microfabrication is used due to its ability to fabricate delicate features by providing more precise control over the shape or geometry of DDSs.

4.1.1 | Microfabrication techniques

Microfabrication for creating delivery devices generally consists of repeated steps, including film deposition and photolithography. The desired two-dimensional (2D) features designed by a computer-aided design (CAD) software beforehand are printed as a photo-mask, and photolithography steps will transfer the pattern to a substrate. Using the standard photolithography processes, features with a fine resolution of 0.5–1 μm have been achieved. Based on the ultimate application of these micron-sized features, a rigid substrate such as silicon can be used as a master mold for making the inverse replica of soft elastomers. In this process of lithography, poly(dimethylsiloxane) (PDMS) is usually used as the soft elastomer material. Combining replica-molding steps with microfabrication techniques allows for the rapid, easy, relatively inexpensive, and precise manufacturing of DDSs. Fine features on a PDMS mold can be used to make channels through which minute amounts of fluid flow, creating a platform called microfluidic. Microfluidic devices have been extensively used in tissue engineering applications, particularly for lab-on-a-chip studies, or as high-throughput platforms for drug screening. Microfluidics has also been used to manufacture controlled-release microparticles and polymeric microcontainers as drug-delivery devices. Various devices have been microfabricated that are capable of delivering drugs locally or through programmable systems. Programmed polymeric systems are designed to deliver therapeutic contents at a predetermined rate, which can be controlled either remotely using operators, known as on-demand devices, or by the activation of the polymer itself.

Based on the considerable number of biomaterials that have been developed during the last few decades and due to the advances in microfabrication techniques used in biotechnology, there has been a substantial increase in the
development of implantable microelectromechanical systems (MEMS) for controlled-release drug-delivery toward more effective treatments. Several MEMS drug-delivery devices have been developed that can sustainably release therapeutics. Based on their actuation mechanisms and their construction, these devices can be divided into two groups: micropump-based and multireservoir systems. Micropump-based systems are generally embedded in microfluidic networks to control the drug release by various actuation mechanisms such as piezoelectrical pumping and battery-free magnetic pumping mechanisms. Multireservoir systems embedded in microchips are able to simultaneously deliver multiple drugs with differential release rates (e.g., pulsatile release) and work based on the electrochemical, electrothermal, and infrared irradiation actuation mechanisms that are applied to reservoir capping polymeric membranes.

4.1.2 Microchip devices for differential drug release

Oral dosage forms have always been the preferred mode of drug delivery for both patients and clinicians. However, many therapeutic molecules suffer from low bioavailability and require other methods of delivery. Local DDSs that ensure the delivery of therapeutics to the right target can enhance treatment effectiveness as it bypasses the first-pass metabolism process in the liver and potentially eliminates the harmful side effects that are often caused by oral drug-delivery routes. Therefore, implantable DDSs have attracted increasing attention to improving local delivery and patient compliance. Implantable microchips with pulsatile drug-delivery patterns are particularly important because the human body secretes molecules such as insulin, growth hormone, and GnRH in a pulsatile manner. The earliest proof-of-concept study was on a silicon microchip that can allow for the on-demand release of drugs. The fabrication of the microchip was a sequential process consisting of silicon wafers and microelectronic processing techniques. In this microchip, single or multiple chemical substances were entrapped in ~25nl reservoirs covered with thin gold membranes acting as anodes (see the scheme in Figure 4A). The electrochemical dissolution of the individual anode membranes upon the application of voltage caused the release from the reservoirs. Photolithography, along with electron cyclotron resonance-enhanced reactive ion etching, was used to pattern the 17 mm × 17 mm silicon nitride layer on the top side of the microchip. Electron beam evaporation and lift-off were employed to deposit and pattern the 0.3-μm-thick gold electrodes over the silicon nitride membranes. The proof-of-concept study indicated sustained, sequential, and pulsatile release profiles of chemical substances by individually triggering each reservoir, and the device appeared to be biocompatible and resistant to biofouling in vivo. Connecting two macroreservoirs to 20 microreservoirs etched on a silicon substrate for increasing the capacity of the delivery systems and adding polyethylene glycol (PEG) inside the reservoir to facilitate drug transportation have been utilized for multiple drugs with well-defined temporal release profiles locally. A modified strategy of the electrochemical mechanism for dissolution of the reservoir capping membranes involves the gradual electrochemical dissolution and rupturing of the reservoir membranes in order to control the drug release in a robust and low-power approach via gas generation from the reactions.

In a microchip DDS platform, the external stimuli to release the drug could be eliminated by using a polymer membrane for sealing the micron-sized reservoirs. The polymeric membrane characteristics that regulate their degradation rates (e.g., molecular weight and compositions) determine the time of release from reservoirs. The main body of the microchip device can be fabricated from a polymer with longer degradation times (e.g., PLA), ensuring the complete release of chemicals from the device before the main body degrades. In contrast, the reservoir-sealing membrane should be made from a faster degrading polymer (e.g., PLGA) with various molecular weights, adjusting their rate of degradation of the reservoirs, and hence the time at which the drugs are released from each reservoir. Such devices showed the ability to release four pulses of multiple chemicals over several months. One limitation with this approach is that tightly controlling the molecular weight of the reservoir-sealing polymer membrane such that it has different values, and hence different degradation rate, for each reservoir well may be a formidable task.

