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Review article

Zero-order drug delivery: State of the art and future prospects

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ABSTRACT

Pharmaceutical drugs are an important part of the global healthcare system, with some estimates suggesting over 50% of the world's population takes at least one medication per day. Most drugs are delivered as immediate-release formulations that lead to a rapid increase in systemic drug concentration. Although these formulations have historically played an important role, they can be limited by poor patient compliance, adverse side effects, low bioavailability, or undesirable pharmacokinetics. Drug delivery systems featuring first-order release kinetics have been able to improve pharmacokinetics but are not ideal for drugs with short biological half-lives or small therapeutic windows. Zero-order drug delivery systems have the potential to overcome the issues facing immediate-release and first-order systems by releasing drug at a constant rate, thereby maintaining drug concentrations within the therapeutic window for an extended period of time. This release profile can be used to limit adverse side effects, reduce dosing frequency, and potentially improve patient compliance. This review covers strategies being employed to attain zero-order release or alter traditionally first-order release kinetics to achieve more consistent release before discussing opportunities for improving device performance based on emerging materials and fabrication methods.

1. Introduction

Drugs are an integral part of the global healthcare system and contribute to both preventing and treating disease. It is estimated that 50% of the global population consumes more than one dose of medication per day, a substantial increase from 33% in 2005 [1]. In the United States alone, 5.8 billion prescriptions were dispensed in 2018 and 85% of adults over the age of 60 are using prescription drugs [2,3]. The importance of prescription drugs and their capacity to improve health is underscored by the efficacy of blockbuster drugs, such as statins. One study found that statins taken preventatively by at-risk patients without prior cardiovascular events reduced the risk of all-cause mortality by 16% [4]. Another study found that for men with high levels of cholesterol, preventative statin use reduced 20-year all-cause mortality, risk of death by coronary heart disease, and risk of death by other cardiovascular diseases by 18%, 28%, and 25%, respectively [5].

Despite the demonstrable benefits of drugs, their impact is lessened by a number of factors including side effects, undesirable dosing regimens, and low patient compliance. It is estimated that patient adherence to drug regimens for chronic diseases is as low as 50% in western society and potentially even lower in developing countries, generally attributed to a combination of drug regimen complexity, socio-economic, and patient-related factors [6]. An estimated 33–50% of the U.S. population is non-adherent to treatment regimens [7], which negatively affects health outcomes and has important economic ramifications, with some estimates suggesting it costs the country $100–290 billion in added health care costs every year [7–9]. One study of diabetic patients over the age of 40 showed that poor adherence to drug regimens increased all-cause mortality by 45% [10].

Most clinically available drugs are administered as immediate release formulations, which include pills and capsules as well as intramuscular, intraperitoneal, and intravenous (IV) injections [11]. While these methods of delivery have important clinical applications, they are all generally limited by their pharmacokinetic profile, which is characterized by initial rapid drug distribution pushing systemic levels above the minimum effective concentration (MEC) but below the minimum toxic concentration (MTC) followed by a drop below the MEC over time as the drug is metabolized and cleared from the body (Fig. 1A) [12]. Remaining between the MEC and MTC is critical because it allows the patient to receive the benefit of the drug without experiencing severe adverse side effects [13]. This is easiest to achieve when the therapeutic window is large or when the biological half-life of the drug is long. A large therapeutic window allows systemic drug

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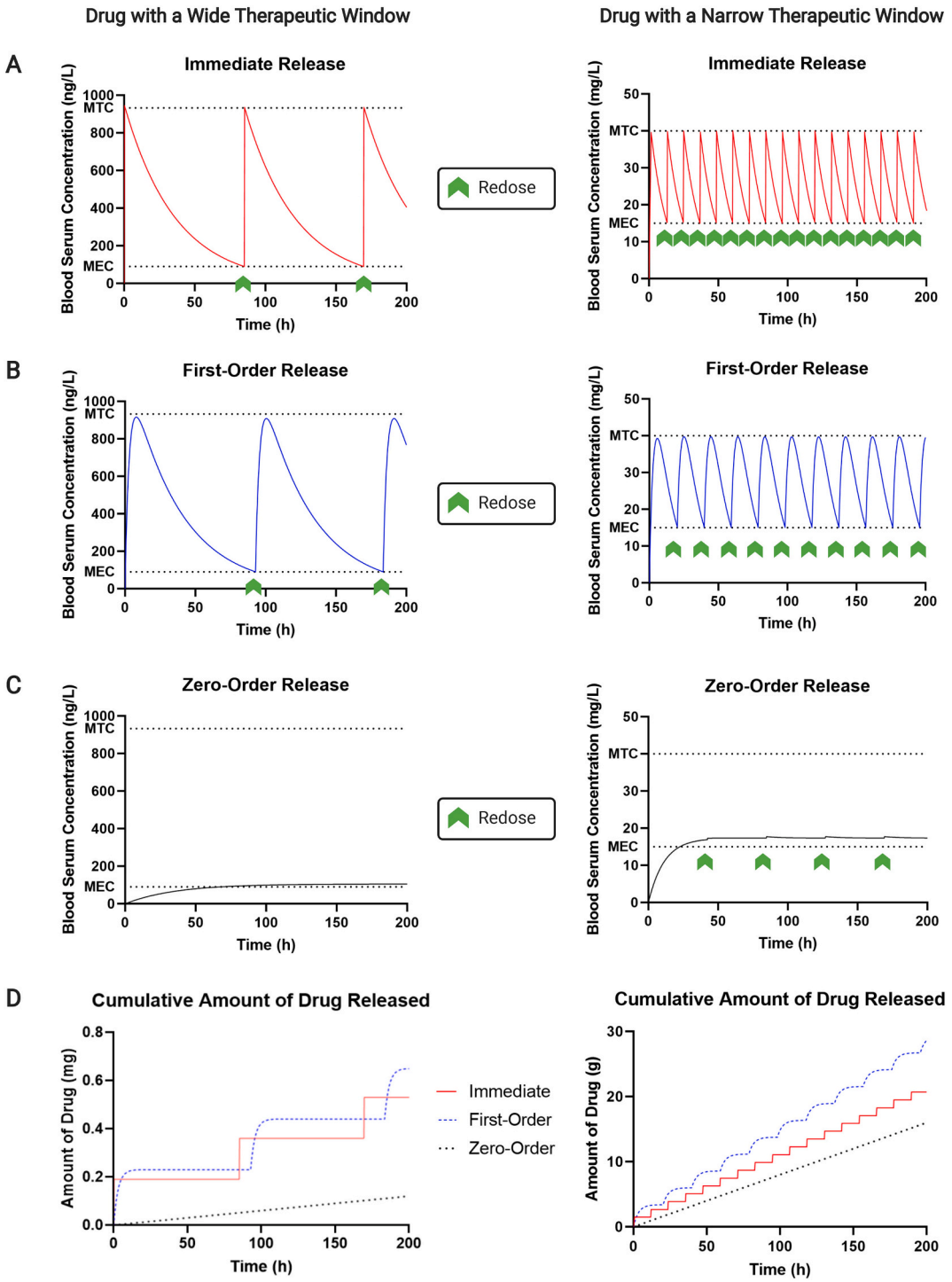

Fig. 1. Immediate, first-order, and zero-order release profiles for drugs with narrow and wide therapeutic windows. Theoretical pharmacokinetic profiles of vancomycin, a drug with a narrow therapeutic window, and etonogestrel, a drug with a wide therapeutic window delivered as (A) immediate-release, (B) first-order release and (C) zero-order release formulation. (D) Cumulative amount of vancomycin and etonogestrel released from immediate, first-order, and zero-order systems. Data based on realistic clinical dosing values.

concentrations to remain safe and effective during both the initial peak and for several half-lives thereafter. Similarly, slow metabolism and clearance can extend the duration that drug levels remain within the MEC and MTC after administration. Unfortunately, not all drugs have a large therapeutic window or long half-life. In these instances, immediate release drug formulations only spend a small amount of time within the safe yet efficacious plasma concentration range before redosing. Compensating for this by increasing the administration frequency, while effective, is disadvantageous due to reduced patient compliance [14]. Fig. 1A demonstrates the difference in dosing frequency for a drug with a wide therapeutic window compared to a drug with a narrow therapeutic window.

Of these immediate release formulations, oral drugs are widely considered to be one of the most convenient modes of drug administration because they are non-invasive, cost effective, and allow for doses to be easily titrated [15]. These factors have made it the most

common mode of administration, with some estimates suggesting that oral formulations comprise 90% of all drugs and about 50% of the drug delivery market [16]. Despite its advantages, oral delivery also presents several physiological and practical challenges that prevent it from being appropriate for all drugs. These limitations include the poor absorption of most macromolecular drugs as well as some small molecule drugs [17], first-pass metabolism [18], systemic dosing [19], variability of digestive residence time [20], and patient compliance issues when frequent administration is necessary due to a small therapeutic window and/or short half-life [7]. Bioavailability—the amount of drug that reaches circulation in an active form—is determined by a multitude of physiologic factors and intrinsic drug properties that affect its absorption through the gastrointestinal tract; factors that reduce bioavailability include alterations in gastrointestinal tract pH [21], the presence of the intestinal mucosa and healthy epithelium, which act as barriers decreasing drug transport into systemic circulation [11], and low drug solubility in water, which can lead to slow and inconsistent absorption [22]. In some cases, disease states can dramatically affect bioavailability, contributing to unpredictable plasma concentrations and shifts outside the therapeutic window [23]. Additionally, oral medications with narrow therapeutic windows are associated with more drug-related adverse events and subsequent increases in health cost [24], morbidity and mortality [25], and are an important cause of severe adverse events resulting in emergency hospital visits by older adults [26].

IV injections overcome several of the barriers facing oral delivery but are subject to other limitations that make them suitable for only a subset of use cases. IV administration allows for the rapid distribution of drugs, can achieve drug bioavailability at approximately 100% by bypassing first-pass metabolism by the liver prior to entering the systemic circulation, and is compatible with both small and large molecule delivery [11]. For drugs with narrow therapeutic windows, continuous IV drug infusion minimizes fluctuations outside the therapeutic window, thereby maintaining a steady plasma concentration [27]. However, this delivery system requires skilled placement by a healthcare professional and prolonged needle access, which exposes the patient to infection and limits mobility [28,29]. Like IV drug systems, other immediate release drugs, such as intramuscular and intraperitoneal injections, also avoid first-pass metabolism [30] but have generally not achieved clinical utility to the same degree as oral delivery, with some exceptions (e.g., insulin, vaccines) [31].

Controlled drug delivery systems seek to overcome the pharmacokinetic limitations of immediate release formulations by delivering drugs in a predetermined manner over a prolonged period of time, ranging from hours to months [32]. Most controlled drug delivery systems—including injectable FDA formulations—exhibit release kinetics characterized by an initial period of rapid release followed by first-order release in which the rate of drug release is proportional to the amount remaining in the device (Fig. 1B) [33–35]. These systems generally enhance drug delivery by delaying a fraction of the drug from entering circulation, thereby retarding metabolism and clearance [36,37]. The result is an extension of circulation time [38] and reduced peak drug concentrations, which can enable these devices to prolong the duration that drug remains safely within the therapeutic window [39]. This benefit can be especially pronounced for drugs with narrow therapeutic windows. Fig. 1B highlights the relative amount of time a device delivering drug with a large therapeutic window spends within the efficacious range compared to a device delivering drug with a narrow therapeutic window. As a result, devices exhibiting first-order release kinetics have been used clinically with drugs with large therapeutic windows and their clinical importance should not be overlooked; however, they have experienced far more limited success delivering drugs with narrow therapeutic windows.

Zero-order delivery systems are a form of controlled drug delivery that can potentially further expand and improve the performance of therapeutics beyond what is possible using current FDA-approved controlled-release systems, including drugs with small therapeutic windows or hepatic toxicity [40]. Zero-order drug delivery systems release drug at a constant rate throughout the lifetime of the device (Fig. 1C). At equilibrium, these devices release drug at the same rate that it is cleared from the body thus enabling stable drug plasma concentrations within the therapeutic window without the need for frequent redosing, thereby minimizing adverse effects and improving patient compliance [41,42]. Importantly, the overall cumulative dose within the body is also reduced compared to immediate-release and first-order release systems, ultimately reducing the risk of chronic toxicity (Fig. 1D). Unfortunately, decoupling the release rate from the amount of drug remaining in the device has often proved challenging, particularly for passive systems, which must be engineered to accommodate transport principles.

Several mathematical models exist to describe drug release kinetics. Of note are the Ritger-Peppas and Korsmeyer-Peppas models which describe drug release from polymeric systems and establish an exponential relationship between drug release and time [35]. Overall, this equation (Eq. (1)) serves to classify release profiles as either first-order or zero-order. For a thin film, when the exponent of release, n, is equal to 0.5, the system is classified as Fickian with diffusion driving first-order release. If $n = 1$, the model is non-Fickian and correlates with zero-order drug delivery, which is governed by forces like swelling and/or polymer chain relaxation. In the case of $0.5 < n < 1$, drug release is determined by a combination of diffusion and swelling.

$$\frac{M_i}{M_\infty} = Kt^n \tag{1}$$

Ritger-Peppas and Korsmeyer-Peppas Mathematical Model. M_∞ represents the amount of drug at equilibrium, M_i represents the amount of drug released over time, K is the release velocity constant, and n is the exponent of release.

