Drug delivery systems for programmed and on-demand release

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ABSTRACT

With the advancement in medical science and understanding the importance of biodistribution and pharmacokinetics of therapeutic agents, modern drug delivery research strives to utilize novel materials and fabrication technologies for the preparation of robust drug delivery systems to combat acute and chronic diseases. Compared to traditional drug carriers, which could only control the release of the agents in a monotonic manner, the new drug carriers are able to provide a precise control over the release time and the quantity of drug introduced into the patient’s body. To achieve this goal, scientists have introduced “programmed” and “on-demand” approaches. The former provides delivery systems with a sophisticated architecture to precisely tune the release rate for a definite time period, while the latter includes systems directly controlled by an operator/practitioner, perhaps with a remote device triggering/affecting the implanted or injected drug carrier. Ideally, such devices can determine flexible release pattern and intensify the efficacy of a therapy via controlling time, duration, dosage, and location of drug release in a predictable, repeatable, and reliable manner. This review sheds light on the past and current techniques available for fabricating and remotely controlling drug delivery systems and addresses the application of new technologies (e.g. 3D printing) in this field.

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1. Introduction

The development of biodegradable/biocompatible materials and novel drug delivery systems (DDSs) represents a revolution in medicine over the years and leading to considerable advancements in other biomedical domains including biomaterials science and tissue engineering [1–6], while developing interdisciplinary collaborations among chemists, biologists, clinicians, and engineers [7]. DDSs, the macro-/micro-/nano-carriers by which therapeutic agents are introduced into the patient body, play a critical role in addressing the deficiencies of conventional drug administration and improving drug safety, patient compliance, and convenience [8–10]. With increasing awareness of the importance of biodistribution and pharmacokinetics for an efficacious treatment, the optimal design and application of DDSs have become more important now than it ever has been in the past [11]. In addition, the short half-life of the new bio-therapeutic agents such as proteins, peptides, and nucleic acids, and their non-specific distribution, potential toxicity, and side-effects have been the driving force for the design of optimal devices which protect them from degradation and control their release at a predetermined rate [12–16].

The concept of sustained release was first introduced in 1960s [17,18], while notable researchers including Folkman, Higuchi, Langer, Peppas, Heller, Ringsdorf, and Speiser have had significant contributions in the rapid development of the field [19–33]. Although the initial DDSs, i.e. macroscopic drug depots, reduced the risk of systemic toxicity through maintaining the concentration of medications within a therapeutic window, their application was eventually confined as they released their cargos over a limited period (e.g. one day) and their surrounding environment (i.e. pH, temperature, ionic strength) had undesired effects on their performance [17,34,35]. Subsequently, DDSs, which can control the release of the agents at constant rates and with high reproducibility in-vitro and in-vivo, have been developed for local or systemic therapy and some have reached the stage of clinical trials [36,37]. The field of controlled release is currently further matured and finds many important applications in every field of medicine for cancer [6,38,39], pain [40,41], diabetes [42–44], ischemia [45–48], and myocardial treatments [49–52].

Despite these significant achievements in drug delivery technologies over the past years, most carriers can only provide monotonic release profiles irrespective of time, patients’ needs, and changes in physiological circumstances. In other words, the encapsulating matrix does not have a specific contribution in tuning the release rate, and only slows drug release. Moreover, specific agents such as vaccines and proteins require a particular administration strategy for a definite period, which considerably affects their stability, bioavailability, and efficacy [53–56]. Therefore, it is crucial to develop DDSs with particular architecture and physicochemical properties, which are able to adjust the release profile under different circumstances.

Due to rapid advancement in materials science and manufacturing technologies, the fabrication of advanced DDSs with a customized release profile is not a dream anymore. The existing DDSs can roughly be categorized into two groups of “controllable” and “uncontrollable” devices. In controllable devices, the release of drug can be adjusted through the interaction between smart materials and changes in their environment (i.e. pH and redox, oxidation, and enzyme concentrations [57–61]) or by an operator remotely controlling the conditions (temperature, magnetic force, light intensity, and/or ultrasound magnitude and frequency [62–65]). Moreover, the advancements in micro-/nano-fabrication technologies (e.g. microelectromechanical systems (MEMS), nanoelectromechanical systems (NEMS), 3D printing, etc. [66–69]) have increased interests in the fabrication of devices with a programed (specific time and location) release profiles. In contrast, release rates for the non-programmed group of carriers mainly follow physicochemical properties of the materials. For instance, the release of drug from conventional polymeric particles is generally controlled by diffusion mechanism, degradation, and surface erosion [70–72]. However, changes to the geometry and architecture of such devices may provide unique opportunity to fabricate simple carriers with tunable drug release profiles.

The aim of this review is to provide an informative account of physical and chemical requirements for the development of advanced DDSs with desired release profiles. The conventional DDSs and preparation techniques with emphasize on polymeric particles will be introduced. Next, the mechanism of controlled release from those drug carriers.
through reviewing the mathematical equation describing the relations among physiochemical parameters will be focused. Particular attention will be paid to pulsatile (programmed and remotely controlled) DDSs using selected examples from the literature, as they have found numerous applications in chronotherapy. Finally, the paper will explore new technologies (microchips and 3D-printing) for the fabrication of novel DDSs with sophisticated profiles.

2. Drug delivery systems with conventional release profiles

Various materials such as mesoporous silica, hydrogels, micelles, sugars, starches and biopolymers have been investigated for development of drug delivery devices. In this section, the role and development of biopolymers in drug delivery is evaluated. Biopolymers are widely used in development of drug delivery devices owing to their biocompatibility and biodegradability [73–77], making it possible for the design of tunable drug releasing systems for both hydrophobic and hydrophilic drugs [78]. Diffusion-controlled models can be broadly applied to reservoir and monolithic (or matrix-based) drug delivery systems where drug release typically occurs before effects of polymer swelling and degradation begins [79]. Monolithic drug delivery devices make up a significant portion in the development of polymeric controlled release devices owing to their relatively straightforward methods for preparation (i.e. dissolution or dispersion of drug throughout the polymer matrix). The drug delivery devices are generally prepared by dissolving the drug and polymer in a suitable common solvent [80], followed by co-precipitation of the drug-polymer matrix via removal of the solvent by evaporation or using an anti-solvent. The well-established fabrication strategies for the preparation of monolithic drug delivery systems will be discussed in Section 2.4. In diffusion-controlled systems, the rate of drug release can be influenced by the drug concentration in the polymer matrix [81], the average size of the drug delivery device, porosity, and the hydrophobicity or hydrophilicity of the polymer matrix [79,82]. These factors can be tuned by the selection of material used for the drug delivery device (Section 2.2) or by control of the fabrication technique selected for the preparation of drug delivery device.

2.1. Permeability and solubility of drugs

2.1.1. Hydrophobic drugs

Under the biopharmaceutics classification system (BCS) by Food and Drug Administration (FDA) [83], drug compounds can be classified according to its permeability and solubility as: High permeability and solubility (Class 1); high permeability and low solubility (Class 2); Low permeability and high solubility (Class 3) and Low permeability and low solubility (Class 4). Hydrophobic or poorly water-soluble drugs (Class 2 and Class 4) face challenges in their therapeutic applications due to poor aqueous solubility and low bioavailability [80,84]. Micro/ nano-encapsulation in a polymer carrier is one of the strategies for improving the solubility and bioavailability of hydrophobic drug compounds by physical modification [84].

In the preparation of monolithic devices for hydrophobic drugs, it is important to understand the solubility of the drug in the wetted polymer matrix. For hydrophobic drugs having low solubility and dissolution rates, release profiles from non-swelling and non-degrading polymers can be categorized into monolithic dispersion and monolithic solution systems [79]. Monolithic drug dispersion can lead to very slow and incomplete drug release after long release times as observed from in-vitro studies with hydrophobic drugs such as paclitaxel and lidocaine [85,86]. In-vitro release and mathematical modeling studies for paclitaxel [86], nifedipine [87] and lidocaine [85] respectively in poly lactic acid (PLA) microparticulate systems validate the diffusion dissolution mechanism proposed by Harland [81].

2.1.2. Hydrophilic drugs

Hydrophilic or water-soluble drugs (Class 1 and Class 3) face challenges in their therapeutic applications due to high aqueous solubility. In the preparation of monolithic dispersion, it is usually not possible to dissolve the drug in a common organic solvent as the polymer [82]. Typically, a water-in-oil emulsion will be produced and subsequently processed via one of the strategies in Fig. 1 to produce the drug loaded polymeric device. In the case of solvent evaporation from a water/oil/water emulsion system, it is difficult to attain high encapsulation efficiency due to the tendency for the hydrophilic drug to diffuse to the bulk aqueous phase during the emulsification/solvent evaporation step, leading to the loss of large amounts of drug [82]. Other strategies include using ultrasonic energy to disperse the hydrophilic drug in an organic solution containing the dissolved polymer [88,89]. Hydrophilic drug monolithic devices generally display large initial burst release profiles.

2.2. Materials for polymeric drug delivery devices

Since the development of drug delivery research, many natural and synthetic polymers have been studied and evaluated for its biocompatibility and application as a drug delivery carrier. A comprehensive overview of polymers used for controlled drug release can be found in Ulrich et al. [73] and in the review article by Park et al. [77]. Table 1 summarizes the biopolymers commonly used in drug delivery research for matrix-based microscale devices and the release profile associated with its application.

The nature of the biopolymer such as polymer chain length, functional groups, end groups, etc., influence the mechanism of drug release (diffusion, dissolution, swelling, surface erosion, bulk degradation, etc.) [73,77,86,100–109]. Fabrication methods can influence the surface morphology, size and size distribution, and the shape of the drug delivery devices (Section 2.4). In the review by Siepmann and Siepmann [79], mathematical equations for reservoir and monolithic drug delivery systems with different geometries were presented, providing useful approximate solutions for modeling microscale drug delivery devices such as microparticles (sphere), microfibers (cylinder), and microfilms (slab). Drug delivery systems with polymer blending [110], multi-layered polymer coating and stimuli-sensitive polymers [111] have also been developed to achieve drug release profiles with “zero order” type release as elaborated further in Sections 3.3 and 3.4.

2.3. Microscale drug delivery devices

Microscale drug delivery devices can be broadly classified into the following categories: Microparticles (MP), Microfibers (MF), and Microporous scaffold (MPS). PLGA has been cited as the “gold standard” and most successful biodegradable polymer for drug delivery [73,100]. Examples of each type of drug delivery devices based on model PLGA polymer is summarized in Fig. 1.