The increasing interest in implantable DDSs led to developing advanced on-demand and programmed microchip platforms where the membrane-covered reservoir design was enhanced to achieve remotely controlled pulsatile release of a protein drug over six months in dogs, which otherwise is poorly bioavailable if taken orally. Instead of the electrochemical approach, the release of the therapeutic protein from 100 individual reservoirs was regulated electrothermally and controlled by telemetry. The local resistive heating generated as a result of an applied electric current directed to the membrane through metal traces caused the removal of the metal membrane covering the reservoir. This method of membrane removal (electrothermal) can be preferable over electrochemistry because it is independent of the chemical compounds of the surrounding environment and is considerably faster. Beyond animal studies, the
Implantable microchip devices advanced to a clinical trial for the human parathyroid hormone fragment to treat osteoporosis. The microchips were controlled by a computer program that sends and receives information wirelessly to and from the implant, driving the precise dose delivery timing. The results obtained from serum markers indicated increased bone formation in response to the device’s once-daily drug dosage. Microchip dosing proved capable of providing pharmacokinetic profiles similar to multiple subcutaneous injections without the burden and pain of injections. This clinical trial demonstrated the potential of this platform to improve current delivery methods for chronic disease treatments, for example, repeated insulin injections for diabetic patients.

FIGURE 4 Microchip devices for adjustable drug release rates. (A) The implantable silicon microchip device for controlling the drug’s release profile using the electrochemical dissolution mechanism. Multi-reservoir systems with an enlarged view of a single reservoir. Reproduced with permission. Copyright 2017, Elsevier. (B) A microchip device containing multiple reservoirs loaded with human growth hormone (hGH), which needs a pulsatile delivery regime. (1) The device and the external guide at the outer skin were magnetically attached. (2, 3) The stimuli-responsive membrane (SRM) was designed so that the generated heat breaks it in 5 seconds upon NIR irradiation. (C) In vitro release profile of the hGH through the microchip device inside the PBS for 28 days. Reproduced with permission. Copyright 2019, National Academy of Sciences of the United States of America.
Most of the earlier microchip devices were too large and bulky for implantation in the human body because of the embedded components such as battery sources and electronic modules inside them. Instead of electrochemical and electrothermal actuation mechanisms, other external stimuli such as near-infrared (NIR) irradiation or magnetic field can trigger the microchip reservoir membranes to achieve on-demand or programmable drug delivery.\textsuperscript{75,76} These external stimuli may address some of the main challenges of electrochemical and electrothermal actuation and accelerate the translation of the implantable microchips to various clinical applications. Although using these stimuli could solve some of the challenges, the continuous drug leakage from microchips is still a limitation of these devices. Besides, the capping membrane permeability needed to be optimized for achieving more complex release patterns. Noninvasive NIR irradiation stimuli have been demonstrated to trigger multiple drug reservoir capped with stimuli-responsive membranes (SRM) having reduced graphene oxide (rGO) nanoparticles.\textsuperscript{71} Human growth hormone (hGH) loaded in each reservoir can only be released upon NIR irradiation, leading to rGO nanoparticles excitation and hence the heat generation. This generated heat breaks specific membranes at certain times, allowing the drugs to be released both in vitro and in vivo at a reproducible pulsatile rate without leakages (Figure 4B, C).

Implantable microchips are attractive means of drug delivery and have proved advantageous. However, these devices come with their limitations. Implantable means of delivery are inherently invasive, requiring implant surgery to place the DDSs and an explant surgery to remove the device from the body after the dosage is completed. Patients may need to take painkillers and anti-inflammatory medications to alleviate the discomfort after surgeries. Current implantable CRSs have not incorporated measurements of the drug concentration after or during the release; however, a closed-loop control on the release is necessary to avoid under- or overdosing of the drug. In addition, the methods used for the opening of the reservoirs in microchip devices are not reversible. Accordingly, quality assurance on whether the membrane will be appropriately removed as programmed or upon external stimulation before implantation has not been reported. In the clinical trial, patients tolerated the implant size, with the microchip device enclosing a few reservoirs. An increased number of reservoirs is necessary for treatments requiring more frequent dosing and more extended delivery periods, associated with larger implant sizes. Recent efforts on using battery-free and small implantable microchips with NIR irradiation actuation mechanism addressed some challenges, including the continuous drug leakage through the membranes. However, the need for external stimuli such as the light source outside the skin will limit their application in clinical settings. Despite the attractive features implantable DDSs offer, their widespread development and use are constrained to these limitations, leaving oral dosage forms yet the most commonly used form of delivery.