Importantly, the Ritger-Peppas and Korsemeyer-Peppas models are appropriate for $\frac{M_i}{M_\infty}$ values less than 0.60, but cannot be validly applied to later-stage release conditions that fail to meet the underlying assumptions used to derive the equation [35,43]. Further, it should be noted that the value of n representing pure Fickian release varies as a function of device geometry with cylinders and spheres having values of 0.45 and 0.43, respectively [43].

This review will cover strategies and advances in temporally controlled drug delivery systems, with an emphasis on strategies that have either achieved zero-order delivery or pushed traditionally first-order delivery systems towards the goal of consistent release over time. These systems include degradable polymeric particles and implantable polymeric devices, diffusion-based devices such as passive microchips, hydrogels, osmotic pumps, intravaginal rings, and microneedles, and actuated devices including active microchips and macroscale implantable pumps. Each system has important advantages and limitations that dictate its potential clinical value, as shown in Table 1. This paper describes the key features of these systems, discusses recent efforts to attain zero-order release kinetics, and identifies opportunities for creating devices that achieve consistent release rates. This review will not discuss direction modification of drugs (e.g., PEGylation) because the release kinetics and therapeutic efficacy of modified drugs vary on a drug-to-drug basis.

2. Degradation-based delivery systems

Biodegradable delivery systems are typically composed of polymeric materials that are lysed by hydrolysis or enzymes into products that can be solubilized and cleared from the body [44]. Polymers undergo bulk degradation, surface erosion, or some combination of the two depending on their hydrophobicity and degradation rate [45]. Bulk-degrading polymers, such as poly(lactic-*co*-glycolic acid) (PLGA), absorb water leading to polymer chain lysis throughout the matrix and a drop in average molecular weight loss. However, the overall mass remains

Table 1
Features of common drug delivery systems.

	Zero-order release consistently attained	Avoids first-pass metabolism	Removable in case of adverse events	FDA precedence	Administration route	Cost	Expected patient compliance
Polymeric particles	No	Yes	No	Yes	Injection	Low	High
Implantable polymeric devices	No	Yes	Yes	Yes	Surgery	High	Low
Microneedles	No	Yes	Yes	No	Topical	Low	High
Hydrogels	No	Yes	No	Yes	Injection or Topical	Low	High
Osmotic pumps	Yes	No	No	Yes	Oral	High	High
Actuated pumps	Yes	Yes	Yes	Yes	Surgery	High	Low
Intravaginal rings	Yes (functionally)	Yes	Yes	Yes	Inserted	Low	High
Passive microchips	Yes	Yes	Yes	No	Surgery	High	Low
Active microchips	Theoretically attainable	Yes	Yes	No	Surgery	High	Low

relatively unchanged until the chains are sufficiently small to become soluble and diffuse out of the network [46]. Alternatively, surface-eroding polymers, such as polyanhydrides, experience degradation exclusively at the polymer surface, which causes them to lose mass as polymer chains on the surface are lysed while the remaining polymer maintains a high molecular weight [47,48].

Both bulk-degrading and surface-eroding polymers have been used in drug delivery, with synthetic polymeric particles being the most widely investigated. Despite extensive research to improve release kinetics, drug delivery by polymeric particles is generally limited to first-order release.

2.1. Polymeric particle systems

Nanoparticle and microparticles systems have been explored as controlled delivery devices for nearly half a century [49]. Nanoparticles are typically 1–1000 nm in diameter and can be delivered locally into a tissue or intravenously into systemic circulation as a suspension through a standard hypodermic needle [50]. Microparticles are 1–1000 μm [51] in diameter and are typically delivered as a localized depot [49,52]. Drug-loaded polymeric particles sequester some proportion of the drug to reduce the initial systemic drug concentration—thereby reducing concentration-dependent drug processing by the body—and then release drug over time to partially counteract metabolism and clearance, ultimately facilitating more consistent drug concentrations [53,54]. Common limitations to these devices include low drug-carrying capacity due to size and loading efficiency [55,56], first-order release kinetics with a pronounced initial burst release [56,57], and an inability to remove the device in response to an adverse event. Despite these limitations, nineteen PLGA particle formulations have received FDA approval, motivating additional research to improve their performance further [58].

2.1.1. PLGA particles: Methods of improving sustained release

Modifiable factors affecting the release profile: particle size, copolymer ratio, molecular weight, porosity

PLGA was first FDA approved as an injectable, long-acting drug delivery depot formulation in 1989 [58]. These systems are valued for their ease of synthesis, ability to encapsulate both hydrophobic and hydrophilic drugs, injectability, and sustained release rates ranging from days to months, which renders them a viable delivery system applicable to many therapeutic regimens.

PLGA undergoes bulk degradation as water diffuses into the polymer bulk faster than hydrolytic cleavage of ester bonds can occur, causing polymer chains to lyse throughout the entire particle and become soluble once they are small, allowing the encapsulated drug to leach out into the surrounding aqueous environment [45]. PLGA degradation undergoes autocatalysis as lysis produces carboxylic acid-terminated degradation products that reduce the microenvironmental pH and accelerate polymer degradation [59]. This autocatalytic effect makes it challenging to design zero-order release devices because degradation is determined by the complex interplay of multiple elements that makes it difficult to predict degradation-dependent release kinetics a priori. Increasing particle size [60–62], lactic acid copolymer content [63–67], and molecular weight [65,68–71] have generally been shown to slow the rate of drug release, though not necessarily alter the profile from first-order kinetics.

Although true zero-order release from PLGA particles has not yet been achieved, there have been methods developed to enable these typically first-order systems to exhibit kinetics closer to zero-order release (i.e., increasing the exponent of release *n* in the Ritger-Peppas and Peppas-Korsmeyer models). One notable system achieved nearly zero-order release of estradiol from lower molecular weight PLGA nanoparticles (Fig. 2), which transitioned to classic first-order release as the molecular weight of the PLGA was increased [65]. The authors hypothesized that increasing the molecular weight caused diffusion-dependent estradiol release instead of degradation-dependent release.

Increased porosity reduces the effects of autocatalysis by providing a diffusion pathway for acidic degradation products into the surrounding media, thus minimizing catalysis within the particle [72]. In practice, several groups have shown that increasing system porosity results in a more constant drug release rate compared to non-porous particles of identical composition [72,73]. Changing particle porosity can be accomplished by modifying synthesis parameters [73,74], the inherent fabrication procedure [75], or by the addition of an excipient [76–78].

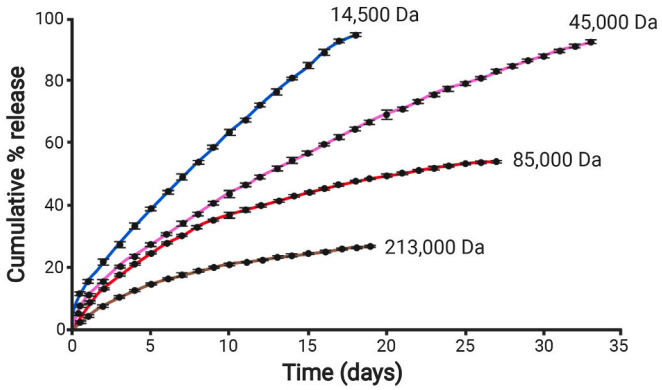

Fig. 2. Effects of molecular weight on cumulative drug release from PLGA nanoparticles. In vitro drug release from four PLGA nanoparticles of different molecular weights; nanoparticles composed of low molecular weight PLGA demonstrate zero-order release and nanoparticles of higher molecular weight demonstrate first-order release. Reprinted from Journal of Controlled Release, vol 119, Mittal G, Sahana DK, Bhardwaj V, Ravi Kumar MNV, Estradiol loaded PLGA nanoparticles for oral administration: effect of polymer molecular weight and copolymer composition on release behavior in vitro and in vivo, pg. 77–85, Copyright 2007, with permission from Elsevier.

2.1.2. PLGA particles: Methods of reducing burst release

Modifiable factors affecting the release profile: particle size, molecular weight, porosity, drug loading, drug/polymer interactions, polymer end-group chemistry

Drug release from PLGA particles is typically characterized by an initial burst phase followed by a slower, more continuous release phase [79]. This initial burst is generally explained by the immediate accessibility of drug on the particle surface that occurs during fabrication [57]. This is problematic for therapeutic efficacy as it can cause toxicity, rapidly deplete the particle's drug reservoir, and complicate redosing [80–82]. A small initial burst from the first dose may be desired to rapidly enter the therapeutic window; however, subsequent redosing may push drug plasma concentration above the MTC since the new dose will be added to existing drug in circulation. It is imperative that the initial burst release from PLGA particles is sufficiently mitigated before these systems can be optimized for drugs with small therapeutic windows. To date, porosity, size, molecular weight, drug loading, and drug/polymer interactions have all been explored as means to alter the initial burst from PLGA particles.

Particle porosity facilitates polymer hydration and subsequent drug release; thus, decreasing porosity has been shown to diminish hydration and decrease burst release [83,84]. A smaller initial burst is also observed with larger particles, due in part to the smaller surface area-to-volume ratio [85–89]. In the commonly-used double emulsion/solvent evaporation process, the extent of porosity and particle size can be modified by tuning fabrication parameters [70,74,83,90,91]. Additionally, higher molecular weight PLGAs are also associated with lower burst release, which is generally attributed to less rapid hydration [70,92,93].

The inherent properties of the loaded drug, its interaction with the polymer, and drug loading also affect burst release kinetics. As expected, a decrease in drug loading was shown to decrease the initial burst release due to the presence of less drug on the particle surface [89,94,95]. Additionally, lower drug loading can decrease surface porosity and internal pore connectivity, further diminishing initial drug release [94]. Regarding polymer structure, uncapped (i.e., carboxylic acid-terminated) PLGA reduces burst release compared to capped PLGA, which is due to interaction of hydrophilic end groups with the loaded drug, either via intermolecular attraction or ionic forces [96,97].

2.1.3. Polyanhydride particles

Modifiable factors affecting the release profile: aliphatic-aromatic copolymer ratio, hydrolytic bond stability

Despite the advances in PLGA particles over the last few decades, zero-order release without an initial burst has not been achieved and their drug release remains difficult to predict. Particles made of surface eroding materials, such as polyanhydrides and polyorthoesters, are potential alternatives to PLGA. These polymers are composed of hydrophobic backbones and hydrolytically labile anhydride bonds that undergo rapid hydrolysis when exposed to water [46]. The rate of polymer degradation occurs faster than water penetration into the matrix, thus confining degradation to the surface of the particle [98]. Theoretically, if these polymers are perfectly surface-eroding, particles should degrade and release encapsulated drug at a rate that is proportional to their surface area [99,100]. This is in contrast to PLGA which contains ester bonds that are more hydrolytically stable and degrade substantially slower than the rate of water penetration into the polymer, resulting in bulk degradation [46]. Because surface-eroding particles are typically spherical in shape, they release drug as a function of a surface area that decreases over time, ultimately producing kinetics very similar to their bulk-degrading PLGA counterparts.

Overall, surface-eroding particles such as polyanhydride particles are relatively unexplored compared to PLGA particles. Although existing polyanhydride particles generally display first-order release kinetics, their surface eroding properties, biocompatibility, and releases rates ranging from days to months make them promising for sustained drug delivery applications. Further, in an idealized state, these systems could be more predictable since degradation and release are isolated to the surface and therefore have fewer non-linear characteristics to predict, unlike the autocatalysis observed in PLGA.

The type of anhydride dictates the polymer's degradation mechanism. Owing to their relative hydrophilicity and therefore the ability of water to access hydrolysable linkages, aliphatic polyanhydrides degrade rapidly within days, whereas aromatic polyanhydrides degrade slowly over weeks [101]. These properties can be leveraged to create aliphatic-aromatic copolymers with tunable release rates, like sebacic acid (SA)-carboxyphenoxypropane (CPP). For example, release of bovine serum albumin (BSA) from entirely aliphatic polyanhydride microspheres, trimellitylimido-L-tyrosine (TMA):SA 20:80, was first-order with an initial burst of 95% and complete release by day 6 [102]. Aliphatic-aromatic copolymers of TMA:SA:CPP 40:30:30 and 0:50:50 copolymer had an initial burst release of approximately 60% and 40%, respectively, followed by sustained release over 40 days. These results indicate that the addition of CPP increased polymer hydrophobicity, thereby reducing water penetration, hydrolysis, and the erosion rate, subsequently decreasing the rate of drug release. Molecular weight data from the same study confirms that increasing CPP slows polymer degradation; 0% CPP resulted in complete polymer degradation by day 5, whereas a copolymer with 50% CPP took over 1 month to degrade. The overall effect on release kinetics was a reduction in initial burst release and a more sustained, though still generally first-order, release profile. The same effect of CPP addition and drug release was observed when releasing human serum albumin or insulin [103,104]. Copolymers of fatty acid dimer (FAD) and SA also reduced the initial burst and prolonged release, with higher amounts of FAD contributing to more amplified effects. FAD, though aliphatic like SA, contains more hydrolytically stable bonds, thereby further slowing degradation when copolymerized with SA [100,105].