2.3.1. Microparticle (MP)

Drug-loaded biopolymeric microparticles have been developed for sustained delivery via nasal delivery, pulmonary inhalation, oral delivery [112] or implant delivery [113]. Microparticle drug delivery devices with PLGA, PLA and PGA are the most commonly investigated due to their promising applications for sustained release. Successful applications include the development of Lupron Depot®, a sustained delivery microparticle-based depot for leuprolide [112,114,115].

2.3.2. Microfiber (MF) and nanofiber (NF)

Common methods for fabrication of drug-encapsulated microfibers include wet spinning/extrusion and electrospinning. Microfibers from biopolymers such as PLGA, PCL, etc., have potential biomedical applications for wound dressings, surgical implants and use as scaffold material. Synthetic drugs and proteins can be encapsulated in micro- and

nano-fibers for sustained drug delivery [116]. Commercial applications of microfiber polymers drug delivery include the Absorv® systems by Zeus Inc. [117], and SNC BEST™ electrospinning technology [118].

2.3.3. Microporous-structured polymer scaffold (MPS)

Microporous polymeric structures can be used as implants for postsurgical biomechanical support as well as drug delivery [113].

Table 1
Polymers commonly used in drug delivery systems.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Type of polymer</th>
<th>Summary and release mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polyesters</strong></td>
<td>Poly(lactic-co-glycolic acid) (PLGA)</td>
<td>The most successful biopolymer in drug delivery. Physical properties and degradation profile can be altered by varying the lactic to glycolic ratio and molecular weight of the polymer [77]. PLGA undergoes bulk erosion with pseudo-first-order degradation kinetics [100]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(lactic acid) (PLA)</td>
<td>Naturally occurring poly lactic acid (PLA) is highly crystalline with much slower degradation rate than PLGA. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(glycolic acid) (PGA)</td>
<td>PGA has very fast degradation rates in-vitro and in-vivo. Release mechanism based on diffusion followed by bulk degradation. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(ε-caprolactone) (PCL)</td>
<td>Biodegradable, semi-crystalline polymer with very slow degradation. Suitable for long term delivery for period of over a year via drug diffusion [100]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(phosphoesters) (PPES)</td>
<td>Degradation rate can be controlled by percentage of phosphate content in the polymer backbone. Combined degradation mechanism of surface and bulk erosion [77,102]. Biodegradable polymers that can be produced using bacteria [103,104]. Insoluble in water and stable in air. Complete degradation to water and carbon dioxide or to methane and carbon dioxide under aerobic and anaerobic conditions, respectively. Drug release and degradation via surface erosion [105]. The copolymer PHBV, poly(3-hydroxybutyrate-co-hydroxyvalerate) is similar to PLA in processing [104].</td>
</tr>
<tr>
<td>Poly(orthoesters) (POEs) [106]</td>
<td>POE I</td>
<td>POE I is hydrolyzed under aqueous environment with autocatalytic hydrolysis reaction, which needs to be stabilized with a base such as sodium carbonate. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>POE II</td>
<td>POE II is highly hydrophobic and requires incorporation of acidic excipients into the polymer matrix to increase surface erosion rate. However, this could accelerate the autocatalytic hydrolysis. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>POE III</td>
<td>POE III exists as a semi-solid polymer at room temperatures. No autocatalytic hydrolysis reaction during degradation. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>POE IV</td>
<td>POE IV is a modified POE II with a short segment of lactic or glycolic acid incorporated into its backbone. Erosion rate can be controlled by specific adjustments of these segments in the polymer. Drug release is primarily by surface erosion. Hydrophilic polymer with good biocompatibility. PEG is commonly used to form copolymers such as the PLA-PEG copolymer, and also attached to therapeutic proteins for prolonged circulation in the body [73]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td>Poly(ethylene glycol) (PEG) (also termed as polyethylene oxide (PEO))</td>
<td>Poly(anhydrides)</td>
<td>(also termed as polyethylene oxide (PEO)) Poly(anhydrides) undergo erosion homogeneously [73]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(anhydride-imides)</td>
<td>Poly(anhydride-imides) appear to undergo predominantly surface erosion in-vitro and have good mechanical properties [107]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td></td>
<td>Poly(anhydride-esters)</td>
<td>Poly(anhydride esters) undergo hydrolytic degradation to release salicylic acid, a compound with medicinal properties [108]. Drug diffusion-dissolution model has been applied for drug delivery devices developed using PLLA [86,101].</td>
</tr>
<tr>
<td>Poly(ester amides) (PEAs)</td>
<td>PEAs</td>
<td>PEAs are polymers with both ester and amide linkages in their polymeric chain, combining the degradability of polyesters with good thermo-mechanical properties of polyamides for biomedical applications [109].</td>
</tr>
</tbody>
</table>

Microporous scaffolds can be produced by solvent casting or phase separation/leaching methods [98]. Supercritical CO2 foaming has gained interest in the production of microporous biopolymeric foams for biomedical applications due to its potential for solvent-free or very low residual solvent final product [99]. Supercritical CO2 foaming has been adapted for the production of indomethacin [119], 5-fluorouracil [120], paclitaxel [99] and gentamicin drug releasing microporous foams [121].

2.4. Fabrication methods for microscale drug delivery devices with normal release profile

Normal release systems or diffusion-controlled systems are mostly monolithic devices [78]. For simple diffusion-controlled systems, the drug is dispersed in a polymer matrix, which does not swell nor degrade during the drug release period. Fig. 1 provides an overview of the common processing strategies used for fabrication of various microscale monolithic drug delivery devices.

2.4.1. Emulsification-solvent evaporation

Solvent evaporation is a widely used technique for the production of drug microencapsulated polymeric systems. Typically, the steps involved in emulsification-solvent evaporation [82,122] include (1) dissolution/dispersion of drug in organic solution with the polymer; (2) emulsification of the organic phase in an aqueous phase; (3) extraction of organic solvent from dispersed phase followed by solvent evaporation; (4) recovery and drying of microspheres. Examples of hydrophobic drugs encapsulated in PLGA include lidocaine [123] and paclitaxel [124].

The encapsulation of hydrophilic drugs typically requires an additional step of dispersion an aqueous phase of dissolved drug into the organic solution before emulsification in the aqueous phase, forming a water-in-oil-in-water (W/O/W) emulsion. Examples of hydrophilic drugs encapsulated in PLGA include doxorubicin [125] and gentamicin [126].

Factors influencing the properties of microspheres (i.e. size, surface morphology and extent of agglomeration, etc.) produced by emulsification-solvent evaporation technique include the properties and ratio of materials (solvent, surfactant, drug, polymer, etc.) used in the process and the operating conditions such as temperature, pressure, geometry of the reactor and agitation (ultrasonic or stirring) energy. A comprehensive review of the factors can be found in Li et al. [82].

2.4.2. Spray drying

Spray drying can be applied to both aqueous and organic solutions for the production of microparticle drug delivery devices. Spray drying is a well-established process applicable for a wide range of formulations [127] for the food, pharmaceutical and materials industries. The first step in spray drying for microencapsulation involves solution preparation similar to step (1) of emulsification-solvent evaporation method described in Section 2.4.1. This is typically followed by (2) atomization of the solution; (3) extraction of organic solvent or water from the atomized droplets; (4) recovery of dried microparticles via a cyclone. In spray drying, the media of extraction of organic solvent can be hot air or nitrogen. Factors influencing the properties (size and surface morphology) of drug-loaded powders produced by spray drying include the properties and ratio of materials (solvent, drug, polymer, etc.) and the operating conditions such as the solution and drying gas flow rate, temperature of drying gas, geometry of the spray dryer and cyclone separator, the geometry of the solution atomizer, etc. A comprehensive review for the particle formation by spray drying can be found in references [127,128].

2.4.3. Electrospaying

Electrohydrodynamic atomization (EHDA), also known as electrospay, involves the breakup of a solution jet into fine droplets...
by the application of an external electrical field at the nozzle [129–132].
Controlling the droplet formation and subsequent solvent evaporation from the droplets lead to formation of microparticles of adjustable size and morphology [129,131]. EHDA can be applied to single or coaxial nozzles [133] for drug delivery microencapsulation. EHDA can be used to process a wide range of polymers ranging from cellulose, chitosan, PLA, PLGA, PCL, polystyrene, and even metals. The size of particles obtained is dependent on the droplet size formed at the nozzle or jet in EHDA. This can be influenced by the solution properties (fluid viscosity, density, conductivity, etc.), the voltage applied, and the configuration of the nozzle. A comprehensive analysis for the development of drug delivery microparticles can be found in the paper by Xie et al. [134].

2.4.4. Supercritical fluids processing

The non-toxic nature and highly tunable properties of supercritical carbon dioxide (CO2) present many opportunities for the development of drug delivery systems with minimal to zero residual organic solvent. In the design and fabrication of drug delivery devices, supercritical carbon dioxide can act as a solvent, co-solvent, antisolvent, drying agent [135] or as a foaming agent [136] to produce microparticles or microstructured polymeric systems. The most common technique using supercritical fluid processing for drug delivery application is the supercritical antisolvent process. In this process, drug–polymer solution is prepared similar to step (1) described in Sections 2.4.1 and 2.4.2. Spraying the organic solution into a high-pressure chamber with supercritical carbon dioxide removes the organic solvent from the solution, leading to precipitation of the drug–polymer matrix as microencapsulates. Drug-loaded formulations for paclitaxel [86], 5-fluorouracil [137], gentamicin [138], etc. have been developed using supercritical CO2 as an antisolvent. The process can be controlled by controlling the phase behavior of the feed material (drug, polymer, solvent) in supercritical CO2, and also by extent of mass transfer between solvent and CO2. Various strategies for drug delivery formulations using supercritical CO2 processing can be found in the review by Davies et al. [139]. A recent review by Nachuchua et al. [135] provides a comprehensive summary of drug delivery particles formulated by supercritical CO2 technologies.

3. Mathematical models for drug delivery systems

Here, the mathematical models for reservoir and monolithic systems are described. The practical benefits of developing a mathematical model for DDS are the elucidation of the governing mechanism of drug release and the simulation of the effect of the design parameters on the drug release profile. In fact, the required composition (drug type and loading, polymer and additives) and geometry (size and shape) of DDS need to be experimentally formulated in order to determine the drug release profile. With a suitable mathematical model, such profile may be theoretically predicted, thereby reducing the number of experiments to be conducted. Overall, the development of new DDS can be greatly facilitated via mathematical models.

3.1. Modeling of drug release from single-polymer matrix

The classification of monolithic solutions and monolithic dispersions can be differentiated based on the ratio of initial drug loading to drug solubility. Assuming uniform initial drug distribution, constant drug diffusivity, and perfect sink conditions, Fick’s diffusion solutions for different geometries can be determined for monolithic solution DDS (Table 2, Eqs. (1)–(3)).