4.2 3D printing technologies for solid oral dosage forms with tunable drug release

Additive manufacturing and 3D printing technologies have emerged as attractive fabrication methods in the food and pharmaceutical industry due to their ability to manufacture objects with delicate features made of multiple loaded materials. Modified release and personalized oral dosage forms also have been fabricated using these technologies. Accordingly, 3D-printed oral CRSs have been the focus of many studies in personalized medicine. Among various types of 3D printing technologies, powder-bed inkjet, fused deposition modeling, and lithography-based techniques are the most commonly used methods for fabricating polymeric controlled-release oral dosage forms. Studies in which 3D printers have been used to fabricate oral tablets can be divided into direct printing of tablets or printing containers or molds, helping in the production of controlled-release tablets indirectly, which are discussed in the next sections.

4.2.1 Powder-bed inkjet 3D printing

The first 3D printed drug to receive FDA approval in 2016 was the antiepileptic drug, Spritam\textsuperscript{®}, based on inkjet printing of a binder solution.\textsuperscript{77,78} The powder-bed inkjet 3D printing process, as shown in Figure 5A, consists of spreading a powder layer onto a plate (bed) with a roller and introducing the binder solution to specific areas onto the powder to bind the powder particles, based on the CAD design to form one layer of the structure of interest. The process is additive, meaning that the same steps are repeated for each additional powder layer until the desired geometry is built. At last, the residual powder is brushed away. The typical fragile structures fabricated by these printers have high porosity, which can be beneficial for the production of immediate-release tablets.\textsuperscript{79} Powder-bed 3D printing has also been used to make highly loaded tablets aiming at individualized therapy. In such settings, the viscosity of hydroxypropyl cellulose solid binder (the most common binder in oral dosage formulations) could control the disintegration and dissolution rate of the tablets, which regulates the drug release rate.\textsuperscript{80} Moreover, what makes this technology desirable is its potential
to produce solid dosage forms in a relatively rapid and high-throughput process.

The first attempt to fabricate solid dosage forms in powder-bed inkjet printing using cellulose powder and spray-dried lactose and cationic methacrylic ester polymer produced tablets that underwent two different release mechanisms, namely erosion and diffusion. In erosion-based tablets, by adjusting the amount of cationic methacrylic ester polymer, lag times (the time before the drug starts releasing) varying from 25 to 50 minutes (Figure 5B) was achieved. Higher polymer contents resulted in longer lag times and hence slower release in simulated intestinal fluid. In diffusion-based tablets, an increase in polymer content reduced the maximum rate of drug release while the delay time was not affected. Results of friability and mechanical strength tests on the printed structures were comparable to standard pharmaceutical products. The release profile characteristics were proved adjustable through modifying the copolymer quantity in the inkjet 3D printer.

Depending on the design, different solid oral dosage forms with distinct release behavior can be achieved (Figure 5C). The design shown in Figure 5C-i is for an immediate/extended-release pattern. These tablets

**FIGURE 5** Direct printing of oral dosage forms using the powder-bed inkjet 3D printing technology. (A) The schematic illustration of the powder-bed inkjet 3D printing steps. (B) Variation of the lag times in releasing the chemicals by adjusting the content of the polymers. Reproduced with permission. Copyright 2000, Elsevier. (C) Four different tablets printed by the powder-bed inkjet 3D printer machine: schematics show (i) an immediate-extended release tablet, (ii) the breakaway tablet. (D) The release profile for the immediate-extended tablet. The first section made of E100 20% w/w started releasing after 10 minutes (lag time). The second section made of RLPO and acetone released its content over an extended period of 7 hours. (E) Pulsatile release tablet designs. (i) The enteric dual-pulse release tablet, and (ii) the dual-pulse release tablet. Reproduced with permission. Copyright 2000, Elsevier.
consisted of two sections, both loaded with the same drug. The two units had different polymeric contents and hence had specific pH-sensitive release mechanisms. The first section was made of cellulose powder mixed with a cationic methacrylic ester copolymer (E100), while the second section consisted of an ammonium methacrylic acid copolymer (RLPO). The drug release from the first section happened with a 10 minutes lag time, whereas the second section released the compound over an extended period of 7 hours (Figure 5D). The second dosage forms were breakaway tablets (Figure 5C-ii) programmed to split into two drug-loaded sections by the fast erosion of the part separating the two. The drug-loaded sections erode in the gastric fluid in 30–45 minutes. The third type of tablet was designed to achieve an enteric dual-pulse release (Figure 5E-i), whereby multiple drug-containing layers were created for erosion-based release. A dual pulse device can also be designed such that a portion of the drug is released in response to the low pH in the stomach, whereas the rest would be released at high pH conditions in the intestine (Figure 5E-ii). Collectively, these designs show the various 3D-printed multilayered tablet possibilities from multiple materials to achieve adjustable release profiles.