While zero-order polyanhydride particle systems have not yet come to fruition, existing systems have demonstrated the predictable nature of release rates from surface-eroding polymers and utility for the delivery of vaccine and vaccine adjuvants [106,107]. However, the ability of surface-eroding polymers to achieve zero-order release is presently limited by their spherical shape and continuously decreasing surface area. Some groups have attempted to mitigate this issue by designing implantable devices to control surface area and therefore drug release.

2.2. Polymeric implantable devices

Like polymeric particles, implantable devices have also been used clinically for drug delivery. These systems, which are generally surgically implanted and last for days to months, offer many of the same advantages that injectable systems do, including the potential for systemic as well as localized delivery, improved patient compliance, lower doses with fewer adverse effects [108–110], and precedence for FDA approval [111]. Implantable devices, however, may be able to deliver larger drug payloads or exhibit more desirable release kinetics than injectable systems, owing to their larger size and thus ease of manipulation [112]. Further, implantable devices are easily removed in case of adverse drug events, minimizing the risk of negative side effects [113,114].

The key drawback of using these systems is the need for surgical implantation, which is expensive and can be associated with complications. The need for surgery can also lower patient compliance relative to injectable systems, though the potential to load more drug and better control release kinetics may justify the use of implantable devices in some use cases [115]. Compared to particles, PLGA and polyanhydride

implantable devices have achieved greater success shifting kinetics towards zero-order release profiles to reduce variability in plasma concentration.

2.2.1. PLGA implantable devices

Modifiable factors affecting the release profile: copolymer ratio, drug structure, surface eroding additives, device geometry

PLGA's biodegradability and biocompatibility make it an attractive polymer for implantable devices. While still difficult to predict, certain properties of these systems can be controlled to yield more zero-order-like release profiles with somewhat sustained release and a moderate reduction in burst release. These properties—copolymer ratio, therapeutic drug identity, and the addition of surface eroding compounds—will be discussed in the context of the few systems that have achieved zero-order delivery.

Generally, increasing lactic acid composition results in steadier, more consistent drug release compared to higher glycolic acid compositions, likely due to slower rates of water penetration and polymer degradation [116]. Additionally, the crystalline structure of a PLGA device, which is determined by its copolymer composition and preparation method, have been shown to affect drug delivery. Sendil and colleagues demonstrated that the release of codeine, hydromorphone, and bupivacaine from PLGA 85:15 rods was both more consistent and more prolonged than release from PLGA 50:50 rods [115]. Higher glycolic acid composition contributed to amorphous regions and subsequently a less dense, less compact rod compared to PLGA with a higher lactic acid content, which produces a more crystalline matrix. This same result was observed for the release of paclitaxel from PLGA 85:15 discs compared to PLGA 50:50 discs [117]. The structure of the therapeutic drug also appears to affect the device's crystalline structure; release of bupivacaine and hydromorphone from PLGA rods achieved more consistent release as compared to release of biphalin [118], which, comparatively, is a bulky, hydrophilic molecule that contributes to a more heterogeneous, amorphous rod structure.

Release kinetics can be influenced by the use of additives, such as the addition of trimethylene carbonate (TMC) to PLGA 50:50, which yielded nearly zero-order release of estradiol with minimal initial burst (Fig. 3) [119]. The authors hypothesized that this polymer undergoes both bulk degradation and surface erosion from PLGA and TMC, respectively, but that surface erosion dominated over bulk degradation.

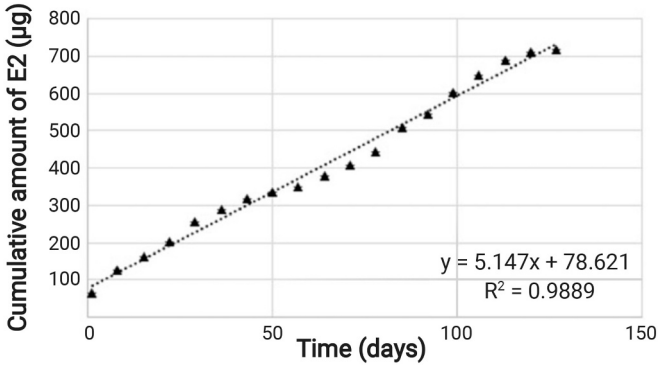

Fig. 3. Cumulative release of estradiol from a polymeric rod. In vitro zero-order release of estradiol content (718 µg) from a poly(L-lactide-*co*-glycolide-trimethylene carbonate) rod over 113 days, with an average daily release of 5.15 µg/day. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer, *Pharmaceutical Research,* Shape-memory terpolymer rods with 17-β-estradiol for the treatment of neurodegenerative diseases: an in vitro and in vivo study, Turek A, Olakowska E, Borecka A, Janeczek H, Sobota M, Jaworska J, Kaczmarczyk B, Jarzabek B, Gruchlik A, Libera M, Liskiewicz A, Jedrzejowska-Szypulka H, Kasperczyk A, Copyright 2016.

Additionally, release kinetics can also be influenced by changes to the device structure, such as the fabrication of solid matrices with holes. One PLGA system enveloped in a biodegradable, drug-impermeable coating with a small cavity drilled in the coating demonstrated that adding a single hole in the coating shifted drug release towards zero-order release kinetics compared to an implant with a hole through both the coating and matrix [120]. In this system, the semi-hemispheric hole expands at a rate proportional to the surface area of a sphere (radius^2) and delivers drug proportionally, as opposed to the cylindrical hole in both the coating and matrix which expands as a function of circumference (radius) to help combat the decreasing drug gradient over time that occurs due to depot depletion. Additionally, the device with a hole in the coating and matrix exhibited a larger initial burst release due to a greater exposed surface area.

The same approach led to near zero-order release of progesterone and sodium salicylate in other polymer systems [121,122]. Use of this method is limited to larger devices, however, since the technology needed to reproducibly create cavities on a smaller scale is lacking.

2.2.2. Polyanhydride implantable devices

Modifiable factors affecting the release profile: drug/polymer interactions, manufacturing techniques

As with injectable systems, polyanhydride implantable devices are relatively unexplored compared to PLGA implantable devices. Gliadel, an SA-CPP wafer designed to release carmustine, a chemotherapeutic, after surgical resection of brain tumors, is currently the only FDA-approved implantable polyanhydride device [123]. It releases most of its drug in the first 5–7 days after implantation but continues to release smaller amounts of drug over a period of 21 days [124,125]. Since the development of Gliadel, polyanhydride implantable devices have been constructed with different release profiles, some of which have shifted drug release kinetics towards zero-order behavior.

Drug interactions within the polyanhydride matrix can be manipulated to achieve sustained release that differs from purely first-order kinetics. Generally, burst release is lower and drug release is slower with hydrophobic drugs since the drug prefers to remain within the device and minimize interaction with the surrounding aqueous environment [126–128]. Highly hydrophobic drugs will only be released when the surrounding polymeric matrix has been degraded whereas hydrophilic drugs will diffuse into the surrounding media as soon as there is a suitable network of pores connecting them to the aqueous environment [126]. The effects of drug hydrophobicity on delivery are even observed with different forms of the same drug; Masters and colleagues found that the hydrophobic form of bupivacaine (free base bupivacaine) was released in a somewhat zero-order fashion for the first week while its hydrophilic form (bupivacaine hydrochloride) was released in a first-order fashion (Fig. 4) [127]. The authors postulated that small amounts of the highly water-soluble bupivacaine hydrochloride on the device surface were rapidly released into the surrounding aqueous environment, which left behind voids that interconnected to form channels that permitted water penetration and rapid drug release. Free base bupivacaine, on the other hand, remained within the matrix and was subjected to release by erosion. However, the effect of polymer-drug interactions must be determined empirically since studies have shown inconsistent results [128].

Release kinetics of polyanhydride implantable devices are also strongly influenced by the manufacturing technique used to make them. Matrices produced using a hot melt technique released dibucaine and bupivacaine in steady, zero-order fashion with very little burst [127]. In theory, this technique produces dense, homogeneous matrices with drug release rates dependent on the device's surface area over time. Compression molded and solvent-casted matrices are not as dense as hot melt matrices and exhibit conventional first-order release kinetics, potentially due to enhanced pore formation, water uptake, and

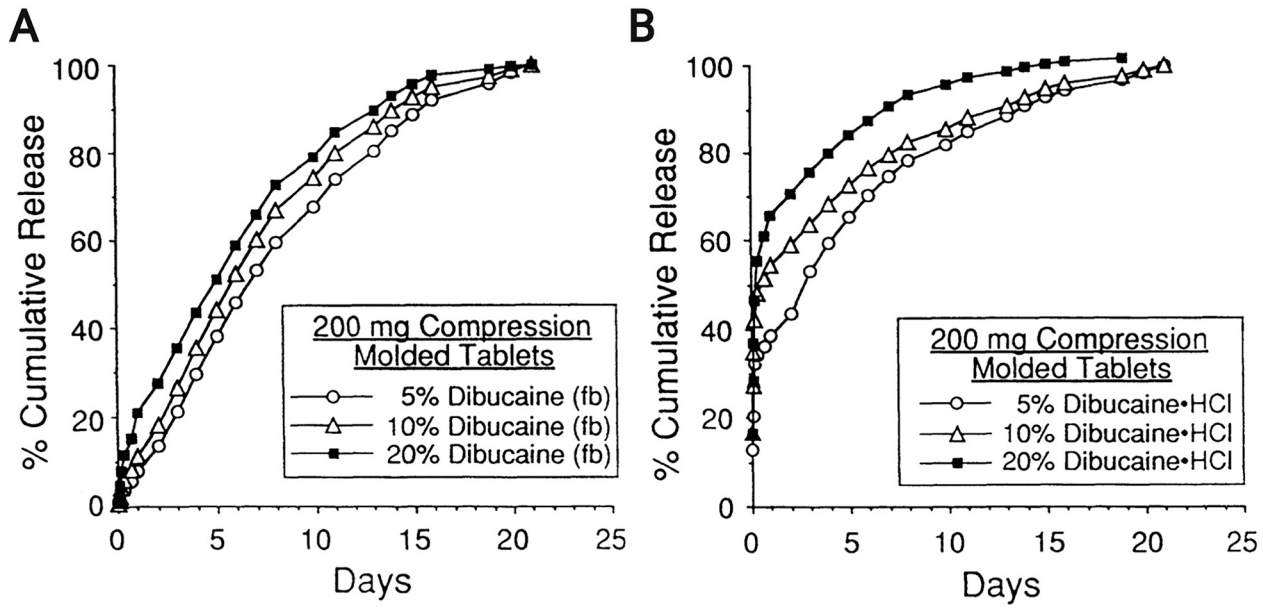

Fig. 4. Effects of bupivacaine hydrophobicity on release from a polyanhydride implantable device. (A) Cumulative release of hydrophobic bupivacaine (free base) showing an early period of zero-order release in vitro. (B) Cumulative release of hydrophilic bupivacaine (bupivacaine hydrochloride) from compression molded devices showing both an initial burst and first-order release kinetics in vitro. The loading of drug did not appear to affect release kinetics. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *Pharmaceutical Research,* Sustained local anesthetic release from bioerodible polymer matrices: a potential method for prolonged regional anesthesia, Masters DB, Berde CB, Dutta S, Turek T, Langer R, Copyright 1993.

subsequent bulk degradation [127,129]. Therefore, it appears that the hot melt technique may be more promising for achieving zero-order release kinetics if devices with appropriate geometry (i.e., constant surface area over time) can be fabricated.

2.3. Microneedles

Modifiable factors affecting the release profile: secondary encapsulation of drug within microspheres

Degradable microneedle patches are another drug delivery system that offer advantages over traditional methods of delivery. These devices typically contain an array of microneedles measuring 50-900 μm tall that breach the stratum corneum and permit entry of drugs, including macromolecules, into deeper layers of the epidermis and dermis [130,131]. Microneedles bypass first-pass hepatic metabolism, do not require surgery, and can be modified to deliver both hydrophobic and hydrophilic drugs [132]; additionally, application can be pain-free if the needles do not penetrate beyond 200 μm, the beginning of the nerve-containing dermis [130,133]. Added benefits of transdermal delivery include rapid delivery via drug diffusion into regional capillaries and the lymphatic system as well as immune system activation by special antigen-presenting cells, all important components for vaccinations [134,135]. Although these properties make microneedle patches desirable for drug delivery, they have only been recently explored as sustained delivery devices.

Polymeric microneedles are perhaps the most promising type of microneedles for achieving sustained release. All major types of microneedles—solid, coated, hollow, porous, and polymeric—demonstrate immediate first-order, diffusion-mediated drug delivery [136–142]; however, polymeric microneedles may be able to dissolve or degrade over time to enable prolonged drug release within the skin [143]. Park and colleagues found that secondary drug encapsulation within microspheres followed by encapsulation within a polymeric microneedle prolonged drug delivery from hours to days compared to drug encapsulated directly within the microneedle, though first order release was still observed [144]. This technique could eventually be used to achieve sustained, long-term release of drugs. Another group showed that delivery of BSA from microneedles applied continuously to the skin was sustained for 8 days with a triphasic release profile [145]. Because this field is still in its infancy relative to particles and implantable drug delivery systems, more research is needed to determine reliable methods for controlling release from microneedles as well as the use cases best suited for a system that is easy and painless to administer, but very limited in dose size.