Simplified expressions for initial and final stages of drug release have been developed for the various geometries [140] instead of the infinite series described above. In monolithic dispersion where there is a high loading to solubility ratio, a portion of the drug is dissolved in the polymer matrix while the rest is distributed as crystalline and/or amorphous undissolved drug particles. For a given initial total drug concentration (c0), the dissolved drug is maintained at its drug solubility concentration (c), while the undissolved drug is maintained at concentration c0 – c. The dissolved drug at and near the surface is released and available for diffusion, but it can be rapidly replaced by dissolution of neighboring drug particles. There is a moving front of dissolution established inside the monolith. The mathematical treatment of this type of drug delivery system is rather complicated, and one can refer to other references for details [141–144]. A simple and accurate solution based on the Higuchi equation [145] for release from both faces of a thin slab is available as follows:

\[ M_t = 2A \sqrt{\frac{2(T_c - T)}{c_0}} \]  

where A is the surface area.

The Higuchi equation has been applied to other geometries. Assuming i) initial drug concentration is much higher than drug solubility (i.e., c0 ≫ c), ii) undissolved drug particles are dispersed and much smaller in size than the dimension of the drug delivery device, iii) swelling or dissolution of the polymer matrix is negligible, iv) constant drug diffusivity, and v) under perfect sink conditions, the fractional drug release for the different geometries can be expressed (Table 2, Eqs. (5)–(7)).

The upper time limits refer to points where the moving dissolution front reaches the center of the device, after which only dissolved drug remains. From this point onwards, infinite series expressions are used to describe the drug release. This typically corresponds to a minor part of the release process, especially when c0 ≫ c.

The earlier described model does not consider the impact of polymer erosion on drug release. Several mathematical models attempt to elucidate the polymer erosion process and could accurately depict the drug release obtained experimentally. In theory, the process encompasses chemical reactions that produce oligomers and monomers in the polymer matrix, and mass transport of drug and degradation products within the matrix. The process is often accompanied by multifaceted physical and chemical phenomena, such as porosity changes, micro-environmental pH changes, and autocatalytic polymer degradation. This complex interplay of multiple mechanisms impedes the establishment of a constructive and precise mathematical model that is able to predict all the different contributions on the resulting drug release kinetics from a bio-erodible polymer matrix.

While there have been several empirical models describing drug release kinetics from a bio-erodible polymer matrix [146–149], this paper will be focusing on mechanistic models describing the erosion process as a combination of polymer diffusion and reaction. Harland et al. [81] established the first dissolution model for a bulk-eroding polymer matrix. The model takes into account the effective Fickian diffusion and dissolution of the solute into liquid-filled pores. The drug transport model is expressed as follows:

\[ \frac{\partial C}{\partial t} = D_e \left( \frac{\partial^2 C}{\partial r^2} + \frac{2}{r} \frac{\partial C}{\partial r} \right) + k(cC_1 - C) \]  

where C and D are the drug concentration and effective diffusivity in liquid-filled pores, respectively, k is the drug dissolution rate constant, ε is the porosity of the polymer matrix and εC is the equivalent drug saturation concentration in the solution found in the pores.

The solution for fraction of drug release under infinite mass transfer and finite convective mass transfer conditions at the surface may be obtained. Under infinite mass transfer condition,
Table 2

Fundamental equations for monolithic solution, monolithic dispersion and reservoir DDS of various geometries.

<table>
<thead>
<tr>
<th>Equations</th>
<th>Definition of parameters*</th>
<th>Remarks</th>
<th>Equation no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\frac{M}{Mt} = 1 - \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$L$: thickness of slab</td>
<td>Thin slab</td>
<td>(1)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = 1 - \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$R$: radius of sphere</td>
<td>Monolithic solution DDS</td>
<td>(2)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = 1 - \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$H$: height of cylinder</td>
<td>Drug release occurs from both faces of the slab</td>
<td>(3)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = 2\sqrt{2 - 2^{1/(n+1)}}$</td>
<td>$t$: 0 &lt; $t$ &lt; $L$</td>
<td>Monolithic solution DDS</td>
<td>(4)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = 1 - \frac{1}{t^2} \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$t$: 0 &lt; $t$ &lt; $R$</td>
<td>Finite cylinder</td>
<td>(5)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = 1 - \frac{1}{t^2} \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$t$: 0 &lt; $t$ &lt; $R$</td>
<td>Monolithic solution DDS</td>
<td>(6)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = \frac{1}{t^2} \left[ \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i}) \right]$</td>
<td>$t$: 0 &lt; $t$ &lt; $R$</td>
<td>Drug release occurs from both faces of the slab</td>
<td>(7)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = \frac{1}{t^2} \left[ \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i}) \right]$</td>
<td>$t$: 0 &lt; $t$ &lt; $R$</td>
<td>Reservoir DDS</td>
<td>(8)</td>
</tr>
<tr>
<td>$\frac{M}{Mt} = \frac{1}{t^2} \frac{1}{\Gamma(n)} \sum_{i=0}^{\infty} \frac{t^i}{i^{n+1}} \exp(-\frac{t^{n+1}}{i})$</td>
<td>$t$: 0 &lt; $t$ &lt; $R$</td>
<td>Reservoir DDS</td>
<td>(9)</td>
</tr>
</tbody>
</table>

where $D_0 = \frac{M_{0}V}{M_{0}}$ and is defined as the dissolution/diffusion number, and $\tau = \frac{Mt}{D_0}$ and is defined as the dimensionless time.

Under finite convective mass transfer condition,

$$\frac{M}{Mt} = 6Sh^2 \frac{1}{\pi R^2} \sum_{n=1}^{\infty} \left[ \frac{D_1 + \alpha_n^2 R^2}{D_1 - \alpha_n^2 R^2} \frac{\exp\left[-\left(D_1 + \alpha_n^2 R^2\right)^{-\frac{1}{n}}\right]}{\left(\alpha_n^2 R^2 + Sh(Sh - 1)\right)} \right]$$

where $Sh = \frac{M_{0}}{D_0}$ and $\alpha_n$ are the roots of the transcendental equation of $\alpha R \cot(\alpha R) + Sh - 1 = 0$.

Some other models applied the Fick's second law, but defined drug diffusivity as a function of polymer molecular weight to account for the increase in drug release during polymer erosion. These models are advantageous since the polymer molecular weight changes with time due to erosion, and the dependence of drug diffusivity on molecular weight can be experimentally determined, thus minimizing the number of parameters that need to be fitted.

During hydrolysis, water molecules attack the polymer chain bonds, leading to a decrease in the average molecular weight of polymer matrix. Charlier et al. [150] postulated that the change in the polymer molecular weight ($M_w$) follows a first-order kinetic process of polymer chain cleavage. The model is used to quantify drug release from PLGA film with a planar geometry:

$$\frac{dM_w}{dt} = -k_{deg}M_w$$

So,

$$M_w = M_w,0 \exp(-k_{deg}t)$$

where $M_w,0$ is the initial polymer molecular weight and $k_{deg}$ is the degradation rate constant.

In addition, the drug diffusion coefficient ($D_e$) during polymer erosion is assumed to correlate inversely to the polymer molecular weight as follows:

$$D_e = \frac{D_0 \exp(k_{deg}t)}{D_0}$$

where $D_0$ is the initial drug diffusion coefficient.

By assuming a linear concentration gradient as predicted in the classical Higuchi model, the rate of drug release is:

$$M_w = S \left( \frac{2C_0C_1 D_0 (e^{k_{deg}t} - 1)}{k_{deg}} \right)$$

where $S$ is the exposed surface area.

In a similar study, Raman et al. [151] considered the presence of lag time in the exponential function. In their model, the drug diffusivity is approximated based on an empirical polynomial fit, relating $\ln(D_e)$ and $\ln(M_w)$, and the initial radial drug distribution is established using data from confocal fluorescence microscopy.

He et al. [152] also described the variation of $D_e$ with time as an exponential function, similar to Charlier's approach. In their model, they considered the diffusion solution developed by Baker and Lonsdale [153] and the pure matrix erosion ($F_E$) by Fitzgerald and Corrigan [154]. The fractional drug release from a sphere is:

$$\frac{M_w}{M_w,0} = 6 \left[ \frac{D_e t}{\pi R^2} - \frac{D_e t}{R^2} + F_E \left( \frac{e^{k_{deg}(t-t_{max})}}{1 + e^{k_{deg}(t-t_{max})}} \right) \right]$$

where \( k_e \) is a measure of relative ease of polymer decomposition branching within the polymer matrix, and \( t_{max} \) is the time to maximum matrix erosion rate.

The proposed model is able to describe the triphasic drug release kinetics observed for bio-erodible polymer matrix, which included i) an initial burst phase, (typically caused by high initial drug release rate due to short diffusion pathways), ii) an intermediate phase of approximately zero order drug release resulting from a combination of drug diffusion and polymer degradation, and iii) a second rapid drug release rate due to matrix erosion.

3.2. Modeling of drug release from reservoir devices

In general, reservoir systems comprised of the drug segregated from a rate-controlling membrane layer (core-shell structure) and can be categorized to have either a constant activity source or non-constant activity source (Fig. 2). For devices with a constant activity source, the initial drug concentration is higher than the drug solubility, and there is an excess of undissolved drug particles within the core. This leads to an establishment of saturated drug solution in the core region. The drug is dissolved and released, and rapidly replaced by partial dissolution of the remaining drug particles. As such, the drug concentration at the inner shell layer remains constant so long the drug is present in excess. For devices with a non-constant activity source, the initial drug concentration is lower than the drug solubility. Subsequently, the drug released across the shell layer is not replaced, and the drug concentration at the inner shell layer declines during the release process.

Consider a drug delivery device comprising of a drug-containing core surrounded by a nearly slow-degrading or surface-eroding polymer layer. The drug release can be accurately modeled based on a reservoir device with a constant activity source. Such drug delivery systems have an outer layer providing a barrier to control the diffusion of water into the core region, allowing drug dissolution. Upon water penetration, only a portion of the drug particles can be dissolved due to limited drug solubility, resulting in a saturated drug concentration maintained at the inner polymer layer. While the polymer layer is slowly degrading, its mechanical integrity is still retained, and the drug release follows a zero-order profile as predicted from a reservoir device with a constant activity source. Assuming perfect sink conditions and negligible changes to the size and structure of the shell layer during drug release, the release rate of drug with a partition coefficient \( K \) for the different geometries can be expressed (Table 2, Eqs. (17)–(19)).