The release kinetic of 3D printed oral dosage tablets is important. In this respect, a zero-order release kinetic (constant release rate) was reported from powder-bed inkjet 3D printing of a doughnut-shaped DDS. The tablet design consisted of a model drug in the middle and release-retardant material containing ethyl cellulose (EC) as the barrier covering the tablet’s top, bottom, and outer surfaces. The release data demonstrated linear profiles, irrespective of the diameter of the central aperture, the outer diameter, or the table height. The decrease in release rate from the outer surface (as the surface area decreases while eroding), the increase in the release rate from the inner surface over time, and the presence of release-retardant EC covering the outer surface ensure the zero-order profile in this tablet design. The release rate was adjustable by modifying the thickness and the EC’s quantity in the outer shell covering the core. This study demonstrated the application of powder-bed 3D inkjet printing for achieving zero-order release kinetics throughout the entire dissolution process.

A method for fabricating solid dosage forms combining inkjet and flexographic printing to achieve controlled-release patterns of therapeutics has also been reported. The active model drugs were printed on the substrate using inkjet printing, whereas flexographic printing was then employed for tablet coatings with various thicknesses using water-insoluble EC polymer films. Release kinetic studies on the tablets suggested that the uncoated substrate showed the highest release rate, whereas the release of drugs from the tablets with triple-coated inkjet paper was the slowest. The release profile can be adjusted to decreasing overtime or constant by changing the number of coating layers and hence the coating thickness. Solvent-free 3D inkjet printing of solid dosage forms (e.g., honeycomb geometry) is also possible by hot melt inject printing in which 3D material jetting of molten wax forms bespoke geometries. This design allows control over drug release rates by modifying the geometry.

4.2.2 Fused-deposition modeling

Another type of 3D printing technology is an extrusion-based technique of fused deposition modeling (FDM). In the FDM method, the most commonly used technique for fabrication of solid oral dosage forms, thermoplastic polymer filaments are extruded in a melted semiliquid form and pass through a nozzle with elevated temperature. Filaments exit the heated nozzle and are deposited on the build plate at specified locations where they will be hardened. FDM 3D printing poses some advantages that made this technology suitable for manufacturing oral dosage forms. It can produce higher-resolution tablets than inkjet 3D printing, allowing for more accurate drug release. FDM-based machines are also capable of printing relatively intricate designs to achieve modified release profiles. More importantly, FDM 3D printing can be easily set up and is relatively cheap.

Goyanes et al. fabricated tablets using the combination of FDM 3D printing and hot-melt extrusion (HME) processing. They showed FDM’s potential in manufacturing oral dosage forms by producing tablets with different geometries, which is not easily achievable using conventional tablet fabrication methods, for example, powder compaction. To overcome the low-percentage drug-loading problem, HME processing was utilized by incorporating drugs into the polymer filaments, leading to a uniform-shaped product. Tablets with five different geometries, namely, pyramid, cylinder, sphere, cube, and torus (donut-shape) were successfully printed by producing a filament that contains a water-soluble polymer (polyvinyl alcohol, PVA) loaded with paracetamol (Figure 6A). The impact of tablet geometry, including the tablet surface area and the surface area to volume ratio (SA/V ratio) on drug release profiles was studied. Interestingly when the SA/V ratios for all the tablets were identical, almost all shapes released 90% of their loaded drugs in 10 hours regardless of the differences in surface areas and volumes of the tablets (Figure 6B), suggesting the utility of FDM 3D printing as a low-cost fabrication process for manufacturing tablets with relatively complex geometries and allowing for controlling the release rate of the drug by adjusting the geometry of dosage forms.
FIGURE 6  FDM 3D printing of tablets. (A) Five different tablet geometries printed by FDM techniques. (B) Tablets released their contents in 2–3 hours when the SA/V ratio for all of them was the same. Reproduced with permission. Copyright 2015, Elsevier. (C) Eight Calcein-loaded PVA/PVA composite tablets (top) and four Calcein-loaded PVA/PLA composite tablets (bottom). (D) By increasing the covering layer thickness, the lag time increased. Reproduced with permission. Copyright 2018, Elsevier. (E) The capsular DDS with different thicknesses produces a two-pulse release profile. (F) Having two different materials for each compartment with consistent thicknesses, two pulse release profiles were achieved. Reproduced with permission. Copyright 2017, Elsevier.
To create timed delayed-release tablets, a dual FDM 3D printing method has been developed. Although this method could not produce high-resolution tablets, it showed the potential of dual FMD 3D printing as a one-step production process for delayed-release oral dosage forms. One advantage of this method is the possibility to produce tablets with zero-order and/or tunable release rates by changing the polymer type and the printed layer thickness (Figure 6C, D). Delivering drugs to specific locations through the GI tract by adjusting the release timing, these tablets with various wall thicknesses can be used as alternatives to pH-sensitive or other externally stimulated DDSs. In addition, FDM can also be utilized indirectly for manufacturing controlled-release tablets to achieve pulse or time-dependent colonic release. The ability to fine-tune the lag phase duration and hence to achieve site-selective release can improve the potential of capsular DDSs with rapid prototyping abilities in manufacturing. Using combinations of compartment wall thickness and polymer characteristics, immediate, enteric, and pulsatile drug release profiles were achieved. As shown in Figure 6E, several combinations of components (e.g., PVA filaments) have been investigated to obtain capsular DDSs with two successive drug release pulses. This design can be particularly advantageous for improving patient compliance by ensuring the dosing schedule of prescribed therapies that are not compatible with the GI tract. The results indicated the comparable performance of the encapsulated devices fabricated using FDM 3D printing with tablets created by injection molding (IM) techniques. Accordingly, the prototyping capabilities of FDM 3D printing can be used for personalized treatments and can be used to produce small-sized batches to design capsular systems before manufacturing them by IM. 3D-printed polymeric containers have been created using commercially available FDM printers to achieve predetermined near zero-order release rates of common over the counter drugs. The composition of tablets determined their loading capacity as well as their degradation rates. To control the drug release from highly loaded tablet formulations, hydroxyethylcellulose is a material of choice, while other tablets containing a low portion of the drugs were prepared of sodium alginate, carnauba wax, and croscarmellose sodium. Considering the importance of the dose personalization, modifying the drug release rate from FDM-printed carriers and containers have been investigated by changing their geometric structures instead of changing their material compositions. Regulating and optimizing the design parameters, including the size of blocks, interblock spaces, and the number of bridges, the desired release characteristics could be achieved, which usually obtained only by complicated chemical formulations. FDM is an interesting substitute for conventional tablet fabrication methods due to its potential in manufacturing desired geometries to achieve a more accurate dosage. Unlike conventional additive manufacturing methods, FDM can be used to create rounded corners, which improves patient compliance. However, there are limitations to this method, which reduces its flexibility and widespread use. The high temperature required during FDM steps can damage thermally labile drugs. Besides, only a few biodegradable thermoplastic polymers can tolerate such high-temperature conditions. Although FDM has been used in the fabrication of various geometries, the resolution of these printers may not be high enough to achieve the desired surface quality and acute angles required in the form of tablets for individualized therapy and precision medicine.