3. Diffusion-based delivery systems

Diffusion-based drug delivery systems are driven by a concentration gradient between the device and the external environment [44]. In a polymeric device, diffusion can either occur on a molecular level in which drug passes between polymer chains, or on a macroscale level in which drug diffuses through pores in a polymer matrix [44]. Simple diffusion-based delivery systems experience decreasing rates of delivery over the lifetime of the device due to a decreasing concentration gradient, which must be overcome to achieve zero-order release [44].

Passive microchip devices [146], simple osmotic pumps [147], vaginal rings [148], and hydrogels [149] all deliver drugs via diffusion. Both microchips and osmotic pumps have demonstrated desirable zero-order release kinetics while vaginal rings have shown consistent release over the period of intended use. In contrast, hydrogels, which are entirely biodegradable, have rarely accomplished zero-order release, although ocular applications of hydrogels have demonstrated long-term, sustained (though generally first-order) release.

3.1. Hydrogels

Modifiable factors affecting the release profile: drug/polymer interactions, surface-eroding materials, encapsulation of drug-loaded nanoparticles, chemical coatings

Hydrogels are highly cross-linked networks of water-soluble polymers [149] with some precedence for FDA approval [150]. These systems are desirable for drug delivery as they easily encapsulate hydrophilic drugs

and, depending on pore size and other properties, can protect entrapped drug from enzymatic degradation [151,152]. Additionally, many hydrogels have been designed to be delivered via a simple injection to form gels in situ [153]. Upon exposure to an aqueous environment, hydrogels take up water to generate a mesh network of open spaces between the polymer chains [154]. The properties of the mesh network and drug, including charge and hydrophobicity, dictate drug diffusion. A mesh size substantially larger than the drug diameter permits free diffusion while a mesh size smaller than the drug diameter requires polymer degradation [154], either mediated by enzyme activity [155,156] or hydrolysis [157,158]. Furthermore, hydrogel swelling, which occurs upon exposure to an aqueous environment, facilitates polymer chain relaxation, increasing mesh size and permitting the release of entrapped drug [159]. The swelling properties of a hydrogel can be exploited by manipulating various parameters including microenvironmental pH [160], ionic strength [161], and temperature [162]. One additional hydrogel modification that can be used takes advantage of the inherent interactions between the therapeutic drug and hydrogel [163–165]. For example, a hyaluronic acid hydrogel at neutral pH was shown to release recombinant human bone morphogenetic protein-2 (BMP-2) in a traditional Fickian fashion, whereas at an acidic pH, BMP-2 release was governed by both diffusion and electrostatic interactions with the hydrogel [166]. Generally, though, most hydrogel systems are controlled by conventional Fickian diffusion, resulting in first-order release kinetics unless advanced formulation techniques are employed [154]. Techniques discussed here include the fabrication of surface-eroding hydrogels and the encapsulation of nanoparticle systems within hydrogels.

Several surface-eroding hydrogel systems have been successful, to varying degrees, in shifting release kinetics towards zero-order release. One system utilized a polymer made of 8 arm polyethylene glycol (PEG) covalently attached by a succinyl linker to either ß-cyclodextrin (ßCD) or cholesterol [167]. Gels formed spontaneously due to the hydrophobic interaction between the cholesterol and ßCD core. Over time, these cholesterol-ßCD inclusion complexes dissociated preferentially at the surface leading to surface erosion and a linear decrease in molecular weight. Despite these erosion characteristics, drug release from a 22.5% (*w*/w) polymer still occurred in a first-order fashion, suggesting that the primary mechanism of release was Fickian drug diffusion. A 35% (w/w) polymer, on the other hand, yielded zero-order release kinetics, perhaps due to the formation of a denser network with a smaller mesh size that shifted release away from Fickian diffusion.

Similarly, a pluronic copolymer made with L-lactic acid spacers and a stereocomplexed pluronic multi-block copolymer produced a hydrogel with a linear mass erosion rate and somewhat-constant release of human growth hormone [168]. One explanation for the divergence from Fickian diffusion is that the interior hydrogel structure was stabilized by stereocomplexed crystalline domains, resulting in preferential degradation and erosion at the hydrogel surface. Another hydrogel system composed of PEG modified with fluorocarbon end groups demonstrated surface-eroding properties, but still produced diffusion-based drug release because the drugs delivered by this system were small enough to diffuse through the pores prior to hydrogel degradation [169]. The authors of that study suggested that larger molecules, like DNA, may experience zero-order release. While this system did not demonstrate zero-order release, it highlights the importance of drug-polymer interactions on release kinetics.

Overall, current research into surface-eroding hydrogels suggest they may be useful for zero-order delivery; however, most studies have been performed in vitro with tightly controlled hydrogel geometries. In vivo results may differ drastically as the hydrogel's geometry will be formed after injection, and thus, surface-eroding systems may achieve inconsistent results due to an inability to reproducibly control hydrogel shape.

Another common technique attempting to attain zero-order delivery from hydrogels is the encapsulation of drug-loaded nanoparticles within the hydrogel. This method facilitates localized delivery and ensures degradation-dependent release, but zero-order release has not yet been achieved using this approach [170–172].

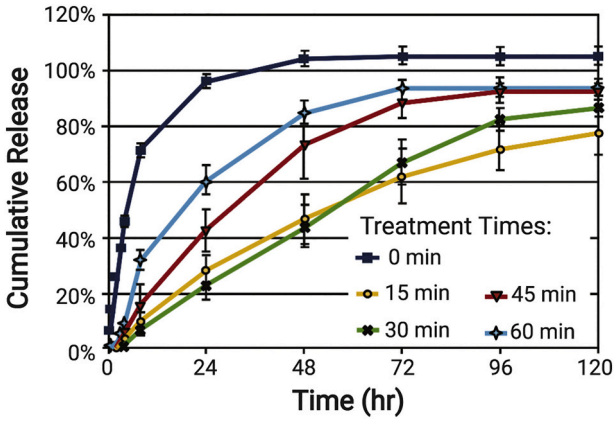

Fig. 5. Release of norfloxacin from surface-modified pHEMA hydrogels. Cumulative release of norfloxacin from pHEMA hydrogels in vitro. Treatment times refer to the amount of time octadecyl isocyanate was allowed to react with the hydrogel surface. Treatment for 15 or 30 min results in a period of zero-order release whereas other treatment times demonstrate first-order release. Reprinted from *Biomaterials,* vol 30, Anderson E, Noble ML, Garty S, Ma H, Bryers JD, Shen TT, Ratner BD, Sustained release of antibiotic From poly(2-hydroxyethyl methacrylate) to prevent blinding infections after cataract surgery, pg. 5675–5681, Copyright 2009, with permission from Elsevier.

Hydrogels, with their low stiffness and flexibility, are attractive candidates for ocular drug delivery [173]. One ocular hydrogel, administered as eye drops, achieved burst-free sustained release of cysteamine from a hyaluronic hydrogel and a gellan gum/kappa-carrageenan hydrogel, which the authors attributed to drug-polymer interactions between cysteamine and hyaluronic acid, gellan gum carboxylic acids, and kappa-carrageenan sulphate radicals [174]. However, this system fell short of achieving zero-order release kinetics. Another system approached zero-order release of gentamicin and dexamethasone from a hydrogel composed of gelatin, polyvinyl alcohol, and chitosan administered as eye drops [175]. Hydrogels with a higher degree of cross-linking yielded more sustained release, likely due to drug-polymer interactions and degradation-mediated release. One fairly successful zero-order delivery system modified the surface of a poly(2-hydroxyethyl methacrylate) (pHEMA) hydrogel with hydrophobic octadecyl isocyanate to administer norfloxacin from a gel disc for the purpose of preventing infection after cataract surgery. This hydrophobic barrier retarded hydrophilic drug release, eliminated the initial burst, and converted the first-order release profile to a zero-order profile for 72 h (Fig. 5) [173]. For this specific system, surface modification with octadecyl isocyanate occurred most efficiently between 15 and 30 min, which provided a sufficient hydrophobic coating and produced zero-order release. This time frame was short enough to avoid disrupting the integrity of the coating, which causes first-order release similar to pHEMA without surface modification. Notably, this system was implanted pre-formed, not injected, which avoids the aforementioned loss of shape control, but requires implantation which may be suitable for use cases that have already exposed the implant site, such as cataract surgery or tumor resection.

Overall, hydrogel-mediated zero-order delivery has generally not been accomplished, although a growing body of promising evidence suggests that it is plausible. Hydrogels are appealing as they can be fabricated from essentially any water-soluble polymer, can load hydrophilic drugs, and can be delivered in minimally invasive manners; however, more improvements are needed to achieve zero-order release over longer periods of time.

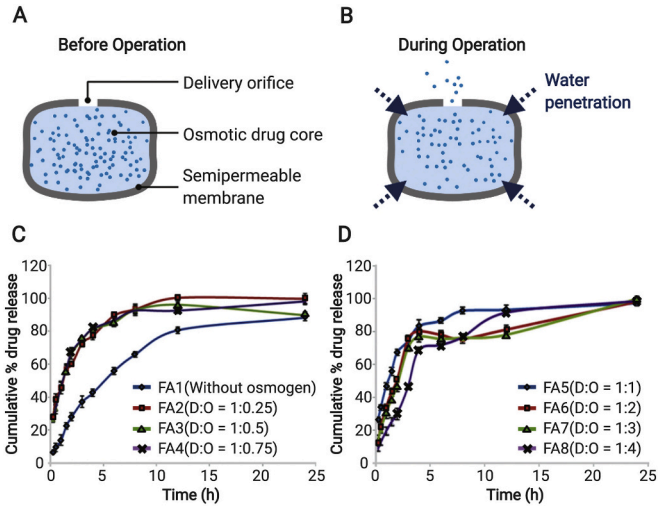

Fig. 6. Elementary osmotic pump design and release kinetics. Schematics of an elementary osmotic pump (A) before activation and (B) after being placed in an aqueous solution. Osmotic pressure causes an influx of water through the semipermeable membrane leading to drug dissolution within the core and an increase in volume—and subsequently hydrostatic pressure— within the device core, triggering drug efflux through the delivery orifice. Cumulative in vitro release of atenolol from an elementary osmotic pump showing (C) classic first-order release kinetics when using sodium chloride as the osmogen within the core or (D) an initial period of zero-order release when mannitol is used as the osmogen. FA1-FA4 and FA9-FA12 represent increasing concentrations of sodium chloride or mannitol, respectively. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer, *International Journal of Pharmaceutical Investigation*, Development, evaluation, and influence of formulation and process variables on in vitro performance of oral elementary osmotic device of atenolol,Arjun N, Narendar D, Sunitha K, Harika K, Nagaraj B, Copyright 2016.

3.2. Osmotic pumps

Osmotic pumps are promising drug delivery systems as they are orally ingested, can achieve zero-order release, and are easily fabricated [147]. These pumps, in their simplest form, consist of a drug core containing an osmotic agent, surrounded by a semipermeable membrane [147]. When placed in an aqueous environment, water is drawn by osmosis into the device core, leading to drug solubilization and an increase in hydrostatic pressure, which pushes the aqueous drug solution out through the delivery orifice [176]. Drug delivery kinetics depend on the osmotic pressure generated by the osmotic gradient [176]. Thus, if the osmotic gradient remains constant, the osmotic pressure, influx of water, and drug release will all remain constant [177].

Other advantages of this system include predictable release rates and drug release independent of physicochemical environments, rendering them unaffected by pH changes in the gastrointestinal tract [178,179]. A major drawback of these systems is that drug delivery is generally limited by gastric residence time (less than 24 h), which limits their application to drugs that require multiple daily doses [180]. Other potential disadvantages include higher manufacturing cost and complexity compared to a traditional pill or capsule due to the need for special equipment to drill the delivery orifice, use of a bilayer press when a bilayer tablet core is required, and application of a membrane coating [181].

A number of FDA-approved osmotic pumps are currently available [182]. These devices are sold as extended release formulations and generally demonstrate prolonged delivery, longer therapeutic plasma concentration levels, and improved oral bioavailability (due to improved solubility, stability, and absorption) over standard oral formulations [182]. Although they typically require daily oral administration and deliver drugs for less than 24 h, they are advantageous for drugs with narrow therapeutic windows or short biological half-lives that would otherwise require multiple daily doses. Regardless, osmotic pumps have demonstrated both zero-order release and clinical utility, making them an exciting option for adapting to new drugs that could benefit from short-term controlled release.

3.2.1. Elementary osmotic pumps

Modifiable factors affecting the release profile: orifice size, osmogen identity/concentration, membrane properties, enhanced drug solubility via solid dispersion

Elementary osmotic pumps (EOPs) are single compartment systems that expel drug as they uptake water (Fig. 6A and B).

The EOP systems that have successfully achieved zero-order release have generally done so by controlling orifice size, osmogen identity/concentration, membrane properties, and drug solubility, Several studies have found that the optimization of orifice size yields zero-order release kinetics from EOPs, highlighting the importance of tailoring device parameters to control the drug delivery profile [183,184]. If the orifice size is too large, bulk diffusion dominates, leading to first-order release [147]. If the orifice is too small, drug release is controlled by the pressure difference through the orifice which varies over time [147]. Additionally, this hydrostatic pressure buildup may also cause deformation of the device and unpredictable delivery rates [184,185].