3.3. Tuning drug release rate toward zero-order profiles

3.3.1. Bulk- and surface-eroding single-polymer microspheres

An initial burst release of drug is typically observed in single-polymer microspheres. This phenomenon is a consequence of several possible factors [155] including:

i) poor encapsulation/solubility of drug particles in the polymer matrix, particularly at high loading levels [156,157].

ii) significant drug transport to the particle surface caused by solvent diffusion in solvent evaporation method of particle fabrication [158] or drying process [159,160].

iii) dynamic pore formation and closure, which transiently controls diffusion paths [161].

Fig. 2. Schematic representations of reservoir devices under perfect sink condition for diffusing drug through the rate-controlling membrane surrounding the drug reservoir with (a) a constant activity source, and (b) a non-constant activity source. The former device consists of an excess of undissolved drug particles (circles), and the concentration of the dissolved drug molecules (stars) at the inner shell layer is maintained at the saturation concentration. The latter device exhibits a decreasing drug concentration at the inner shell layer. The shell layer thickness and permeability remained unchanged during the release process.

Redrawn from [140].

Despite the large number of studies investigating drug release from degradable single-polymer microspheres, limited success to obtain zero-order release has been achieved. Some general strategies that may attain the goal of zero-order release are highlighted in the following sections.

3.3.2. Drug release from events of diffusion-controlled and bulk-degradation

One strategy is to utilize a timely optimization of drug release from diffusion-controlled and bulk-degradation processes to achieve a nearly zero-order release profile [155]. Upon hydration of the polymeric matrix, the drug can be solubilized and released before the occurrence of polymer degradation. The drug diffusion rate is typically higher during the initial period, dependent on several factors such as polymer’s wet state glass transition temperature, polymeric matrix’s surface area and porosity, and drug particle’s hydrodynamic radius. PLGA’s glass transition is near to the biological body temperature, resulting in enhanced plasticization and higher drug diffusion rate. The drug diffusion rate eventually decreases with time upon reaching the exhaustion of undisolved drug particles. However, the bulk degradation of the polymer matrix would release the embedded drug and drive the increase in drug diffusivity. In this strategy, a careful selection of hydrophilic, diffusable drug, and bulk degrading nature of polymer would be required to achieve the goal of zero-order drug release (Table 3). It is important to note that the goal of zero-order drug release for the desired application requires the relevance of the chosen in-vitro parameters as compared to in-vivo conditions.

Zhao et al. [162] developed PLGA microspheres for the delivery of a novel antipsychotic isoperidone, a prodrug of paliperidone, with an aim to enhance liposolubility. Pharmacokinetic studies in-vivo indicated a one-week plateau phase, followed by a quasi-zero-order release for two weeks. The sustained release of isoperidone resulted in a significant suppressive effect in the established schizophrenic mice model as compared to the oral administration or blank control groups. The primary mechanisms by which the drug was released included diffusion and degradation. Vora et al. [163] prepared PLGA microspheres loaded with cholecalciferol, a more bioactive form of vitamin D, as an injectable controlled drug release system. The release profiles followed a zero-order release for over 35 days. The corresponding in-vivo pharmacokinetic study of cholecalciferol-loaded microspheres showed significantly higher $t_{1/2}$ as compared to the control formulation with sustained plasma concentration for one month. Despite having four times higher in dose for the PLGA microspheres than the control formulation, the former avoided acute toxicity with no death observed for the treatment group. The zero-order release of cholecalciferol may be attributed to the hollow geometry of the microspheres where the length of drug diffusion pathway from microspheres is lesser than the filled spheres.

3.3.3. Drug release from blending bulk-eroding polymers

In general, for hydrophobic drugs or large molecules, the access of huge amounts of water for drug dissolution or large pore sizes for drug diffusion is required. During the initial period, an absence of drug release or extremely slow release period is observed, often known as “lag phase”, where drug diffusion is slow after initial hydration of the polymer matrix. Drug release will occur upon significant water penetration and increase in porosity within the polymer matrix, translating into an “S” shaped drug release profile. The degradation of bulk-eroding polymeric microspheres shows a clear association with the molecular weight of the polymer. Park [164] observed that low molecular weight oligomers were initially released from PLGA microspheres, followed by low molecular weight degradation products, regardless of the molecular weight of polymer used. For microspheres comprising of lower molecular weight polymers, the degradation products increase with time and matrix exhibited a decrease in molecular weight. In contrast, for microspheres comprising of high molecular weight polymers, the molecular weight of the matrix remained constant for a longer period. Thus, the blending of high molecular weight polymer with a small portion of a low molecular weight polymer has been proposed as a strategy to ensure continuous release of peptides and hydrophobic drugs.

The blend of two polymers of different molecular weights allows the manipulation of the timing associated with the degradation release. Ravivarapu et al. [165] prepared leuprolide acetate loaded microspheres based on a mixture of 8.6 and 28.3 kDa molecular weight of PLGA using a solvent evaporation method. By increasing the content of the smaller molecular weight PLGA, the initial release of peptide was facilitated as compared to the 28.3 kDa PLGA. It was hypothesized that the more hydrated domains of 8.6 kDa PLGA within the matrix accounted for the initial release, and the more prominent 28.3 kDa PLGA domain dictated the subsequent release in the later period. In another study, Mi et al. [166] prepared chlorambucil-loaded microspheres based on a blend of 40 kDa PLGA and chitin using a solvent evaporation method. A two-phase release model was used to describe the drug release from the PLGA/chitin blended matrix, consisting of 60% drug release during the early stage, followed by slow release sustaining for over 200 h. Due to

<table>
<thead>
<tr>
<th>Technique</th>
<th>Drug candidate</th>
<th>Polymers and functional additives</th>
<th>Release profile</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent evaporation method</td>
<td>Isoperidone (a prodrug of paliperidone)</td>
<td>PLGA microspheres</td>
<td>Lag phase for 8 days, followed by constant drug release rate till 20th day</td>
<td>[162]</td>
</tr>
<tr>
<td></td>
<td>Apomorphine (dopamine receptor agonist)</td>
<td>PLGA microparticles</td>
<td>Zero-order drug release rate for 10 days</td>
<td>[173]</td>
</tr>
<tr>
<td></td>
<td>Cholecalciferol (more bioactive form of vitamin D)</td>
<td>PLGA microspheres and tocopherol succinate (stabilizer)</td>
<td>Zero-order drug release rate for 35 days</td>
<td>[163]</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone (steroidal anti-inflammatory drug)</td>
<td>PLGA microspheres</td>
<td>Initial burst release, followed by a lag phase and a secondary zero-order phase</td>
<td>[174]</td>
</tr>
<tr>
<td></td>
<td>Leuprolide acetate (peptide)</td>
<td>A blend of 28.3 and 8.6 kDa PLGA polymers/microspheres</td>
<td>Initial release during first three days, followed by sustained release over 50 days</td>
<td>[165]</td>
</tr>
<tr>
<td></td>
<td>Ovulbumin (protein antigen)</td>
<td>A blend of 100 kDa PLGA or 34 kDa PLGA or 63 kDa PLGA and 8 kDa PEG polymers</td>
<td>A small burst release, followed by a short lag phase prior to a steady release over four weeks</td>
<td>[167]</td>
</tr>
<tr>
<td></td>
<td>Choromabucil (anticancer drug)</td>
<td>A blend of 40 kDa PLGA and chitin polymers</td>
<td>Two phases: over 60% of chloromabucil is released at the early stage of quick release, followed by slow release sustained for over 200 h</td>
<td>[166]</td>
</tr>
<tr>
<td>Pellet die compression method</td>
<td>Chlorhexidine, clindamycin and minocycline (antimicrobial)</td>
<td>Salicylic acid-based poly(anhydride-ester) disks</td>
<td>Zero-order drug release rate for over 140 h</td>
<td>[171]</td>
</tr>
<tr>
<td>Solvent evaporation and cryogenic atomization methods</td>
<td>Ovalbumin (protein antigen)</td>
<td>1,8-bis (p-carboxyphenoxoy)-3,6-dioxoactane-based poly(anhydride) microspheres</td>
<td>Nearly zero-order drug release rate for over 30 days</td>
<td>[172]</td>
</tr>
</tbody>
</table>
the hydrophilic chitin matrix, it exposed the dispersed PLGA particulates and enhanced their hydrolysis which resulted in faster drug release rate. The same effect could also be attained by blending the polymer matrix, preferentially in a water free preparation technique, with water-soluble polymers [167] or other porogens [168].

Drug release rate is highly dependent on the surface area to volume ratio of the microspheres. Small-sized particles typically exhibit shorter diffusion lengths and are associated with high drug release rates. In contrast, larger sizes of particles could exhibit a lag phase as time is required for water penetration and hence displaying slower diffusion rates. By blending preformed, uniform-sized single-polymer microspheres of different sizes, a zero-order drug release profile could be achieved [169]. Other studies have illustrated the release of peptide by mixing microparticles of different individual release profiles, which were fabricated from various PLGA blend ratios and PLGA molecular weights [165].

3.3.4. Drug release from surface eroding polymers

It is difficult to achieve zero-order drug release profiles for drugs that do not readily diffuse in bulk-eroding matrix or in materials that do not have a porous structure. It is often believed that surface-eroding polymers such as polyorthoesters (POEs) or polyanhydrides (described in Table 1) could achieve zero-order drug release profiles since degradation products are not accumulated, and drug diffusion is not the rate-controlling factor. However, zero-order release may be theoretically possible for certain matrix geometries with a minimal change in surface area during erosion [170]. Studies on modified surface-eroding polymers have been investigated and illustrated to offer constant drug releases. Johnson and Uhrich [171] developed a polymer blend of antimicrobials in a salicylic acid-based poly(anhydride-ester) as adjunct treatment for periodontal disease. In-vitro release of each admixed antimicrobial showed a zero-order profile for over 140 h. In another study, Lopac et al. [172] developed ovalbumin-loaded polyanhydride microspheres using two non-aqueous methods mainly solid/oil/oil double emulsion technique and cryogenic atomization. In-vitro release of ovalbumin from 1.8-bis(p-carboxyphenoxy)-3,6-dioxoacetaic based polyanhydride microspheres showed a nearly zero-order profile for over 30 days.