### 4.2.3 Lithography-based 3D printing

The term stereolithography (SLA) was coined by Charles Hull in his 1986 US Patent. SLA technology is based on the photopolymerization process in an additive manner, similar to other 3D printing technologies, where for each layer, a CAD design guides the depth of the laser focus and eventually produces the 3D object of interest. SLA offers several advantages over other 3D printing methods previously reviewed. In contrast to FDM methods, SLA does not expose the materials to high temperatures, and therefore it is suitable for fabricating DDSs with thermally labile therapeutics. SLA’s resolution is superior to other 3D printing technologies and is only restrained by the laser width. Digital light processing (DLP) 3D printing is also a lithography-based method with higher resolution and printing speed than the SLA 3D printing technique. SLA utilizes lasers to cure the photocurable solution point by point, while DLP uses a digital projector to cast and cure an entire slice of objects. There has been a significant increase in using lithography-based techniques for manufacturing oral dosage forms during the past few years because of advances made in the rapid manufacturing of complex structures.

The use of SLA technology for printing oral dosage forms was initiated by utilizing polyethylene glycol diacrylate (PEGDA) and polyethylene glycol 300 (PEG 300) as monomers in different ratios, aiming at obtaining different release kinetics. For instance, tablets with two different drugs (paracetamol and 4-ASA) were printed in torus shapes (Figure 7A-i), which are otherwise complicated to achieve by other manufacturing methods. The torus shapes offer increased surface area compared to conventional shapes and maintain an almost constant area during the dissolution process. The effect of PEGDA to
FIGURE 7  Lithography-based printing of tablet structures with controllable release profiles. (A) High-resolution tablets created by SLA 3D printing machines. (i) Donut-shaped SLA-printed tablets with paracetamol (top row) and 4-ASA (bottom row) as model drugs. Each row from left to right shows tablets with different PEGDA to PEG 300 ratios. (ii) Drugs released from tablets with varying ratios of polymers. Slower release from tablets with a higher portion of PEGDA. Reproduced with permission.\textsuperscript{100} Copyright 2016, Elsevier. (B) Multilayered polymeric tablets created by SLA 3D printers. (i) The ring-shaped tablet 3D design made of six different drugs. (ii) Raman mapping of the spatially separated six drug layers. (iii) Cumulative drugs released from the multilayered ring tablet. Reproduced with permission.\textsuperscript{106} Open access. (C) DLP 3D printing along with microfabrication for high-scale and high-resolution manufacturing of personalized oral tablets. (i) Scalable microfabricated platform for creating tablet core features. (ii) Multiple-arm drug-loaded tablets with adjustable release profiles. (iii) Releasing adjustable and higher drug dosage through multiple-arm tablet designs. Reproduced with permission.\textsuperscript{110} Copyright 2020, IOP Publishing.
PEG 300 ratios on release kinetics was evaluated using a gastrointestinal model with a dynamic environment (e.g., changing pH values over time), mimicking the intestine condition. As shown in the drug release profile graph (Figure 7A-ii), the release kinetics proved independent from pH changes confirming the potential of SLA 3D printing in the fabrication of high-resolution oral dosage forms from thermally labile drugs, with adjustable release rates to achieve immediate or extended drug release. To further demonstrate the ability of SLA 3D printers in the fabrication of pharmaceutical polymeric tablets, the SLA-based production of ibuprofen-loaded cross-linkable hydrogels was also reported.