Another important factor controlling drug delivery from EOPs is the osmotic pressure gradient between the core and the external environment, which is generally controlled by modulating the type and concentration of osmogen. Arjun and colleagues found that sodium chloride produced accelerated, first-order release of atenolol (Fig. 6C) while mannitol produced sustained, zero-order drug release (Fig. 6D) [183]. The authors speculated that sodium chloride increased the osmotic pressure drastically by up to 356 atm, compared to mannitol which increased the pressure by only 38 atm. Furthermore, increasing the concentration of osmogen increased the rate of delivery, although a zero-order profile was maintained [184,186].

Membrane properties have demonstrated influence over both release rate and release profiles. Increasing membrane thickness decreased water imbibition and decreased core liquefaction and subsequent drug release, converting first-order release kinetics closer to zero-order kinetics [184,187]. But for systems that have already achieved zero-order release, one study demonstrated that the rate of zero-order release could be modified by changing membrane thickness [188]. Similarly, the addition of PEG400 into the semipermeable membrane as a porogen increased the rate of drug release [189]. Once zero-order release has been achieved, the release rate can be customized easily by manipulating membrane properties.

Although EOPs can deliver large payloads and are cost-effective, they are generally limited to delivery of moderately water-soluble drugs [190]. Highly water-soluble drugs experience first-order release as they readily solubilize and quickly diffuse through the orifice whereas low-solubility drugs remain entrapped within the device despite water penetration [190]. Drug solubility and subsequent release can be modified by adding different compounds to the EOP core. For example, the addition of sodium chloride to the core decreased the solubility of diltiazem hydrochloride via the common ion effect and prolonged first-order release [190]. Conversely, several methods, such as the inclusion of pH modifying agents, have been devised to deliver poorly water-soluble drugs. Ouyang and colleagues incorporated sodium chloride into the core to increase pH and to enhance glipizide solubility, achieving a near-zero-order release profile [191]. Another system utilized hot melt extrusion to increase the solubility of a solid drug dispersion; a powder solution of insoluble drug and water-soluble polyvinylpyrrolidone was heated, extruded, cooled, milled into a powder less than 250 μm in size, and prepared as an EOP tablet [192]. Solid dispersions are thought to enhance solubility of poorly water-soluble

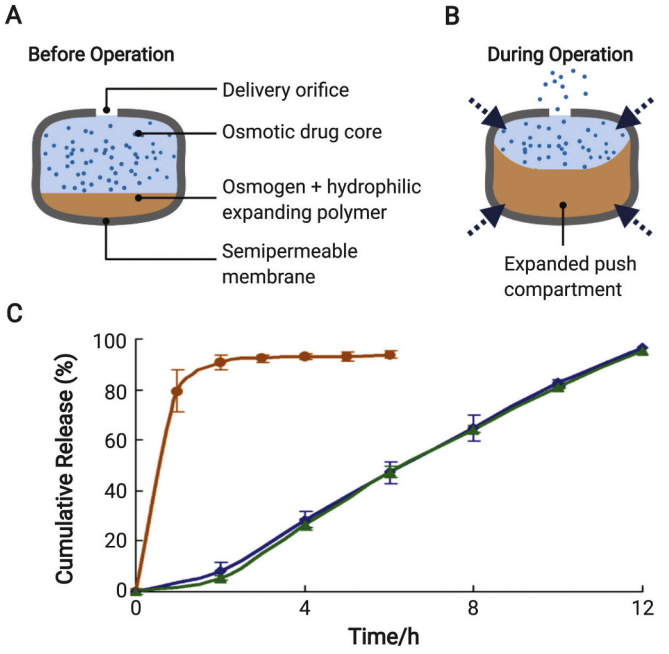

Fig. 7. Push-pull osmotic pump (PPOP) design and release kinetics. A schematic of a push-pull osmotic pump (A) before operation and (B) when placed in an aqueous environment. Water imbibes both compartments leading to a volumetric increase in the hydrophilic expanding polymer in the lower compartment forcing the drug suspension within the upper compartment out through the delivery orifice. (C) Cumulative in vitro release of nimodipine from a push-pull osmotic pump showing rapid release from a reference tablet (orange line), and zero-order release of two different formulations of micronized drug dispersed in the osmotic core (blue and green lines). Reprinted from *International Journal of Pharmaceuticals*, vol 461, Liu X, Wang S, Chai L, Zhang D, Sun Y, Xu L, Sun J, A two-step strategy to design high bioavailable controlled-release nimodipine tablets: The push–pull osmotic pump in combination with the micronization/solid dispersion techniques, pg. 529–539, Copyright 2014, with permission from Elsevier. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

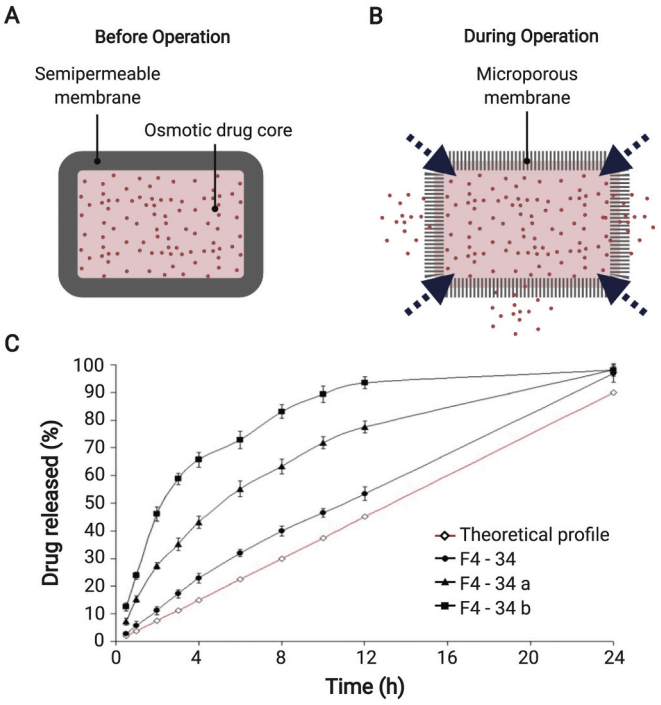

Fig. 8. Controlled porosity osmotic pump design and release kinetics. Schematics of a controlled porosity osmotic (A) before ingestion and (B) after entering an aqueous environment. Water imbibes the membrane leading to the formation of pores, water uptake, drug solubilization, and release through the pores. (C) Cumulative release of etodolac from a controlled porosity osmotic pump showing that lower concentrations of pore-forming PEG400 yielded zero-order in vitro release kinetics whereas higher PEG400 content produced first-order release. F4–34, F4–34a, and F4–34b correspond to 5%, 10%, and 20% (*v*/v) PEG400, respectively. Reprinted by permission from Springer Nature Customer Service Centre GmbH: Springer Nature, *AAPS PharmSciTech,* Development and in vitro/in vivo evaluation of etodolac controlled porosity osmotic pump tablets, Abd-Elbary A, Tadros MI, Alaa-Eldin AA, Copyright 2011.

drugs by suspending them in a hydrophilic polymer matrix; this increases not only solubility, but also dissolution rate and oral absorption [193]. The results of this study found that a solid dispersion formed by hot melt extrusion improved oral bioavailability and extended zero-order drug release to 12 h compared to 8 h for molten tablets, suggesting added benefits to the use of hot melt extrusion.

3.2.2. Push-pull osmotic pumps

Modifiable factors affecting the release profile: osmogen identity/concentration, membrane properties, suspending agent concentration, enhanced drug solubility via mesoporous silica nanoparticles & micronization

Push-pull osmotic pumps (PPOPs) were originally designed to overcome EOP limitations and deliver poorly water-soluble drugs [147]. These systems (Fig. 7A and B) consist of an upper compartment containing the drug, a suspending agent to enhance suspension of a water-insoluble drug in an aqueous solution, and an osmotic agent and a lower compartment containing a hydrophilic expanding polymer and an osmotic agent. The entire system is encapsulated in a semipermeable membrane with a delivery orifice drilled over the drug compartment.

Importantly, these systems have demonstrated zero-order release of several drugs with narrow therapeutic windows and otherwise unpredictable release patterns, like lithium, pramipexole, and ropinirole to treat bipolar disorder, restless leg syndrome, and Parkinson's disease, respectively [194–196].

The ability of PPOPs to deliver poorly water-soluble drugs can be further improved in a number of ways. Owing to their large surface area and highly porous structure, mesoporous silica nanoparticles can encapsulate large amounts of poorly water-soluble drug and their small pore size of 5-20 nm prevents drugs from crystallizing, thus maintaining them in a highly soluble state; however, these nanoparticles are characterized by an initial burst release [197]. Combining drug-loaded mesoporous silica nanoparticles with PPOPs led to successful zero-order delivery and improved oral bioavailability of poorly water-soluble fenofibrate and felodipine, cholesterol lowering and anti-hypertensive medications, respectively [197–199]. Like EOPs, the rate of zero-order release from PPOPs can be controlled by altering the semipermeable membrane thickness, the osmotic agent, and its concentration in the lower compartment [197–199]. Zero-order release from PPOPs can be further controlled by altering the concentration of the suspending agent in the upper compartment; increasing the concentration increases suspension viscosity and decreases the release rate [197–199].

Micronization, a technique that reduces particle size, is another method of improving delivery of poorly soluble drugs. Reducing drug particle size to micron levels increases its surface area, enhancing interaction with aqueous media and improving dissolution [200]. Importantly, micronized drug particles dispersed in hydrophilic matrices permits the delivery of otherwise water-insoluble drugs and improves oral absorption [193]. For example, micronization and dispersion of nimodipine, a commonly prescribed calcium channel blocker, in the hydrophilic matrix of a PPOP facilitated nearly zero-order release for 12 h and had higher oral bioavailability compared to commercially

available nimodipine tablets (Fig. 7C) [201].

3.2.3. Controlled porosity osmotic pumps

Modifiable factors affecting the release profile: osmogen identity/concentration, osmogen-to-drug ratio, membrane properties, porogen identity/concentration, nano- & micro-suspensions of porogen and membrane

Controlled porosity osmotic pumps (CPOPs) have also achieved zero-order release. These pumps incorporate a drug/osmogen core, surrounded by a semipermeable, hydrophobic membrane containing porogens (Fig. 8A and B). CPOPs, unlike EOPS, do not require advanced equipment to drill an orifice, which can lower production cost [147].

Achieving zero-order delivery requires control over osmogen identity, osmogen-to-drug ratio, semipermeable membrane composition, and porogen concentration and type. The manipulation of these parameters has led to the successful release of both hydrophilic and hydrophobic drugs. Generally, increasing the osmogen-to-drug ratio or the use of an ionic osmogen increases the drug delivery rate, which can be counteracted by selecting the right porogen and decreasing the porogen content [202–204]. Abd-Elbary and colleagues achieved zero-order delivery of etodolac utilizing fructose as the osmogen, a cellulose acetate membrane, and PEG400 as the pore forming agent [202]. In vivo data demonstrated effective plasma concentration for 18 h compared to standard oral delivery of 9 h (Fig. 8C). Other studies demonstrated relatively zero-order release of pseudoephedrine and tapentadol hydrochloride from optimized CPOPs [203,204].

A major challenge of CPOP fabrication is the identification of an organic solvent that solubilizes both the hydrophobic membrane and the hydrophilic porogen [205]. Using slightly less hydrophilic polymers often mitigates this issue; however, this introduces a lag time between administration and the onset of drug release as they are not readily water soluble and therefore do not form pores immediately [205]. Bahari and colleagues mitigated this issue by creating a nano-suspension of sucrose (hydrophilic porogen) dispersed within cellulose acetate (hydrophobic membrane) and achieved zero-order release of 2-amino pyridine without a substantial lag time [205]. Likewise, a micro-suspension of sucrose within cellulose acetate delivered diltiazem hydrochloride in a zero-order fashion with only a small lag time observed [206].

Osmotic pumps are highly promising systems with important applications for water-soluble and insoluble drugs. These systems' ease of administration combined with zero-order release offer key advantages for some drugs. However, at present, osmotic pumps are limited in duration and are expensive to manufacture.

3.3. Actuated pumps

Modifiable factors affecting the release profile: flow rate, device design, propellant pressure

Actuated macroscale pumps are among the most successful zero-order drug delivery systems to date, with a number of FDA-approved devices used in patients for several decades [207]. These pumps can accurately supply drugs at constant, preset flow rates over long periods of time. The most common type of medical pumps used today are insulin pumps, which are worn externally by diabetic patients to dispense insulin both on-demand in response to rising blood sugar levels or semi-continuously in small doses to provide a basal insulin level [208]. Insulin pumps have evolved to become closed-loop, continuous blood glucose monitoring systems as a response to unique patient basal rate profiles [209–212]. This type of external pump has several key advantages, such as the ability to easily refill the system and change doses. However, while effective, external pumps are generally not preferred by patients due to their burdensome nature as well as an increased propensity of infection from a chronically open wound. As a result, there has been a great deal of effort to develop insulin in other forms including oral [213], transdermal [214,215], and inhalable formulations [216]. Implantable pumps offer an opportunity to avoid the continuous inconvenience of external pumps, which deters patient compliance, but comes with the need for surgery and more challenging refilling protocols.