3.4. Double-walled and multi-layered microspheres

The problems associated with using single-polymer microspheres are the initial burst release of water-soluble drugs found on or near the external surface and the difficulty in achieving zero-order drug release. To attain well-controlled drug release rates, double-walled microspheres comprising of a polymeric shell layer surrounding a drug-encapsulating particle core may be introduced [175–184]. The double-walled microspheres can offer greater freedom in controlling drug release through the manipulation of various parameters such as shell layer thickness, structural configuration and polymer type, making zero-order drug release an achievable goal. From this perspective, double-walled or even multi-layered microspheres can provide an attractive and robust approach in drug delivery. Recently, these drug delivery systems have been illustrated with the added advantage of allowing different drugs to be loaded in core/shell regions and releasing them in a parallel or sequential manner to attain synergistic therapeutic effects required in tissue engineering and tumor inhibition models [175–177].

Several fabrication techniques on the production of core-shell structured microspheres have been reported (Table 4). By using a solvent evaporation technique, Lee et al. [185] synthesized double-walled PLGA/PLL-co-polymer microparticles loaded with doxorubicin (DOX) and paclitaxel (PTX) in the shell and core phases, respectively. Through careful adjustment of the shell layer thickness, there was a reduction in the initial burst of DOX while sustaining the release of the two drugs over a two-month period in a near zero-order manner. The resultant microparticles demonstrated a greater reduction in MCF-7 spheroid cell growth as compared to single-drug-loaded microparticles or free drug [186]. Double-walled or multi-layered microparticles may be fabricated using a coaxial electrospray technique [175,176,187–190]. Nie et al. [176] demonstrated the versatility of loading hydrophilic and hydrophobic drugs such as PTX and suramin (SRM) in double-walled PLGA (PLLA) microparticles. When loading with PTX and SRM in core and shell phases, respectively, >70% of SRM was released within the first three days, after which the release was nearly linear until day 30. PTX exhibited a slight initial burst, but was released nearly linear over 30 days. This microparticle formulation was illustrated to produce a greater tumor inhibition against subcutaneous U87 glioma xenograft in BALB/c nude mice as compared to the other microparticle or control formulations [175]. Double-walled microparticles may also be produced using a precision particle fabrication technique [191–194]. In an attempt to enhance the therapeutic efficiency of combined chemotherapy and gene therapy on human hepatocellular carcinoma HepG2 cells, double-walled PDLA/PLLA microspheres were used to deliver 53 NPs and DOX loaded in the shell and core phases, respectively. This microparticle formulation allowed the release of 53 NPs first, followed by simultaneous release of DOX and 53 NPs at a near zero-order rate. Overall, the double-walled microspheres present a promising dual anti-cancer delivery system for such combined treatment.

By using scanning electron microscopy, laser scanning confocal microscopy and gel permeation chromatography, Xu et al. [195] elucidated the degradation behavior of double-walled PDLA(PLGA) microspheres. During the initial period of incubation, the PDLA shell layer was effective in preventing the premature release of DOX into the aqueous medium. The PLGA core degraded significantly, which led to the acidic degradation products accelerating the erosion of the shell layer. Similar erosion time scale was observed for shell layers of different molecular weights. Lee et al. [196] examined the degradation of triple-layered PLGA/PLL/EVA microparticles. It was found that the PLGA outermost shell layer degraded rapidly, leaving behind the double-walled PLLA (EVA) microparticles. However, the middle PLLA layer degraded more rapidly than expected because of the migration of PLGA oligomers that created a hydrophilic and acidic microenvironment in the PLLA layer. This could accelerate the release rate of the drug that is encapsulated in the middle layer or polymer core. These studies provide useful insights to the design of multi-layered microspheres for zero-order drug release profiles.

4. Drug delivery systems with programmed (pulsatile) release profiles

As previously mentioned, the ultimate goal of drug delivery systems is to maximize drug efficacy and to minimize undesirable side effects [188,201,202]. Despite considerable progress in the development of sustained and controlled release devices, most are not so responsive to the dynamic behavior of biological systems and release their cargoes at predetermined rate irrespective of patient needs or changing physiological circumstances, where the release of the agents is controlled only by encapsulating matrices [203–205]. In addition, there are many cases in medicine where controlled release systems with a non-uniform drug administration would be more beneficial [205]. Therefore, scientists have proposed pulsatile release patterns, particularly for the bioactive agents (e.g. hormones) that can be easily denatured by metabolic enzymes and/or develop biological tolerance upon continuous availability at their target sites [206,207]. The pulse release may also improve the efficacy of the treatment for drugs with extensive first-pass metabolism, and for those that require nighttime administration [208].

Pulsatile release is defined as the rapid release of a drug after a well-defined lag time or time gaps [209]. No drug is released from the carrier within the off-release periods. Based on the biological and physicochemical conditions, drug carriers used for pulsatile release can be classified into “on-demand” and “programmed” drug delivery systems, where the drug release is triggered by changes in the physiologic
4.1. Circadian rhythms

Circadian rhythm is the physical, biological, or mental behavioral changes that regulates body functions in human beings on a daily basis (Fig. 3). Sleeping in darkness (overnight) and resuming activities every day is the most common example for the circadian rhythm functions [211–213]. The disease pathophysiology studies have revealed high-amplitude circadian rhythms with day-night patterns in patients. These circadian patterns can be expressed as short- ($t < 0.5$ h), intermediate- ($0.5 \, h < t < 6$ days), and long-period ($6 \, days < t$) oscillations and show great contributions in the success of a prescribed therapy. Therefore, the recognition of the rhythms and their consecutive effects particularly on the treatment of acute and chronic diseases has become very interesting over the past few years [209]. The oscillations of less than and more than one cycle per 24 h are known as infradian and ultradian, respectively [214,215].

Due to considerable advancements in fields of biology, medicine, and pharmacology, the modern therapeutic delivery approaches have introduced a new concept of “chronotherapy” in which therapeutic agents are delivered to a patient in a staggered profile. In chronotherapy, the knowledge of the (i) circadian time structure, (ii) circadian rhythms in disease pathology, (iii) chronopharmacology (i.e. chronodynamics and chronokinetics), and (iv) emerging technologies in drug delivery converge to develop a more precise DDS which provides a right chronotherapeutic dosage to yield a better outcome and less side-effects. Pulsatile drug delivery is a concept that combines environment or by the inner mechanisms of the carrier defined during the preparation, respectively [210].

Table 4

<table>
<thead>
<tr>
<th>Technique</th>
<th>Drug candidate</th>
<th>Configuration of polymers and drugs</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solvent evaporation method</td>
<td>Doxorubicin (DOX) and paclitaxel (PTX)</td>
<td>PLGA (shell)/PLLA (core)</td>
<td>[185]</td>
</tr>
<tr>
<td></td>
<td>Peroxisome proliferator-activated receptor (PPAR) γ/δ agonist GW501516</td>
<td>DOX and PTX localized in shell and core phases, respectively PLGA (shell)/PLLA (core)</td>
<td>[197]</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin HCl (DOX) and paclitaxel (PTX)</td>
<td>GW501516 localized in core phase. Multiple configurations: i) PLGA (shell)/PLLA (core)</td>
<td>[186]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DOX and PTX localized in shell and core phases, respectively ii) PLGA/PLLA/PCPH (shell to core)</td>
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<tr>
<td></td>
<td></td>
<td>DOX found in PLGA outermost shell and PCPH core; PTX found in PLLA and PCPH mid-layers.</td>
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<tr>
<td></td>
<td>Ibuprofen (IBU)</td>
<td>PLGA/PLLA/EVA (shell to core)</td>
<td>[198]</td>
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<tr>
<td></td>
<td></td>
<td>IBU localized in EVA core phase</td>
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<tr>
<td></td>
<td>Ibuprofen (IBU), lidocaine base (ICB), and metoclopramide HCl (MCA)</td>
<td>PLGA/PLLA/PS/EVA (shell to core)</td>
<td>[199]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MCA localized in PLGA outermost shell; ICB in PLGA and PLLA; IBU localized in EVA core</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ibuprofen (IBU) and metoclopramide HCl (MCA)</td>
<td>PLLA (shell)/PLGA (core); Shell phase of microparticles impregnated with PCL particulates</td>
<td>[200]</td>
</tr>
<tr>
<td>Coaxial tri-capillary electrospay</td>
<td>Budesonide and epigallocatechin gallate (EGCG)</td>
<td>IBU and MCA localized in shell and core phases, respectively Multiple configurations (shell to core): i) PLGA/budesonide + EGCG</td>
<td>[190]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) PLGA/budesonide/EGCG</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>iii) PLGA/PLGA-budesonide/PLGA-EGCG</td>
<td></td>
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<tr>
<td>Coaxial dual-capillary electrospay</td>
<td>Paclitaxel (PTX) and doxorubicin HCl (DOX)</td>
<td>PLGA/PDLLA-PTX/PLGA-DOX (shell to core)</td>
<td>[189]</td>
</tr>
<tr>
<td></td>
<td>p53 NPs and nutlin-3a</td>
<td>PDLLA-p53 NPs (shell)/PLGA-nutlin-3a (core)</td>
<td>[188]</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin HCl (DOX) and suramin (SRM)</td>
<td>PDLLA (shell)/PLGA-DOX (core)</td>
<td>[187]</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel (PTX) and suramin (SRM)</td>
<td>Multiple configurations:</td>
<td>[175,176]</td>
</tr>
<tr>
<td>Precision particle fabrication</td>
<td>p53 NPs and doxorubicin HCl (DOX)</td>
<td>i) PLGA-SRM (shell)/PLLA-PTX (core)</td>
<td>[192,194]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ii) PLGA-PTX (shell)/PLGA-SRM (core)</td>
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<tr>
<td></td>
<td>Bovine serum albumin (BSA)</td>
<td>PDLLA (shell)/PLGA (core)</td>
<td>[191,193]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p53 NPs and DOX localized in shell and core phases, respectively PDLLA (shell)/PLGA (core)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>BSA localized in core phase.</td>
<td></td>
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</tbody>
</table>

EVA: Poly(ethylene-co-vinyl acetate).
PCL: Poly(caprolactone).
PCPH: Poly((1,6-bis-carboxyphenoxy) hexane).

![Fig. 3. Schematic illustration of circadian rhythm (the time of highest/lowest activity of the various organs) in human beings on a daily basis (Note: the position of organs in this picture has been selected randomly).](https://doi.org/10.1016/j.addr.2018.07.002)
chronobiology (i.e. biological rhythm and their mechanisms) and pharmaceutics in a single word known as “chronopharmaceutics” [209,216]. Over the past decades, the use of pulsatile DDSs is becoming more essential, particularly for the treatment of diseases in which a biological rhythm and mechanisms have been scientifically justified as summarized in (Table 5).

To achieve the desired release profiles based on the circadian rhythms of diseases or optimal treatment procedure designed by clinicians, various DDSs have been developed so far, as described in Section 4.2–4.3.