The effect of tablet geometry (e.g., disc, cube, sphere, pyramid) on drug release profiles of SLA 3D-printed tablets in a dynamic dissolution environment showed similar drug release rates from tablets with identical initial SA/V ratios. Considering the importance of the tablet geometry to achieve different drug release rates needed in personalized medicine, poly(ethylene glycol) dimethacrylate (PEGDMA) network were printed in different shapes after being loaded with ascorbic acid. Among the printed coaxial annulus, honeycomb, small and large, and four-circle pattern tablets, the first two showed higher release rates. This work demonstrated the potential of SLA 3D printers to create hydrogel-based solid oral dosage forms loaded with water-soluble vitamins that can achieve adjustable release profiles of drugs by altering the tablet geometry, particularly its SA/V ratio.

The SLA 3D printing method has also been used to fabricate tablets with multiple drug-loaded layers to enhance treatment efficacy. Each layer was printed separately at a specific spatial location. Two different shapes of multilayered tablets, including the cylindrical and ring-shaped printlets were fabricated. As shown in Figure 7B-i, a ring-shaped tablet was printed using six different model drugs loaded in PEGDA and PEG 300. Raman microscopy images showed the spatial separation and interaction of different layers as well as the drug diffusion through them (Figure 7B-ii). Sustained release of multiple drugs from these tablets was achieved in a dynamic dissolution test (Figure 7B-iii). The drug release was controlled by changing the tablet geometry (from cylindrical to ring-shaped) and by altering the tablet composition (e.g., adding excipients). Although the SLA 3D printing technique showed the capability of manufacturing multilayered solid oral dosage forms, the potential drugs–photopolymer chemical reactions and interactions of drug-loaded layers limit its application, indicating the importance of appropriate polymer selection processes.

DLP 3D printing technique utilizes a micromirror device that allows for creating each layer in a single exposure step, accelerating the tablet fabrication process. Moreover, the volume of the reservoir containing the drug-loaded resin is customizable, and hence a smaller amount of photopolymers are needed for manufacturing tablets. As a modified version of the SLA 3D printing method, DLP 3D printing has been used for manufacturing solid oral dosage forms. Perforated and nonperforated oral formulations were fabricated with zero, two, and six holes embedded in the tablet structures. Tablets were made of PEGDA and PEGDMA loaded with a model drug. The immediate or extended drug release profiles were controlled by changing the tablet’s in-contact surface area, which resulted in faster drug release from tablets with higher effective surface area, that is, the tablets printed with more holes. The drug release rates decrease due to the higher crosslinking density of tablets made of higher concentrations of PEGDA. Adding some hydrophilic polymers and excipients such as PEG 400 and mannitol could accelerate the drug release rates in tablets with slow drug diffusion and molecular mobility.

Due to DLP 3D printer’s rapid and high-resolution process, it has been used to create molds in which polymeric tablets with complex geometries can be produced. Cylindrical and cuboid tablets made of photocrosslinkable polyanhydrides were fabricated within PDMS wells created by DLP 3D-printed master molds. The effect of different structural (e.g., tablets’ geometry and compositions) and environmental (e.g., pH, temperature, and convective force) parameters that mimic the physiology of the GI tract on tablets’ erosion rates were investigated. The release kinetics could be controlled by the tablet initial SA/V ratio and their compositions. To realize the commercial viability of personalized polymeric tablets with adjustable release profiles, a scalable platform was developed using lithography-based microfabrication and DLP 3D printing technologies. As shown in Figure 7C-i, the tablet cores with intricate features were fabricated through a connected microfluidic network, while tablet shells were formed within cylindrical PDMS wells created by DLP 3D-printed master molds. The core-shell drug-loaded tablets were made of a single erodible polyanhydride instead of multiple materials, accelerating the tablet production process and avoiding potential interactions between different polymeric compartments. Multiple-arm tablets (Figure 7C-ii) with higher loading capacity were fabricated to release high drug dosage and to lower the risk of UV-induced damages to loaded drug molecules. Figure 7C-iii shows the improved cumulative drug released from multiple-arm tablets with tunable release rates. The designed core-shell tablets in conjugation with the rapid and high-scale platform allow for the mass-production of personalized tablets with tunable release profiles.

Lithography-based 3D printing technologies have offered benefits over conventional 3D printing methods.
that are promising for further advances in fabricating personalized oral dosage forms. The main limitation associated with the use of these 3D printing technologies for direct printing of solid oral dosage forms, however, is the limited number of photopolymer resins that are at the same time nontoxic, safe, and biocompatible. Table 1 summarizes the advantages and limitations of the different fabrication methods to manufacture advanced delivery systems with adjustable drug release toward personalized medicine.