Actuated implantable infusion pumps come in two forms, programmable or continuous flow, with catheters that ensure the release of drug occurs in the desired area. Programmable pumps can be set to variable flow, bolus injection, or continuous flow, which we focus on here [217]. Alternatively, continuous flow infusion pumps are not battery powered, but instead rely on the pressure of a compressive fluorocarbon propellant to push drugs out of the reservoir [218]. There are several potential advantages of macroscale implantable devices over micro- or nano-scale devices that make them suitable for particular use cases. With large reservoirs of up to 50 mL, macro devices require less frequent dosing and can last for up to a decade with periodic refilling, unlike many small-scale devices that may deplete their payloads much more quickly [219,220]. However, the large volume of these devices can also be a substantial drawback. At up to 87.5 mm in diameter, they require more space in the body than micro-scale devices and require a complicated surgery in which the pump has to be implanted in the abdomen while the catheter, a critical component for targeted delivery, is implanted separately [217]. These pumps are typically expensive which, added on top of implantation surgery, can cost more than $10 per day when averaged out over device lifetime [219,221]. While the advantages of pumps are numerous, FDA-approved use is currently limited to specific therapeutics, such as delivery of morphine sulfate and ziconotide, primarily routed to the cerebrospinal fluid (CSF) through an intrathecal catheter for severe chronic pain management [219,222].

One of the most widely used programmable pumps is the SynchroMed™ II drug infusion pump from Medtronic (Fridley, Minnesota). Within the pump, a pressurized gas chamber sits below the drug reservoir and pushes drugs into the pump tubing. A peristaltic pump moves the drug through the catheter and to the site of drug infusion, usually the CSF [223]. A few studies have demonstrated the long-term accuracy of SynchroMed ™II pumps, which was measured by withdrawing the entire drug reservoir and calculating the volume delivered in the number of days between refill visits [224]. For intrathecal and intravenous drug delivery, Synchromed™II pumps had a typical delivery error of just 1% with only minor under-infusion occurring over time [224–226].

Another programmable pump, Prometra® (Flowonix, Mt. Olive, New Jersey), contains a propellant to expel drugs from the reservoir with battery powered microvalves to help regulate the flow [222]. One study found that the device maintained its accuracy in delivering continuous intrathecal morphine sulfate for a year, as demonstrated by 97.1% mean-per-patient accuracy at 6 months and comparable 97.9% accuracy after 1 year [222,227]. A larger study concluded that Prometra® pumps have the potential to be used for the accurate delivery of drugs not currently approved for pump use, expanding the possible use of implantable pumps [228].

Arguably, the most prominent continuous flow infusion pump is the Codman® 3000 Constant Flow pump (Johnson & Johnson, Raynham, Massachusetts). Flow rate is set during manufacturing, unable to be changed, and determined by constant propellant pressure and flow restrictor [229]. The mean accuracy per refill of intrathecal baclofen, a muscle relaxant used to treat severe spasticity, was 94% [230]. One group altered the pump to deliver a viscous anti-HIV agent, darunavir, to the vena cava of two male beagle dogs, and achieved constant plasma drug concentration, highlighting the potential to be adapted to a variety of drugs [231]. Although the Codman® 3000 pump was discontinued due to raw material constraints, its ability to achieve consistent flow rates has been well characterized and was FDA approved for multiple

disease treatments [219,232].

A major advantage of continuous flow pumps over programmable pumps is the absence of battery limitations. Without a battery, continuous flow pumps are more compact and lightweight; they have the ability to last a lifetime, meaning fewer surgeries and a lower risk of complications compared to programmable pumps that must be replaced periodically [217,233]. Also, due to their pre-programmed nature, refilling the devices does not require a specialized surgeon and can be done by anyone trained in the technique, including the patient themselves or a caretaker [230]. Unfortunately, these pumps exhibit minimal flexibility which could present a problem if the patient requires a change in dose. For continuous flow pumps, adjusting drug dose according to patient need requires complete emptying of the drug reservoir to replace it with a different concentration of drug or, if needed, implantation of a new pump with desired flow rates. In contrast, programmable pumps have no issues responding to a change in dosing; however, their battery lifetime is between four and 10 years [223,234] at which point the pumps, and potentially the catheter, must be replaced [221,235].

In general, continuous and programmable pumps, depending on flow rate and model, only need to be refilled every 1–3 months which has a considerable impact on patient compliance [222,231]. For example, oral baclofen can require up to six tablets per day [236], while intrathecal often requires just one refill injection per month [220]. Implantable pumps also have the advantage of delivering drugs directly to the target site, resulting in lower total drug dosing. A lower required dose decreases potential drug side effects and extends refill time by only pumping small amounts from the high concentration storage reservoir [237]. Refilling continuous flow pumps, done percutaneously, must be done with extreme caution as a subcutaneous injection [238] or incorrect port injection can result in life-threatening overdoses [239]. Done correctly, the long duration between required refills could increase patient compliance and accessibility.

Although pumps offer many advantages, they require invasive surgical procedures to implant the main device in the abdomen and, if appropriate, catheters into the CSF, which typically requires a neurosurgeon [240]. Surgical implantation comes with the risk of device complications, including pump and catheter movement and catheter failure [222,230]. Other common adverse effects include nausea and implant site procedural pain, erythema, and effusion [222,224,228]. Risk also arises from a variable flow rate between manufacturer variation, which can result in under-dosing or overdosing. Physicians must titrate and re-titrate drug dose for replacement pumps to attain safe, effective dosages [224]. An obvious risk is that pump malfunction can cause delivery of lethal doses of any drug held in the large reservoir [241]. Furthermore, the accuracy of implantable pump flow rate is affected by environmental factors, such as changes in body temperature, elevation, and magnetic resonance imaging [217,234,242].

Given that current pumps can achieve a largely constant drug delivery rate, recent technological advances have been largely incremental. As introduced previously, some research is attempting to expand application of these pumps to non-aqueous drugs [231]. Others are attempting to improve refill technology and safety. For example, ultrasound has been proposed to visualize the port location, replacing the current clinical technique of identifying the reservoir port via palpation [243–245]. Overall, these pumps are very accurate and reliable, but improvements can be made to decrease environmental effects on pump flow rate. Also, smaller devices and longer battery life could ease surgical procedures and lessen surgical risk.

Overall, the use of implantable large reservoir drug pumps allows patients to achieve a higher quality of life not attainable by treatments that require repetitive injections or ingestion of drugs, especially when the drug needs to reach the CSF to be effective. Patients are able to receive continuous doses of pain medication, chemotherapeutics, and other drugs that require continuous administration. Currently, implantable infusion pumps are limited to patients being treated for severe chronic pain or for patients with extremely limited therapeutic options. Furthermore, the potential risks of surgical implantation, device malfunctions, refill complications, and cost substantially reduce the patient population for which these pumps are appropriate. Improvement in any of these categories could make pumps attractive to a greater number of patients. Testing of new drugs for new treatments is also critical for expanding device use. While implantable infusion pumps are currently limited to very few chronic diseases, the accurate release profile shows promise for use in many other treatments where the risks are outweighed by the need for zero-order release.

3.4. Intravaginal rings

Modifiable factors affecting the release profile: torus shape, drug's ring composition, membrane composition, core length

Intravaginal rings are controlled drug delivery systems capable of insertion and removal by the patient, which allows for elective discontinuation in the event of adverse effects or a shift in patient needs [246]. In addition to sustained drug release, intravaginal rings have many other advantages including long term delivery [148,247], avoidance of first-pass metabolism [248], convenient application [246,248], and relatively large drug loading capacity [148,249]. These devices have successfully accomplished sustained release of drugs for extended periods of time, making them a desirable alternative to daily oral therapeutics. FDA-approved systems include the Nuvaring® (etonogestrel/ethinyl estradiol) which delivers contraceptives for over 21 days as well as the Femring® (estradiol acetate) and Estring® (estradiol acetate), which are hormone replacement therapy devices that function for 90 days [250–252].

These devices have achieved consistent, sustained release of drugs with large therapeutic windows. The Nuvaring®, for example, is a flexible ring composed of an ethylene vinyl acetate (EVA) copolymer that releases etonogestrel and ethinyl estradiol at 120 μg and 15 μg per day, respectively, for 21 days [253,254]. This device is produced by hot-melt extrusion and delivers drug via diffusion through the elastomer [255]. Sustained release is achieved as drug molecules experience a uniform diffusion pathway length within the torus. In vitro and in vivo data show that the Nuvaring® demonstrates an initial burst release followed by a slow decline in the rate of drug release over 35 days, although the systemic drug concentration consistently stayed above the minimum concentration achieved by daily oral dosing [253,254]. Importantly, the Nuvaring® delivers two drugs with wide therapeutic windows, a key factor in its clinical success. For example, one study demonstrated that efficacy was maintained between etonogestrel plasma concentrations of 2.2 ng/mL on the first day of insertion down to 1.8 ng/mL 28 days later [256]. This data suggests that while the Nuvaring® is not perfectly zero-order, it is sufficient for delivery of drugs with reasonably large therapeutic windows. Additionally, it is advantageous over conventional oral contraceptives that require daily administration and produce daily peaks and troughs in drug plasma levels.

Drug release kinetics from EVA devices can be enhanced by the addition of a membrane coating to minimize burst release [256], which is important as the initial Nuvaring® burst is associated with nausea and vomiting in the first 2 days of use [257]. Burst release that occurs with first-time device insertion may be desirable to rapidly enter the therapeutic window; however, removing and replacing the device on the same day (e.g., chronic treatments) may be adversely affected by burst release. One system, Ornibel®, delivered the same drugs as Nuvaring® but did so without an initial burst; the authors attributed this difference to the use of a polyurethane core surrounded by an EVA membrane, which, unlike the Nuvaring®, permits etonogestrel/ethinyl estradiol to be loaded in the polymer below its saturation limit [256]. Similarly, Helbling and colleagues reduced initial burst release by 20–40% by

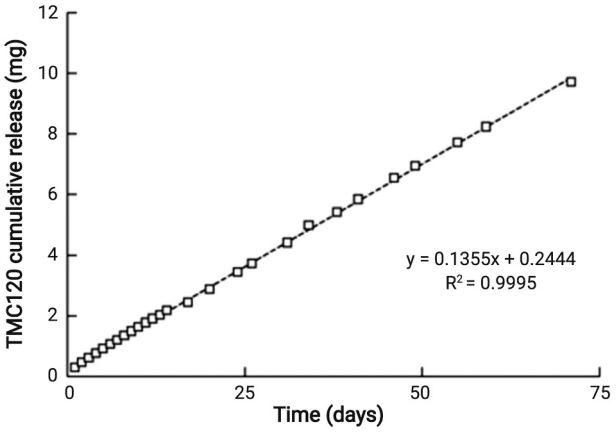

Fig. 9. Dapivirine release from an intravaginal ring. Cumulative in vitro release of dapivirine from an intravaginal ring. Importantly, only 2.5% of the drug payload is released over 71 days. Reprinted from Malcom RK, Woolfson AD, Toner CF, Morrow RJ, McCullagh SD, Long-term, controlled release of the HIV microbicide TMC120 from silicone elastomer vaginal rings, *Journal of Antimicrobial Chemotherapy,* 2005, vol 56, published online, by permission of Oxford University Press.

coating a progesterone-containing EVA intravaginal ring with cellulose acetate [258].

Silicone elastomer rings, like Femring® and Estring®, have also successfully delivered drugs for an extended period of time in a mostly zero-order fashion [251,252]. These rings are composed of solid drug dispersed in a silicone elastomer core further encased in a non-medicated silicone elastomer sheath [259]. The drug is released as it dissociates from the drug crystal lattice and diffuses through the silicone core and non-medicated silicone sheath into the surrounding media [260]. These systems, like the EVA rings, have an initial burst that is largely attributed to the fabrication process; high temperatures associated with curing contribute to enhanced dissolution of drug within the core and subsequent deposition within the sheath layer upon cooling, leading to an initial burst when placed in solution [148]. Following the depletion of the drug within the sheath layer, the drug diffuses out of the torus-shaped device at a steady rate defined by the sheath thickness. Importantly, the silicone membrane coating and core length can be easily modified to change the magnitude of release rates [260].

Silicone elastomer intravaginal rings have also been developed to deliver various microbicides to prevent HIV transmission. Woolfson and colleagues created a system that delivered 4% of its payload, dapivirine, a non-nucleoside reverse transcriptase inhibitor, over 28 days; importantly, the amount released per day was therapeutically efficacious and potentially capable of inhibiting HIV transmission [148]. Because of the time scale, this release profile suggests either zero-order delivery or, more likely, the early stages of first-order release kinetics. In the case of the latter, the device could be routinely replaced to stay within the quasi-linear window of release. For example, the difference in release rate between a device at 100% capacity and 98% capacity are very similar, even when following first-order release kinetics. This is advantageous for inexpensive therapeutics and it can effectively accomplish zero-order release by modulating device application instead of device fabrication. Of course, this is not a feasible solution for devices that cannot be easily retrieved or for drugs that are very expensive, since a vast majority of the drug is discarded in the partially-depleted device. Modification of the same system by increasing the dapivirine core content resulted in zero-order release of approximately 2.5% of its payload for at least 71 days (Fig. 9) [261]. Importantly, the sustained release rate concentration was predicted to remain higher than the minimum inhibitory vaginal concentration required to prevent HIV transmission. Based on 50% total drug released in the study, the authors predict that this system could maintain therapeutic drug concentrations for up to 4 years [261].