### 4.2. Osmotic micropumping devices

Osmosis is a fundamental mechanism, which adjusts the water balance necessary for cell living and regulating cellular pathways. In general, when a semipermeable membrane separates two solutions with different solute concentrations, the solvent crosses the membrane toward the concentrated solutions and causes a hydrostatic pressure difference between the two compartments [231] (Fig. 4a).

An osmotic delivery system utilizes the abovementioned concept to adjust the delivery rate of drugs at a prescribed condition. Osmotic micropump comprises of a drug reservoir and/or osmotic agent, a solvent, a semipermeable membrane, a piston, and an osmotic engine that provides a pressure difference in response to the diffusion of moisture through the membrane [232] (Fig. 4b–d). Once a crucial pressure is produced, the osmotic engine pushes the piston forward and opens the orifice for ejecting the drug. The decrease of pressure upon drug release drives the piston backward and closes the orifice. The cycle repeats frequently until the drug reservoir is empty.

The Van’t Hoff equation, based on ideal diluted mixture, is commonly used to predict the osmotic pressures. According to this theory, the solute concentration and temperature proportionally contribute to the osmotic pressure (π) (Eq. (20)):

\[ nV = i\cdot n\cdot R\cdot T \rightarrow \pi = i\cdot C\cdot R\cdot T \]

where n is the number of moles of solute (mole), V is the volume of the solution (L), C is the solute concentration (mol L\(^{-1}\)), R is the molar gas constant (8.314 J mol\(^{-1}\) K\(^{-1}\)), i stands for the mole of solute dissolved in the solution to the total moles of solute ratio. i is equal to one if the solute does not dissociate.

Eq. (22) (Table 6) describes the net flow rate of solvent across the membrane. When the chambers are sealed, the hydrostatic pressure Δp and the osmotic pressure Δπ are equal. Therefore, the net flow rate is zero. In drug delivery applications, the release of drug containing solution into the surrounding environment provides a driving force (pressure difference) between the compartments and causes dv/dt > 0 (Eq. (22)), where the mass flow of the drug release is calculated via Eq. (23). As Δπ ≫ Δp, Eqs. (22) and (23) can be combined and simplified to obtain Eq. (24) which is a fundamental equation for all types of osmotic micro-pumps shown in Fig. 4b–d.

### 4.2.1. The design of osmotic pumps

According to the interior design, osmotic micropumps are classified into four different categories (Fig. 4b–d) known as single-compartment, double-compartment, multi-compartment, and monolithic systems.

#### a) Single-compartment

In the single-compartment devices, the drug plays the role of osmotic agent and a semi-permeable layer separates it from the surrounding environment containing the solvent [233]. Therefore, the concentrations of the drug (C) and the osmotic agent are equal in Eq. (24).

The LiRIS®, Lidocaine Releasing Intravesical System, is a single-compartment osmotic pump, where the encapsulated drug (lidocaine) is also used as the osmotic agent. The LiRIS® is an implantable and biodegradable device that provides the right dosage of the drug(s) for patients suffering from interstitial cystitis/bladder pain syndrome (IC/BPS) (i.e. a painful bladder conditions) [234]. Based on a study published in 2011, 3.3 to 7.9 million women in the United States have diagnosed with IC/BPS symptoms (bladder pain, urinary urgency, frequent voiding) [235,236]. Although lidocaine is recommended as a standard treatment for IC/BPS, its short half-life and urination compromise the

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**Table 5**

Examples of medical conditions with scientifically established circadian rhythms.

<table>
<thead>
<tr>
<th>Medical conditions</th>
<th>Examples</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Many clock genes are involved in regulatory loops.</td>
<td>[204,217–220]</td>
</tr>
<tr>
<td></td>
<td>• CLOCK: BMAL1 or NPAS2:BMAL1 protein dimmers are responsible for the activation of Per and Cry (clock genes).</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clock genes alterations may happen in cancer cells.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The alterations in clock genes may cause the difference in cell cycles.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In-vivo studies revealed the animal survival rates were greater for those received combinations of 6-mercaptopurine and methotrexate in evening dosing compared to morning dosing.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The treatment of cancer through continuous infusion of 5-FU showed higher cytotoxicity side-effects compared to circadian pattern administrations at 4 a.m. and 10 a.m.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Despite negligible changes in arterial blood pressure, tumor size, and body weight, the tumor blood flow is higher in night time than that of day time.</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Pains show different circadian rhythms.</td>
<td>[221,222]</td>
</tr>
<tr>
<td></td>
<td>• In arthritis, the concentration of C-reactive protein and interleukin-6 in plasma change over time.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Brain concentration of opioid peptides such as substance P is the highest at night.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Osteoarthritis patients feel less pain in the morning than at night.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rheumatoid arthritis pain is the highest in the morning and reduces throughout the day.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Renal colic is more painful in the morning regardless of gender and presence of kidney stones.</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>Insulin is released in cyclic pattern of 8–30 min and it is further regulated by a secondary feedback signal.</td>
<td>[223]</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>The vascular reactivity and capillary resistance are higher in the morning and the risks decrease later.</td>
<td>[224-226]</td>
</tr>
<tr>
<td>disease</td>
<td>• Due to higher platelet agreeability and fibrinolytic activity during morning to noon, the frequency of sudden cardiac death and myocardial infarction is higher in that period.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Atrial arrhythmias: a higher frequency in the daytime.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Myocardial ischemia, acute myocardial infarction, and sudden cardiac death are more frequent in the morning, late afternoon, and early evening.</td>
<td></td>
</tr>
<tr>
<td>Bronchial asthma</td>
<td>Airway resistance is considerably higher at night.</td>
<td>[227,228]</td>
</tr>
<tr>
<td>Infectious</td>
<td>The elevation of body temperature due to bacterial infection is higher in the evening time.</td>
<td>[215,229,230]</td>
</tr>
<tr>
<td>diseases</td>
<td>• The endocrine glands, autonomous nervous system, and central nerve system disease exhibit complex time structures.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• In glaucoma, the intraocular pressure is generally higher between 2 and 4 a.m. and lower in the late afternoon.</td>
<td></td>
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</tbody>
</table>
efficacy of the therapy. In contrast, LiRIS® can provide the drug for an extended duration (~two weeks) to control the flare-ups of the disease. LiRIS® is a double-lumen tubular device in which an elastomeric (e.g. medical grade Polydimethylsiloxane (PDMS)) drug reservoir lumen is filled with lidocaine tablets and the other is made of a shape-memory wire. The superelastic properties of the wire accommodate the insertion of the device through a non-invasive procedure using cystoscopy or catheter. Upon insertion, the PDMS cover plays the role of the semi-permeable membrane and facilitates the release of lidocaine from an orifice made on its wall (Fig. 5a). This technology has

![Diagram](image)

**Fig. 4.** (a) Osmosis phenomena: the principles of osmotic flow and osmotic pressure (Note: The arrows illustrate flow direction across a permeable membrane); the schematic illustrations of (b) single-compartment, (c) double-compartment, and (d) multi-compartment osmotic pumps. (Note: the thickness of the arrows represents the relative volume of water which penetrates into the pumps). Redrawn from [231].

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Fundamental equations for the osmotic processes [232].</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ 1 + \alpha (v - 1) ]</td>
<td>( \alpha ): degree of dissociation; ( v ): number of ions</td>
</tr>
<tr>
<td>( \frac{dV}{dt} - K \cdot A \cdot (\alpha \Delta \pi - \Delta P) )</td>
<td>( dV/dt ): volumetric flow rate across the membrane</td>
</tr>
<tr>
<td>( \frac{dm}{dt} - \frac{dV}{dt} \cdot C )</td>
<td>( dm/dt ): drug release rate from the osmotic pump</td>
</tr>
<tr>
<td>( \frac{dm}{dt} = K \cdot A \cdot C \cdot \pi )</td>
<td>( \pi ): concentration of the drug</td>
</tr>
</tbody>
</table>

been employed for the treatment of bladder diseases such as overactive bladder and bladder cancer in pre-clinical stages [237].

In contrast, IntelliDrug™ is a single-compartment osmotic pump with a more sophisticated design compared to the LiRIS®. It was initially designed to operate in oral cavity for the controlled release of the drug to buccal mucosa. The system provides more patient compliance and eradicates the disadvantages (poor bioavailability, unpredictable plasma levels, etc.) associated with the conventional treatment method. In this device, a micro-valve and flow sensor used for monitoring the flow rate and the drug concentration in the expelled solution controls the pressure of drug solution. Consequently, the concentration of the drug on the buccal side and the duration of the treatment can be precisely controlled by the clinicians [231,238,239] (Fig. 5b). The device has also been utilized for treatment of Alzheimer’s disease [240,241] and drug addiction [242].

Double-compartment: This class of osmotic pumps was introduced by Theeuwes and Yum in 1976 [247]. In double-compartment osmotic pumps, the osmotic agent and the therapeutic formulation are stored into two compartments separated by a movable barrier, where the expansion of agent compartment causes the expelling of drug solution into the surrounding environment. As the osmotic agent and drug compartments are separated, the drug release rate is solely controlled by the osmotic properties of the agent and the pumps can be utilized for the controlled release of therapeutic solutions or suspensions with different physiochemical properties. In addition, these devices reduce the risk of hydrolytic degradation of drugs due to the absence of water and protect temperature sensitive agents from pre-mature degradation at body temperature. In contrast, the double-compartment devices have lower capacity for the
storage of drug formulations and require complicated technologies for the design and manufacturing compared to single-compartment devices [231].

The ALZET® osmotic pumps developed in 1970s are still one of the prominent examples of precise osmotic pumps [245,247]. The device was commercialized by DURECT Corp., Cupertino, CA, USA. As illustrated in Fig. 5c, the pump has a cylindrical shape made of a hydrocarbon elastomer and a cellulose ester functioned as a semi-permeable membrane. The inner layer of the cylinder is covered with an osmotic agent and the drug reservoir is placed at the center of the cylinder. A cannula is connected to the pumps to adjust the flow rate of drug solution, to minimize the pre-mature release of the drug during unpredictable conditions, and to prevent water diffusion into the drug reservoir. The pump is commercially available at three different capacities (100 μL, 200 μL, 2 mL) and the delivery rates of 0.11 μL/h–10 μL/h [245]. The pump with attached catheter can precisely and locally control the delivery of the therapeutic agent into any tissue or organs at predetermined time intervals.