### 4.3 Gastroretentive oral drug formulations

Since the concept was first suggested for veterinary medicine,\(^\text{112}\) the translation of gastroretentive oral drug-delivery devices to humans has been a pipe dream for several decades. Although this idea is deceptively simple, it has proven to be a formidable task. In a gastroretentive drug-delivery strategy, a standard size oral tablet is swallowed. Once it reaches the stomach, it should be retained for an extended time, delivering a predefined amount of drug without being affected by routine gastric emptying.

Several oral tablet designs such as floating, mucoadhesive, and magnetic\(^\text{113}\) have been suggested, but their feasibility to deliver drugs for more than 8 hours in the stomach is still a challenge.\(^\text{114}\) Furthermore, there are practical difficulties in these designs. For instance, in the magnetic system, the patient needs to carry an external magnet to manipulate the location of the magnetic depot tablet in the stomach, whereas the floating system is practical only in the fed state. Despite the challenges, gastroretentive oral dosages are beneficial for drugs with a narrow absorption window (those absorbed in the first part of the GI tract) and for drugs with a very short half-life.

Advances made in new material discoveries and microfabrication technologies opened opportunities to push the design boundary further. In this regard, an appealing approach is expandable gastroretentive oral drug-delivery configurations in which (i) an oral tablet is packaged small enough to be swallowed, (ii) upon arrival to the stomach, the delivery system expands to a size larger than the pylorus (mean diameter of 12.8 mm ± 0.7 mm in humans\(^\text{115}\)) to prevent passage to the intestine, (iii) after releasing all of the drugs, it either collapses to a small size or breakdown into smaller pieces to be safely evacuated through the GI tract. For instance, oral tablets covered...
Figure 8 Expandable gastroretentive oral dosage forms. (A) Ingestible hexagonal and star-shaped gelatin capsules and their geometric arrangements. The degradation rates of the polymeric linkers (black and yellow parts) determine the drug release timing. Reproduced with permission. Copyright 2016, The American Association for the Advancement of Science. (B) Once-a-week antiretroviral oral capsule with multiple drug-loaded arms sustainably releasing drugs for effective treatment of HIV. Reproduced with permission. Open access. (C) A coil-shaped antibiotic-loaded pill made of a shape memory alloy wire delivers high doses of medications for tuberculosis treatment over a prolonged time (almost a month). Reproduced with permission. Open access.

by a gastric-juice permeable polymer for the controlled release of drugs in the GI tract with a delayed pyloric passage have been reported. Riboflavin, levodopa, and furosemide have been incorporated into expandable gastroretentive oral tablets/capsules. In addition to in vitro and animal model studies, furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage administration were investigated in healthy volunteers. This drug was chosen because of its narrow absorption window in the upper part of the GI tract, and its dissipation of the natriuretic effect before the next dose of the drug is given. It is interesting to note that compared to floating, swelling, and mucoadhesive dosage gastroretentive oral dosage forms, the expandable form appears to provide better retention in the human stomach.

Recently, more elegant design concepts in expandable oral dosage forms were introduced (Figure 8A). By solvent-welding of a flexible plasticized methacrylic acid and methyl methacrylate copolymer with rigid PCL-based polyurethane segments, star-shaped and hexagonal drug-loaded designs can be packaged into a gelatin capsule for ease of ingesting. Upon swallowing and subsequent gelatin dissolution in the stomach, the system expands to the original shape that is larger than the pylorus sphincter and could deliver drugs for an extended period of time. The antimalarial drug ivermectin was released from such a system over a 2-week period. Although this study made excellent progress, it is not clear how the star and hexagonal shape gastroretentive devices eventually pass through the pylorus. PCL is a very slowly degrading polymer and, the only plausible mechanism is the solvent welding sites weaken over time, leading to fragmentation of the elastomeric and PCL pieces so that it can easily pass to the intestine. This suggests that the system relies on welding sites mechanical failure rather than polymer degradation in the stomach. Another challenge with this system is that the drug was loaded to the PCL segment at a higher temperature, which may not suit thermally sensitive drugs. One of the attractive features of gastroretentive DDSs is in addressing patient compliance issues, especially those with cognitive impairment. With the aim of delivering multiple antiretroviral drugs for HIV, the design was modified whereby the drug-loaded arms are made of different types of degradable polymers for regulating the release rate of multiple antiretrovirals (Figure 8B). For therapies that required a large dose over an extended time
(up to 30 days), a series of tuberculosis antibiotic drug pills loaded onto a nitinol shape memory alloy wire (Figure 8C) where the device forms a coil-shape upon reaching the stomach is also reported.\textsuperscript{123} This device is not ingestible but requires a catheter to deploy it to the stomach through the esophagus. Furthermore, after the targeted time of drug delivery, the device must be retrieved magnetically. The delivery and retrieval approach are akin to gastric balloons that are used in weight loss management in bariatrics.