Intravaginal rings are important drug delivery devices with many clinical applications, owing primarily to their ability to deliver clinically relevant therapeutic doses for sustained periods of time. Additionally, the ability to easily insert and remove the device without physician guidance is advantageous compared to conventional oral therapeutics. Of course, these devices are limited to use in the vagina, which reduces the potentially addressable patient population by half and is also only compatible with drugs that can transverse through the vaginal mucosa and epithelium.

3.5. Microchips

The application of microfabrication technology in recent years has led to important developments in healthcare-related devices, ranging from diagnostics to drug delivery systems, including microchips. These devices are small, implantable systems containing a drug reservoir that can be released passively or actively (Fig. 10) [146]. Passive microchips contain a biodegradable polymeric membrane that either permits drug diffusion through the membrane or degrades and releases drug [262]. Active microchips contain a membrane that is disrupted by some form of electrical, mechanical, or magnetic stimulation [146]. Because of the high degree of control offered by microfabrication, these systems offer several key advantages including precise control over drug reservoir release, prolonged protection of drugs within a sealed environment, and potential to leverage localized delivery [146,263]. Disadvantages include substantial limitation on dosages, a high cost of manufacturing, and the need for surgical implantation, which may dissuade patients from choosing this system [264].

3.5.1. Passive microchips

Modifiable factors affecting the release profile: membrane properties, channel diameter relative to drug size, channel length & cross-sectional area

Drug release from passive microchips can be degradation or diffusion-mediated. Passive microfluidic devices release drug upon membrane degradation, in which the rate of release depends on membrane parameters including composition, thickness, degradation properties, and porosity [265]. In contrast, drug release that occurs by passive diffusion through the membrane is governed primarily by inherent drug diffusivity properties and osmotic factors [265]. Similar to passive micropumps, passive microchip behavior cannot be altered after implantation (unlike active devices) and they do not require a source of power [265], thereby decreasing their bulk and cost and enabling them to be composed of completely biodegradable components. Additionally, the ability to control membrane characteristics and device parameters, such as channel size and geometry, offers interesting opportunities for drug delivery.

Using a passive microchip, the Ferrari group successfully demonstrated zero-order release of BSA, lysozyme, and interferon by modifying the channel diameter [266,267]. They found that decreasing the release channel diameter to only slightly larger than the drug diameter produced zero-order release kinetics. Notably, zero-order release was maintained over a period of 6 months through at least 70% of drug release (Fig. 11) and was unaffected by tissue encapsulation, supporting its potential for long-term clinical use [268]. The group went on to further explore release of leuprolide, a chemotherapeutic used to treat prostate cancer [269]. Similar to their previous studies, they found that minimizing channel size to only slightly larger than the drug size produced zero-order release [269]. Sustained delivery of chemotherapeutics is clinically desired to avoid spikes outside of the narrow therapeutic window—a common feature of this therapeutic class— that can occur with the current standard of care and yields high systemic

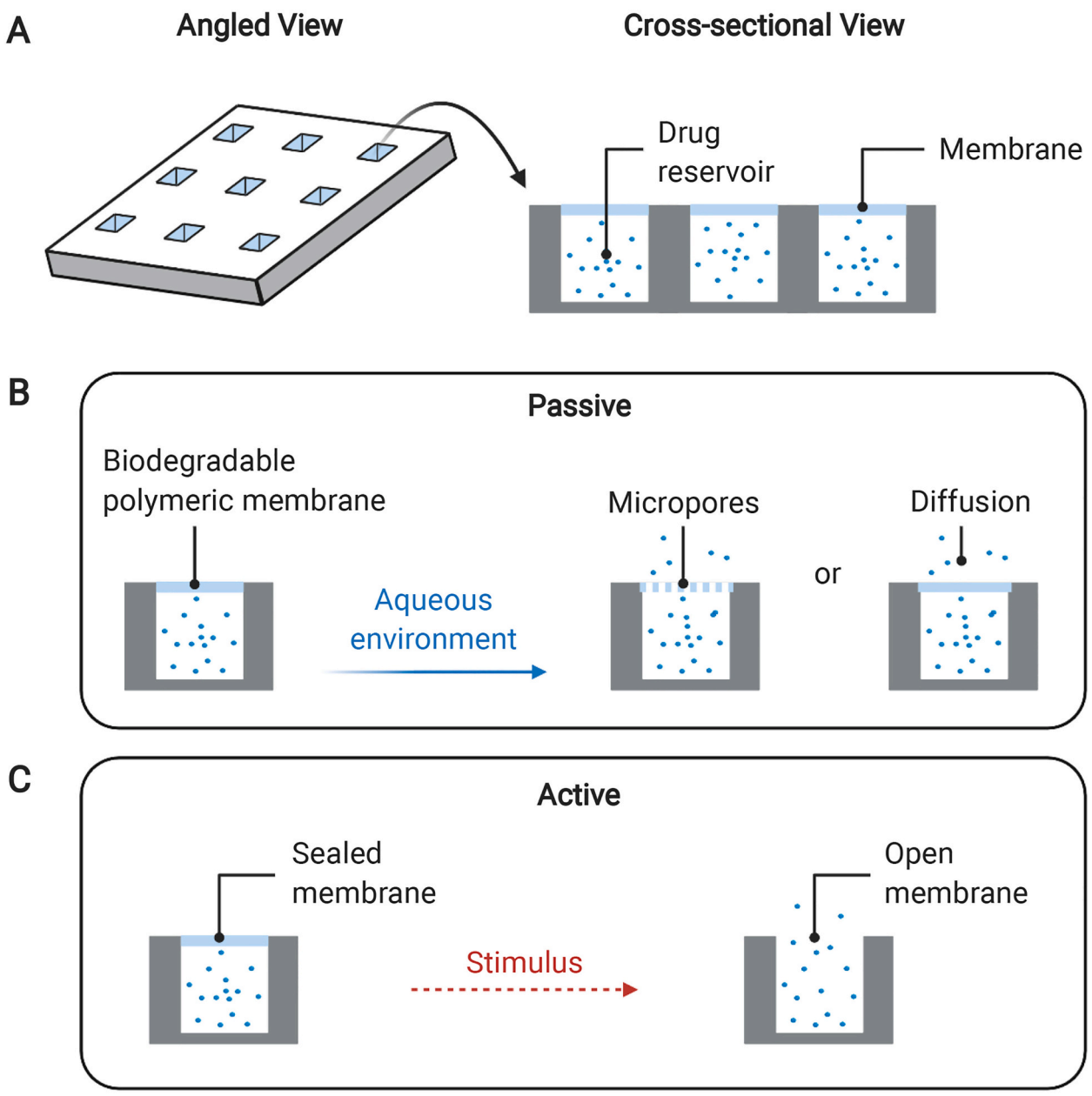

Fig. 10. Drug release from passive and active microchips. (A) Angled and cross-sectional views depicting a passive microchip device containing membrane-covered drug reservoirs prior to use. Devices are either (B) passively activated by diffusion- or degradation-induced disruption of the reservoir membrane or (C) activated by a stimulus that compromises membrane integrity resulting in subsequent drug release.

drug concentrations [270,271]. The authors postulated that steady release rates could be accomplished by this device for up to 6 months based on the reservoir volume of 1 cm^3 loaded with a 20 mg/mL leuprolide solution that delivered 100 μg/day for over 3 days.

Another study achieved zero-order release from a fully biodegradable passive microchip and found that the rate of drug delivery was affected by channel geometry, mainly length and cross-sectional area [272]. However, this device was limited by poor drug diffusion, which was attributed to a combination of poor channel wetting and pH dependent drug solubility. Lee and colleagues examined the effect of the ratio of channel cross-sectional area to length (A/L) on drug delivery [273]. This device, made of non-degradable hydrophobic poly(methyl methacrylate), overcame wetting issues by supplementing the drug-filled wells with PEG, which drew water into the channel and solubilized the drug. Decreasing A/L delayed drug release due to the greater amount of time water took to reach PEG while increasing A/L facilitated an initial burst release and increased drug release rate overall. The authors found a combination of three channels with different A/L ratios that produced zero-order release of diclofenac, an analgesic with sparingly water-soluble properties, for 30 days without any initial burst. Taken together, these studies highlight the ability to achieve zero-order release by manipulating device geometry. The controllable properties of this device contribute to consistent performance, which could be a tremendous advantage over other easily fabricated but less controllable systems for some use cases.

3.5.2. Active microchips

Modifiable factors affecting the release profile: membrane activation timing, reservoir loading

Active microchip devices contain a drug reservoir with a membrane disrupted by electrical, mechanical, magnetic or other stimuli [146]. These micro-electromechanical systems (MEMS) typically contain

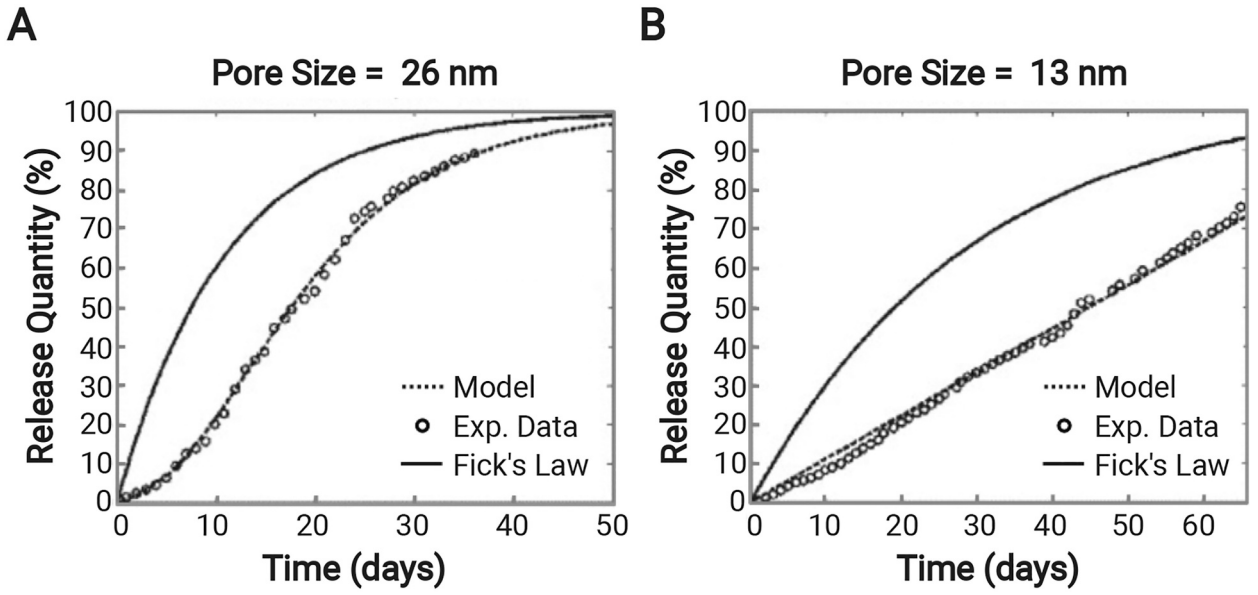

Fig. 11. Bovine serum albumin release from passive microchips with varying channel size. (A) Cumulative release of fluorescein isothiocyanate-labeled bovine serum albumin (BSA) from a passive microchip containing 26 nm channels in vitro demonstrating first-order release kinetics after an initial lag period. (B) Cumulative BSA release from a passive microchip containing 13 nm in vitro demonstrating zero-order release kinetics. Both graphs also feature theoretical release curves based on Fickian diffusion modeling and a model developed to evaluate these systems. Reprinted from *Journal of Controlled Release,* vol 102, Martin F, Walczak R, Boiarski A, Cohen M, West T, Cosentino C, Ferrari M, Tailoring width of microfabricated nanochannels to solute size can be used to control diffusion kinetics, pg. 123–133, Copyright 2005, with permission from Elsevier.

reservoirs on a silicon chip that open and release drugs on command [274]. Compared to passive microchip devices, these systems have been successfully utilized to deliver complex pharmacokinetic profiles in preclinical studies and early-stage clinical trials [264]. For example, one MEMS device has achieved pulsatile delivery of parathyroid hormone to treat osteoporosis; this system has undergone human trials and has been shown to have the same efficacy as the current standard of care, daily subcutaneous injections over 20 days [264]. Other active microchips have been used to achieve rapid delivery of vasopressin to treat various cardiac pathologies [275] and temozolomide to treat glioblastoma [276–278].

It is clear that active devices are capable of complex drug release profiles; however, their ability to achieve zero-order drug release is relatively unexplored. Theoretically, a device containing many reservoirs could be regularly triggered to release small doses of drug, thereby keeping the therapeutic drug concentration in a small range and maintaining near zero-order release. Pirmoradi and colleagues accomplished relatively zero-order release of docetaxel from a magnetically actuated microchip [279]. This device contained a drug reservoir sealed by a magnetic polydimethylsiloxane membrane with a single aperture. Upon application of a magnetic field, the membrane flexed into the drug reservoir and permitted release of drug through the aperture. Daily magnetic actuation achieved relatively constant release over 35 days. The study also found that increasing the magnetic field and number of actuation cycles increased the amount of drug release, further confirming controllable drug release from this system. The need to apply this stimulus, however, may negatively affect patient compliance.