Viadur® is an osmotic pump implant developed by ALZA that utilized DUROS® platform for drug delivery to prostate cancer. DUROS® consists of a titanium alloy cylinder (diameter: 4 mm; length: 45 mm) that incorporates an orifice and a semi-permeable membrane at each end [246,248]. An osmotic agent compartment is placed next to membrane and is separated from the drug reservoir by an elastomeric piston. Based on the final application of the device, the diffusion moderator and orifice are designed as a simple capillary channel or a sophisticated path (Fig. 5d). Although the implant demonstrated a zero-order delivery profile, not a pulse profile, over one year at ~120 μg/day [249], the explanation of the empty device may raise patient complaints after the treatment. The DUROS® platform has been also utilized by Intarcia Therapeutics for the long term delivery of α-interferon and exenatide against Hepatitis C and type 2 diabetes, respectively [248,250,251].

c) Multi-compartment: Multi-compartment osmotic pumps have three or more storage chamber filling with osmotic agents, the drug, and the solvent. Therefore, they can provide a constant flow rate (e.g. 1 μL/h) over a prolonged period of time (e.g. 1 year) requiring neither an external power nor body fluids [249]. The devices are able to provide a constant rate of the drug in any orientation, elevated temperature, or high-pressure conditions observed during a treatment procedure.

ACUROS is an osmotic pump (Fig. 5e) developed by Acuros GmbH (Germany), based on the osmoregulation concept [252]. The device consists of a salt chamber and hollow fiber channel that connects the salt chamber to an extrusion chamber. Upon water penetration into the hollow fiber channel and the elevation of osmotic pressure, the solvent flows to the extrusion chamber and pushes a moveable barrier forward. The movement of the barrier causes a constant flow of the drug solution and releases the drug to surrounding environment. However, to continue the process through providing a constant osmotic pressure, the connection of the hollow fiber channel and extrusion chamber is designed to be permeable to water. Therefore, there is flow of water permeating across the connection parts and into salt chamber. The release rate of the drug solution can be manipulated via adjusting the length of the hollow fiber channel placed within the water chamber. The pump can provide flow rates range from 1 μL/h to 2.0 mL/h. Due to the sufficiently high backpressure (~300 kPa), it can provide a continuous stream, independent of the injection site or blood pressure.

Over the past decades, stimuli-responsive polymers have been extensively utilized in controlled release devices where the drug is released only in the presence of an external trigger such as pH or temperature [253]. Hydroscopic polymers that show a swelling transition in the presence of a liquid can be used in osmotic pumps for fluid sampling and microdispensing in pulsatile fashion [248,254]. The polymers can be used as osmotic agents where the concentration of the polymer suspension continuously decreases due to absorption of water. Therefore, to achieve a constant drug dispensing over the predetermined period, the quantity of water provided has to be less than that the hydrogel needs for swelling to reach the equilibrium. Based on this theory, Richter et al. fabricated an osmotic pump that uses poly(N-isopropylacrylamide) (PNIPAAm) as osmotic agent [255,256]. Once the swelling agent is provided to the hydrogel actuator, the pressure increases inside the chamber where the gel pushes the self-locking piston toward a drug ampoule (i.e. drug reservoir) and causes the drug release through the outlet. The drug release rate of the pump can be adjusted through controlling the swelling behavior of the hydrogel and the stiffness of the spring that pressurizes the reservoir of the swelling agent.

d) Monolithic systems: These systems are considered as single-compartment systems in which there is no separate semipermeable membrane. The particles encapsulating drugs used as osmotic agents are distributed within a polymeric matrix, which plays the role of a semi-permeable membrane. When the water penetrates into the polymer matrix, it dissolves the particles containing drug molecules, dilutes the drug solution inside the matrix, and causes swelling, microcracks, and rupture of the particles. By increasing the pressure inside the matrix, bigger cracks may form and the drug leaks out to the surrounding environment [55,68,257–260]. Several factors including the density of encapsulated agent, osmotic activity, mechanical properties of the polymer matrix, and the dissolution and diffusion of compounds may contribute to the performance of the device [68,261].

4.3. Microparticle applications for pulsatile release

4.3.1. Monolayer microparticles

The application of microparticles with various architectures and functionalities as controlled release devices has gained considerable attention in biomedical domain, particularly in drug delivery and tissue regeneration. Depending on the ultimate application of the delivery systems, different geometries (i.e. monolayer (single-compartment), core-shell (double-compartment), multilayer (multi-compartment)) and consequently different release profiles are required. For instance, a single dose immunization is the major goal in vaccination, where a pulsatile profile can accommodate the prescribed condition. Cleland et al. [262–265] fabricated monolayer microparticles with different PLGA compositions for the delivery of HIV-1 vaccine. The antigen release profile showed a significant initial burst release followed by a lag period of several weeks. Finally, the vaccine was gradually released over 4 weeks without demonstrating pulsatile behavior (Fig. 6a).

The results of the study performed by Rosas et al. [266] revealed the effect of polymer chemistry on the release profile. Around 60% of the encapsulated SPI66 malaria vaccine released from monolayer PLGA (75:25) microparticles over 120 days after an initial burst release of ~40%. While the monolayer PLGA (50:50) microspheres could control the initial burst release (~20%) and released the vaccine continuously over 120 days. In addition to polymer properties, the differences in protein structures, charges, and molecular weights make each protein unique that require specific formulation for the encapsulation and subsequent delivery. Therefore, based on the release profiles of proteins and vaccines from different monolayer microparticles, the carriers were classified into four different categories as defined by Ye et al. [267];

i) high initial burst release plus negligible additional release.
ii) low initial burst release plus negligible additional release.

iii) high initial burst release plus a steady state release.
iv) low initial burst release plus a steady state release.

The story is almost similar for small molecule drug-loaded microparticles. Depending on the physicochemical properties of the drugs, the profile shows an initial burst release, particularly for hydrophilic agents, where the drug molecules encapsulated on or near the surface of microparticles are quickly dissolved in the surrounding medium. After the initial step, the release profiles gradually move upward in which release rates depend on carrier degradation, water penetration, and drug dissolution rate and diffusion. Overall, the results of these studies showed that monolayer microparticles with a simple geometry are not suitable to produce a pulsatile release profile.

To obtain a pulsatile release profile, several approaches (e.g., co-administration of drug delivery devices with different controlled onset release, encapsulation of smaller particles in bigger particles, preparation of core-shell microparticles) were developed over the years [268–270]. In 1994, Khoo and Thiel [271] proposed a PLGA-based delivery device for the pulsed-release of antigens. They encapsulated the antigen in a dibasic calcium phosphate coated with Eudragit S100, where a layer of PLGA/ethyl cellulose subsequently was coated on Eudragit S100 layer. Upon the hydration of the particles, PLGA degrades and forms porous shell, which facilitates the penetration of water into the inner matrix. Consequently, the dissolution of Eudragit layer causes the release of antigen. Their results confirmed the significant effects of Eudragit on the lag period, before initial release, while the agent released quickly from the particles without the Eudragit layer upon hydration. To obtain pulsed release over a prolonged period (after 1 and 75 days), both coated and uncoated particles were administered via a single injection.

Over the years, biomacromolecules (e.g., proteins, DNA, siRNA) have been extensively used as therapeutic agents for disease treatment [15,272,273]. The pharmaceutical formulation of these agents in aqueous solutions is highly desirable as it reduces destructive effects of organic solvents on the molecule structure. However, it considerably confines the applications of polymers dissolved in organic solvents used for the encapsulation of those agents. In 1999, Franssen et al. [274] introduced degradable dextran (dex-HEMA) hydrogels for the
encapsulation of IgG. The microparticles were degradable at physiological conditions (37 °C, pH 7.0), where the carbonate ester bonds of the cross-linker were hydrolyzed in aqueous solutions (Fig. 6b). They controlled the premature release of the proteins through adjusting mesh size (smaller than the hydrodynamic size of the protein) and the crosslinking density. Increasing crosslinking density could delay the onset of release for ~15 days, whereas the booster protein release was observed over a week. To further adjust the release of the agents in a pulse manner, the group designed liposome-loaded dextran microparticles (Fig. 6c). Their results confirmed the preservation of liposomes integrity during the microfabrication process and revealed the effects of initial water content, type of hydrolytically sensitive spacer present in the cross-linkers, and the degree of cross-linker substitution on the release kinetics, while it was independent of liposomes size (0.1–0.2 μm).

4.3.2. Core-shell carriers

Despite the success of monolayer microparticles in encapsulating therapeutic agents, their simple structures confine their applications where complicated release profiles are required. Therefore, the addition of a biodegradable polymer shell surrounding a polymeric drug-loaded microparticle and the formation of a core-shell structure provide an opportunity to tune the release rate (Fig. 6d). 1) The thickness of the shell layer, 2) drug distribution inside the core and shell compartments, and 3) the degradation mechanism of the polymeric materials used for the core and shell layers are the main parameters directly influence the release profiles (discussed in Section 3.4). In addition, the selection of solvent may alter the localization of the agent and its subsequent release profile. Use of a highly volatile solvent for the shell layer causes the rapid formation of a polymer-rich shell surrounding the core encapsulating the agent. Pack’s group [191] studied the release profiles of BSA from core-shell microparticles where ethyl acetate (EtAc) and dichloromethane (DCM) were used to dissolve PLA. Their study revealed the effects of solvent volatility on the fast and slow formation of the shell layer whereas the slow shell layer formation allowed the BSA solution to migrate into the shell compartment and resided near the outer surface. While the use of EtAc quickly formed a polymer-rich layer and prevent the premature migration of BSA solution. Therefore, they observed a delay at the initial stage of the release profile followed by a pulsatile release over an extended period.

4.3.3. Surface eroding carriers

Polyanhydride and poly(ortho)ester matrices, shown in Table 1, undergo degradation by surface erosion [275–277]. As the surface hydrolysis of the polymer is faster than the bulk degradation, mass is lost more rapidly from the surface than from the bulk. It has been suggested that the rate of surface degradation is more predictable in surface eroding than bulk degradation matrices. The degradation of polyanhydrides forms non-toxic diacid monomers [278]. They are also can be prepared from inexpensive resources via a single step (no purification) reaction of safe dicarboxylic acid building blocks. Polyanhydrides have been extensively used as a candidate for controlled release applications including local anesthetics, neuroactive drug delivery, brain tumors treatment, and chemotherapy [279–284].

Wuthrich et al. [276] investigated the release of lysozyme (model protein, molecular weight: 14,000) using a poly (ortho ester) matrix. They observed a pulsatile release profile dependent on polymer molecular weight and could be extended to 3–6 days. Although the protein molecules retained their activity over the release period, the 6-days release may not be sufficient for many antigens. In addition, simple surface erodable carriers with a single depot have confinements in providing multiple pulses over an extended period.