5 CONCLUDING REMARKS AND FUTURE PROSPECTS

The development of advanced manufacturing techniques, along with improved knowledge of diseases and pharmacology, encouraged the design and fabrication of state-of-the-art controlled DDSs with adjustable release rates required for patient-specific treatments. Biodegradable polymers play an integral role in the design and fabrication of these CRPs due to their tunable properties. Implantable microchip devices and 3D-printed solid oral dosage forms are the two most studied micro- and macroscale polymeric controlled DDSs used to regulate the drug release characteristics for personalized medicine.

Each patient has different genetics as well as specific physiological patterns and lifestyle. Therefore, medications with specific therapeutic regimens are required for optimal treatment of each individual patient. When patients have similar pharmacogenomics information, they can be treated in a similar way through precision medicine. Personalized and precision medicine can significantly reduce the adverse drug reactions and side effects by preventing the conventional one-size-fits-all dosing and type of prescriptions. New manufacturing techniques such as 3D printing and high-resolution microfabrication technologies have the potential to revolutionize the biopharma industry as they are able to efficiently produce patient-specific formulations that can tailor the dosage of APIs over the course of treatment based on the patient’s need.

Microfabrication has been utilized to create microchip devices implanted in the body to release drugs at predetermined rates. Although researchers reported successful clinical trials with implantable microchips, there are still challenges to overcome before their widespread adoption. For instance, a control system is required to monitor the effectiveness of the microchips in releasing the therapeutics properly. Other challenges include the inevitable surgeries to implant and explant the microsized devices, concerns about the biocompatibility of the implanted microchip, and the potential side effects of the incorporated wireless communication modules on sensitive organs such as the brain. In addition, these microchips can become heavy or bulky, for example, when embedded with actuators to stimulate the reservoirs’ polymeric membranes. These limitations have left the oral controlled drug delivery as the most common administration route, which is noninvasive, affordable, and safely and conveniently taken by the patients themselves.

In recent years, 3D printing technology has been widely used for creating solid oral dosage forms allowing the production of intricate structures without the need for manufacturing expertise. Besides, 3D printers can fabricate structures made of various materials in a single step, not easily achievable by conventional tableting steps (e.g., mixing, milling, granulation, drying, and compression). Numerous studies show substantial progress in manufacturing polymeric tablets with tunable release profiles using 3D printing technologies, most of which reported a sustained drug release for a prolonged time. In contrast, some others have achieved more complex release rates, including pulsatile or sequential. Despite their interesting features, most 3D printers are slower than the current manufacturing methods used in the pharmaceutical industry, such as compression molding. Therefore, it is challenging to scale up these printing processes for large-scale tablet manufacturing. Although earlier powder-bed inkjet 3D printers allowed the fabrication of immediate- and extended-release tablets, they could not achieve adjustable drug release rates. In addition to the high cost and hence unavailability of commercial powder-bed inkjet 3D printers, finding a reliable ink jetting and handling the powder are among other limitations of these printers. In contrast, inexpensive commercially available FDM 3D printers have been used for printing solid oral dosage forms with controllable release profiles. FDM printers are, however, limited to thermoplastic resins and drugs that are stable at very high temperatures during the melting process.

The 3D printers’ resolution and their production accuracy affect the precision of the drug release rate from polymeric tablets. Common inexpensive FDM machines have a relatively low resolution when utilized for either direct printing of polymeric tablets or printing molds for indirect fabrication. Lithography-based 3D printers, on the other hand, have the highest resolution and can accurately print complex geometries required in the fabrication of personalized oral dosage forms. Nevertheless, a limited number of photopolymers can be used as resins for SLA and DLP printers. The degradation of the drug under the UV laser also needs to be taken into account in these lithography-based printers.

Moreover, scalability is a critical characteristic of any successful manufacturing method of advanced controlled DDSs. Most of the studies so far have reported manufacturing a single tablet with a low level of reproducibility in a time-consuming process, reducing their chances of
clinical or industrial adoption. The combination of rapid 3D printing and microfabrication techniques capable of high-resolution manufacturing of miniaturized features could potentially tackle both the precision and scalability issues. Such hybrid fabrication methods can utilize the effectiveness of conventional pharmaceutical manufacturing processes with the advantages of 3D printing for mass production of tablets with controllable release rates.

In summary, polymeric controlled DDSs with adjustable release profiles have the potential to improve the effectiveness of disease treatments substantially. 3D printing technologies have shown significant promise for manufacturing polymeric systems such as solid oral dosage forms with tunable release profiles and can be further explored for their potential in obtaining higher-resolution structures and in producing complex geometries with intricate designs. To further advance the research in this area and to use 3D printers in clinical settings, the next steps should be to develop and utilize Generally Recognized as Safe (GRAS) resins for 3D printers. In order to take 3D printer technology to the tablet manufacturing industry, steps are needed to be taken to speed up or parallelize the process and consequently scale up the tablet production. In addition to optimizing manufacturing methods for the fabrication of various oral tablets with adjustable drug release, the impact of the GI tract dynamic environment on the kinetics of the drug release and absorption should be considered in tablet design processes to enhance the treatment efficacy by producing robust and efficient solid oral dosage forms.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

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