Active devices are capable of zero-order release; however, the current state of research into these devices demonstrate an aptitude for more complex drug delivery profiles. Additionally, active devices are currently not biodegradable, thus requiring explantation. As a result, these systems may be overengineered for zero-order release. Passive devices, on the other hand, have demonstrated zero-order drug release by facile manipulation of device geometry and membrane properties and can be entirely biodegradable. Passive microchip devices may be preferable over active devices for many applications that require zero-order delivery.

4. Perspectives & opportunities

Zero-order drug delivery devices offer the potential to precisely tune release kinetics to prolong drug concentrations within the therapeutic window. As a result, these systems can improve drug efficacy, reduce side effects, and reduce the frequency of administration, which can all contribute to improved patient compliance and disease management. However, the most appropriate drug delivery system for a particular indication depends on a number of factors including: (1) the drug half-life, therapeutic window, and dose size; (2) the severity of both the disease itself and the side effects of exceeding the MTC; (3) the duration of the therapy (i.e., chronic vs acute); and (4) the frequency and inconvenience of existing therapies.

The ideal drug delivery system for most chronic diseases would be easy-to-administer, inexpensive, and achieve consistent drug concentrations within the therapeutic window for a prolonged period of time at the site of therapeutic benefit. Oral or topical delivery methods are often preferred by patients but have inherent challenges that need to be overcome to achieve long-term release. For oral systems, improved residence time and consistency are key challenges, in addition to the poor oral bioavailability of some drugs, particularly macromolecules.

True zero-order drug delivery systems have been limited to large and expensive devices that are not attractive for most use cases because of their high cost, limited duration, and inconvenient use, which can require surgery. Implantable pump systems certainly have the ability to achieve consistent drug release for long periods of time but are only useful for a small subset of patients and diseases due to their high cost and need for surgical implantation.

On the opposite end of the spectrum are microneedles and hydrogels, which are easily administered but have not achieved zero-order release; additional work is required to improve these systems' release kinetics before they can be used to control the release of drugs with small therapeutic windows. One promising system achieved transdermal delivery of rivastigmine, a drug used to treat Alzheimer's and Parkinson's disease, from electro-responsive poly(acrylamide)-grafted-dextran and poly(acrylamide)-grafted-pullulan hydrogels [280,281]. Application of electrical stimulation enhanced drug permeation with

higher rates of drug permeation associated with higher electric currents, ultimately suggesting the possibility of an on-demand, transdermal, hydrogel delivery device.

Out of the current FDA-approved controlled-release systems, vaginal rings stand out as a leader in achieving consistent, sustained drug release. Interestingly, in most cases these devices do not appear to truly attain zero-order release, but rather deplete so little of their reservoir prior to removal that the gradient between the inside and outside of the device remains relatively unchanged, effectively approximating zero-order release. This is only feasible because they can be removed prior to more substantial depletion. It also helps that the drug used in these devices is generally inexpensive since a majority of the drug is discarded. Unfortunately, premature removal is not realistic for many other systems. Further, this approach is limited by biological sex and is only possible with drugs that can pass through the vaginal mucosa and epithelium.

Biodegradable particles are an integral part of existing drug delivery strategies. These systems are easily administered, can deliver a wide range of therapeutics, and have well-established biocompatibility and precedence for FDA approval. Nevertheless, their lack of consistent, zero-order release prevents them from further extending the treatment's duration efficacy and limits their utility for drugs that have very narrow therapeutic indices. Polymeric particles created using an emulsion-solvent evaporation process also suffer from substantial burst release that presents a challenge for redosing. Additionally, this process produces a distribution of particle sizes that can exhibit low encapsulation efficiency [282]. In designing next-generation devices, scientists strive for systems that can be easily applied to both water-soluble and water-insoluble drugs, deliver drugs for an extended period of time, are cost effective, and improve overall convenience to the patient to improve compliance. However, strategies to shift their profile from first-order to zero-order release have thus far experienced limited success. Combining PLGA particles with other delivery platforms is another approach that has been explored, with some promising results. One study demonstrated that combining PLGA nanoparticles with poly(ethylene-*co*-maleic acid) resulted in a shear-thinning colloidal gel that achieved near zero-order release of dexamethasone over 2 months [283].

Surface-eroding polymers may have the potential to overcome the limitations of bulk-degrading polymeric particles. These polymers have demonstrated linear erosion accompanied by proportional drug release and have shown excellent biocompatibility [284]. Like bulk-degrading polymers, the majority of drug delivery research involves the study of surface-eroding particles, which is inherently limiting as surface area, and thus the rate of drug release, decreases over time. Deviation from this shape to different geometries that have more consistent exposed surface areas over time could allow these particles to achieve zero-order release.

Microfluidic fabrication is a novel method of particle fabrication that may enable the tuning of drug release kinetics from polymeric particles. This technique permits a high degree of control over production parameters and produces a monodisperse particle population not previously accomplished by emulsion-solvent evaporation methods [285–288]. Monodispersity from microfluidic particles, importantly, can impact release kinetics by reducing the initial burst release and thereby maintain more consistent drug release rates over the lifetime of the particles [289]. However, like more traditional formulation methods, microfluidic fabrication is generally limited to the production of spherical particles which inherently precludes zero-order release, though several research groups have modified the microfluidic process to make non-spherical shapes such as disks, rods, and hemispheres, suggesting the possibility of applying microfluidics to make other shapes with zero-order release properties [290–292].

3D printing is another promising technique that could be utilized to produce non-spherical surface-eroding polymeric particles. There is clinical precedence for 3D printed devices in the form of the FDA-approved Spritam (levetiracetam) that entered the market in 2015 [293]. 3D printing offers a degree of control over particle geometry that is not seen in other methods of formulation and could be explored further to control device geometry and thus the release kinetics of polymer microdevices. These techniques are relatively unexplored for particle formulation but one study using piezoelectric inkjet printing created PLGA particles with distinct geometries and demonstrated the ability to alter drug release profiles [294]. Given their high reproducibility and customizable geometry, these techniques could be very useful to pattern light-responsive, soluble, or flowable surface-eroding polymers, particularly if their resolution was sufficient to fabricate particles small enough to be injected.

Implantable biodegradable devices share some of the advantages of their injectable counterparts, but also generally exhibit first-order release kinetics and require implantation, which may undermine their clinical acceptability. Ultimately, the only real advantages these systems have over injectable biodegradable drug delivery devices are their ability to deliver more drug and a potentially easier pathway to achieve zero-order release owing to the greater control of fabrication options at a larger scale.

Alternatively, oral drug delivery is convenient and inexpensive compared to other delivery methods and does not require costly or invasive administration procedures. However, this administration route is traditionally limited by gastric residence time. Osmotic devices are an important drug delivery tool because they are self-administered, orally ingested systems and are capable of releasing both water-soluble and poorly water-soluble drugs in a zero-order fashion with improved oral bioavailability. However, this approach is limited to drugs that are orally bioavailable and drug release is currently limited by gastric residence time to less than 24 h. Systems that improve gastric residence time and enhance oral bioavailability could be used to improve the applicability of these systems to other drugs and indications. Several technologies are currently under exploration that could augment the duration of current zero-order oral delivery systems by leveraging mucoadhesive properties, anatomical barriers to gastrointestinal transport, and gastric floating.

Mucoadhesive drug delivery devices can be administered in various forms such as tablets, mucoadhesive films, patches, and gels/ointments to delay passage through favorable interactions with the mucosa [295]. In addition to prolonging gastric residence time, these devices may also be able to enhance absorption, reduce absorption time, and avoid first-pass metabolism when delivered via buccal, vaginal, or rectal routes [296,297]. Mucoadhesive systems may even be able to enhance the stability and absorption of unstable bioactive molecules including peptides like thyrotropin-releasing hormone and insulin [298].

Another method of improving gastric residence time is physical restriction of the device within the stomach. One device delivered the anti-malarial drug ivermectin for over 2 weeks in a sustained first-order fashion, supplanting the need for daily administration [299–301]. This device consists of a six-armed, drug-loaded star folded into a rapidly-degradable capsule. Once ingested, the star unfurls, physically blocking its passage into the intestines. Drug is released until the core is dissolved, at which point the arms break off and pass through the digestive system without causing any blockages. This device has important applications for sustained drug delivery because it can be loaded with different types of drugs and is orally ingestible. This combination of factors suggest it can contribute to the sustained delivery of drugs for many conditions and enhance patient compliance if it could be paired with zero-order release kinetics.

Another physically restrictive device sought to improve adherence to tuberculosis dosing regimens by releasing drug from a coil placed in the stomach [302]. The device, which is administered and removed through a nasogastric tube, can deliver grams of drugs over 4 weeks and does not perforate or obstruct any portion of the gastrointestinal tract. The dose and duration of therapy can be tailored by modifying the length and composition of the device and different drugs can be delivered. Unlike most controlled drug delivery systems, this device can deliver large payloads, which is attractive for low-potency drugs including many antibiotics. Ultimately, the utility of this approach will

largely be governed by patient acceptance of delivery via nasogastric tube. Potential applications of this coil technology could expand further if it could be tailored to achieve zero-order release kinetics.

Floating gastric devices are low-density, buoyant systems that float on top of the gastric contents causing an increase in gastric residence time and decreased fluctuations in plasma drug concentration [303,304]. One novel floating drug delivery device encapsulated domperidone, a water-insoluble weak base with a short half-life that typically requires three administrations per day, in a 3D printed hydroxypropyl cellulose filament produced by hot melt extrusion [305]. Results from this study demonstrate an improvement in oral bioavailability by about 220% compared to the conventional orally administered domperidone tablet and reduced dosing frequency to twice daily. Currently there are no FDA-approved floating devices; however, their ability to improve drug gastric residence time and ease of administration suggest that patients would view them as desirable. Some systems have already combined osmotic pumps with flotation techniques, thus improving gastric retention and sustaining delivery. In their simplest form, these systems have been designed with an additional air compartment to facilitate buoyancy [306]. Other designs include an osmotic pump with a core containing a poorly water-soluble drug (famotidine), PEG, and sodium chloride surrounded by an asymmetric membrane in which a thin dense membrane covers a thick porous membrane [307]. The device is effectively hollow due to the low bulk density of the powders in comparison with the highly porous membrane. This floating system released famotidine in a zero-order fashion for 12 h, doubled half-life compared to the reference standard, and increased oral bioavailability by 1.6-fold compared to the reference.

Khan and colleagues created a floating osmotic pump by coating the pump in a gas-generating gel layer surrounded by an enteric coating [308]. A chemical reaction between the gel layer and gastric contents produced carbon dioxide which was entrapped within the device by the enteric coating causing the device to float and release diethylcarbamazine citrate, a highly water-soluble drug, for 24 h in a nearly zero-order fashion [308]. This development suggests the potential for a once daily administered osmotic device that is capable of delivering water-soluble and poorly water-soluble drugs in a controlled fashion. These devices could supplant conventionally delivered drugs that require multiple administrations per day in the relatively near future and improve patient compliance.

Passive and active microchips are an exciting avenue of drug delivery as they exhibit tight control over drug release—suggesting their potential value for drugs with narrow therapeutic windows—and can be tailored to deliver drugs with specific release patterns. Both systems have demonstrated zero-order release and developments in microfabrication techniques like photolithography, soft lithography, film deposition, and etching and bonding allow for unprecedented control over device features and surface architecture, ultimately permitting control over the device's delivery properties that is not observed in most other drug delivery systems [309,310]. However, in their current state, active and passive microchips are expensive, have low drug loading capacities, and require surgical implantation and removal, reducing their widespread appeal [274]. There are substantial ongoing efforts to mitigate these limitations. One group of researchers circumvented the need for surgery by developing an orally ingested microchip that can be activated by biosensors or stimulated by a radio frequency transmitter [311]. Another group developed a resorbable microchip that successfully delivered a chemotherapeutic agent to treat brain cancer to take advantage of an open cavity after surgical tumor resection without the need for a second removal surgery [312]. In the future, these devices could be further miniaturized to reduce the invasiveness of implantation surgery and thereby improve patient acceptability.

5. Clinical and commercial impact

Drugs have played a key role in improving quality of life and lifespan over the past century. Low patient compliance to drug therapies is a substantial global problem that contributes to poor health outcomes and unnecessary financial costs. The development of zero-order drug delivery systems has immense potential to improve drug efficacy, reduce side effects, and increase patient compliance by facilitating sustained delivery of therapeutics for extended periods of time without relying on patient adherence. Reducing the frequency of administration and delivering drugs with narrow therapeutic windows opens the door for delivery of therapeutics that currently require repetitive dosing and/or constant supervision by a healthcare provider (e.g., chemotherapeutics). Accomplishing this task has proven to be difficult, but emerging formulation methods and materials offer the potential to overcome historical limitations to create broadly applicable drug delivery systems that exhibit prolonged zero-order release kinetics.

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