To overcome these difficulties, surface erodable materials were employed for the fabrication of complicated controlled release systems where a multilayer drug carrier that consisted of drug-containing and drug-free layer (defining the length of lag time) was employed. However, to achieve a desirable release profile [285]:

1) the drug diffusion/release from adjacent layers must be restricted.
2) the frequency of the lag phases must be controlled via drug-free layers.

One of early studies on the use of multilayered surface erosion carriers were reported by Göpferich [286] who fabricated implants consisted of a core and several coating layers with diameters of 4–6 mm. They fabricated three layered carriers of a poly[1,3 bis(carboxy phenoxypropane)-co-sebacic acid] (20:80), p(CPP-SA), core loaded with drug, surrounded by a drug-free layer of p(CPP-SA) which was coated with a PLA layer (via dip coating) used to confine the early erosion and premature release of carboxyfluorescein (CF). Finally, an erodable layer contained brilliant blue (BB) covered the construct (Fig. 6e). The polymers such as p(CPP-SA) 20:80, p(CPP-SA) 50:50, and p(CPP-SA) 85:15 were reported to erode at constant rates [287]. The release tests showed an immediate release of BB, while CF was released after 2 weeks in a pulsatile manner. Their results also indicated the significant effects of drug hydrophilicity and the molecular weight. To achieve a complete pulsatile behavior (from 4 days to 70 days), PLGA or PLA coatings were treated in silicon oil to close pore.

Another type of multi-layered devices used for pulsatile release have been proposed by Jiang and Zhu [288] for protein delivery. The device had a cylindrical shape filled with protein-loaded and isolating polyanhydride layers to provide lag-release sequences. The device was isolated with polycarbonate, while it kept open from one end. The protein was released from this device at predetermined sequences, while the duration of the pulse release and the lag time could be tailored by varying composition of the layers and their thickness. Dang et al. [289] have recently reported the local pulsatile parathyroid hormone (PTH) delivery via a biodegradable drug delivery device consisting polyanhydride and compared the repair of calvarial bone defect after pulsatile or continuous treatment in a mouse. In pulsatile delivery device, they used sebacic acid (SA), 1,3-bis (p-carboxyphenoxy) propane (CPP), and poly(ethylene glycol) (PEG) as isolating layer between two consecutive Alginate/PTH layers, and subsequently sealed it with polycaprolactone (PCL) (Fig. 6f). Using the pulsatile release device promoted bone regeneration while the continuous delivery suppressed the healing process. It also reduced the systemic side-effects compared to standard PTH injection.

5. Exogenous stimuli for on-demand release

Stimuli-responsive DDSs release their therapeutic payloads upon physical and/ or chemical changes imposed by external or internal triggers. These DDSs have been widely used in the treatment of various diseases such as diabetes [290–293], cancer [294,295], and stroke [296], where triggers [297] (e.g. light [298], heat [299], electrical [300], magnetic fields [301], and ultrasound [302]) allow to precise control of time, magnitude, duration of drug release. The external stimulus cause changes in the level of various energy sources, transform the chain dynamics and alter molecular interactions at critical onset point [303]. Moreover, the spatial control of drug exposure can be achieved through the precise control of triggers over a particular organ tissue. In this section, we only review the methods of active triggering which refers to the devices that are induced to release their payloads by a decision made by a physician, patients or predefined algorithms.

5.1. Temperature regulated release systems

Temperature elevation is the only type of stimulus that can be considered as both a physiological stimulus and an external stimulus. A key difference between tumor tissue and its surrounding healthy tissue lies in the distinct temperature gradient, which can be considered as an internal (passive) trigger. Besides, artificially applying heat at specific locations using an external source can increase blood flow and improve vasculature leakiness, which yield higher extravasation of drug/nano-
carriers. This type of triggering signal is the most studied in stimuli-responsive DDSs [304]. Over the past decades, extensive research has been done on thermo-responsive hydrogels for pulsatile release [305–307]. These exhibit volume changes, due to the alteration in the polymer hydration states with change in temperature. The threshold at which the solution changes into a gel is known as the lower critical solution temperature (LCST), whereas the temperature at which these thermo-responsive polymers become soluble is called Upper Critical Solution Temperature (UCST), and this phenomenon is called sol-gel transition. Below the LCST of the polymer, the hydrogen bonds between the water molecules and the functional groups attached to the polymer, make these polymers swollen, however, with the increase in temperature, the hydrophobic segments are strengthened and hydrogen bonds are broken due to entropy reasons and the polymer shrinks, causing gel formation [308]. In contrast, polymeric solutions may undergo sol-gel transition after reducing the temperature and form hydrogels, which will exhibit UCST behavior. Fig. 7 includes the various thermo-sensitive drug vehicles and their most commonly used shapes, thermos-responsive polymers and their release profile.

McBride et al. [312] patented a solute delivery system comprising of a thermo-sensitive cellulose gel structure loaded with a solute to be released. This gel structure is placed over a medical device. The temperature of the solute carrying gel structure is increased after positioning it near its target location. Increase in temperature of the gel, causes it to deswell, thereby releasing the solute. The temperature of the gel carrying the biologically active solutes such as proteins, genes, heparin and cisplatin, with the medical device as the substrate, can be increased be subjecting it to the body temperature or external fluid.

In contrast, thermally activated reservoir devices were developed by Santini et al. in 2003 [313]. It is an implantable biocompatible medical device comprising of a minimum of one substrate with numerous reservoirs which are filled with molecules and sealed by reservoir caps. When these reservoir caps are subjected to sufficient heat, they rupture and release the molecules.

ThermoDox developed by Celsion Corporation, uses lysolipid thermally sensitive liposome to carry doxorubicin for breast cancer and primary liver cancer [314] (Fig. 8). When subjected to radio frequency ablation, temperature at the tumor site increases and the temperature sensitive DOX-loaded liposomes changes structure at 40–45 °C, thereby releasing the drug into the targeted tumor.

5.2. Light regulated release systems

This type of pulsatile release systems can be realized using biocompatible material attached with photosensitive functional groups (derivatives of azobenzene, nitrobenzene etc.) which enable them to absorb light of a specific wavelength (Fig. 9). These materials can be tuned to absorb electromagnetic radiation especially in UV, visible and NIR [318]. When subjected to electromagnetic radiation, photo-responsive DDS can release its entire therapeutic payload all at once due to irreversible structural damage. Pulsatile release profile can be developed by applying alternating light/dark cycles, thereby causing reversible structural damage and controlled release of the encapsulated drug. Studies have shown the human body can be subjected to electromagnetic radiation having wavelengths 2500–380 nm, hence photosensitive DDS can be used for localized drug delivery especially in parts of the body, which are difficult to access [319–321]. Radiation of wavelengths below 700 nm (visible and ultrasound region) cannot penetrate >1 cm into the tissue as the major tissue chromophores such as melanin, hemoglobin, and myoglobin have strong absorption in these regions [322–325]. Hence is used to treat conditions located on or under the skin or on the external layers of some organs. Similarly, radiation above 900 nm has low tissue penetration due to light absorption by hemoglobin, and myoglobin have strong absorption in these regions.

![Fig. 7. Temperature controlled drug delivery. (a) Various thermo-sensitive carriers. (b) Chemical structures of common thermo-sensitive polymers. (c) Typical release profile of a temperature-controlled DDS. (d) Commonly used shapes of gold nanoparticles. Rysmon® TG is a temperature responsive eye drop for the treatment of glaucoma developed by Wakamoto Pharmaceutical Co., Ltd, Tokyo, Japan. It is a timolol maleate formulation based on methylcellulose (MC), polyethylene glycol and sodiumcitrate, which are used to reduce temperature-controlled DDSs.](https://doi.org/10.1016/j.addr.2018.07.002)
Fig. 8. (a) Comparative paradigms for liposomal delivery: i. Leaky tumor vessels through which non-temperature sensitive liposomes preferentially extravasate (37 °C). ii. Heat enhances vascular permeability, thereby increasing non-temperature sensitive liposome extravasation (39–40 °C). iii. Thermally mediated release from Lysophosphatidylcholine-thermosensitive liposomes. Reproduced from [315]. (b) Schematic showing how thermal ablation alone would miss the microscopic deposits of tumor cells around the tumor periphery, but how, with ThermoDoc® in the bloodstream, drug release is triggered in the 39–50 °C thermal zone. Reproduced from [315]. (c) Release profile of carboxyfluorescein (CF), gemcitabine (dFdC), doxorubicin (DOX). Reproduced from [316] with permission from DOVE Medical Press. (d) In-vivo experiments show after 1 h at 42 °C, heat sensitive formulation delivered greatest volume of DOX to the tumor. Reproduced from [317].

Fig. 9. Light responsive drug delivery: Schematic representation of light responsive drug delivery, different types of photo-responsive drug vehicles and moieties.

water [326]. However, NIR light has a wavelength of 650–900 nm and is a suitable triggering signal as the endogenous absorbers (hemoglobin, lipids and water) have the lowest absorption coefficient in the NIR region but often lack sufficient energy to cause photo-responsive chemical reactions. Recently, studies have shown it is possible to upconvert photon energy from NIR wavelength to visible/UV wavelengths (Fig. 9). Extensive research is being conducted on gold nanomaterials as they can absorb light of different wavelengths depending on their shape [327,328]. Scientists are working on gold nanorods that can absorb radiation in the NIR region to study their photothermal ablation properties and their potential for cancer treatment [298,329].

Visudyne® is a liposomal formulation containing verteporfin, a photosensitizer, developed by QLT Ophthalmics, Inc., Menlo Park, CA, U.S. for the treatment of choroidal neovascularization due to AMD, presumed ocular histoplasmosis or pathologic myopia. Visudyne® is intravenously administered for 10 min and a cold laser is used to release the encapsulated verteporfin, thereby closing the abnormal blood vessels without damaging the surrounding healthy cells in the retina (Fig. 10a).

Santini et al. developed implantable microchip device arrays containing numerous reservoirs loaded with molecules, which can conform to curved surfaces such as the eye [330]. In one embodiment, this device can be implanted onto the surface of the eye of the patient, it is then subjected to light energy such as ophthalmic laser which could pass through the reservoir caps and cause the release of the drug.

On Demand Therapeutics, Menlo Park, CA, U.S. developed a multi-reservoir implantable device to achieve ocular drug delivery to the back of the eye by using laser activation. The preclinical product consists of a biocompatible injectable rod containing multiple discrete reservoirs that are hermitically sealed to protect the stability of the drugs contained in the reservoir (Fig. 10b). This device is intravitreally injected into the periphery of the vitreous in the region of the pars plana. A Goldmann mirror and a slit lamp are used to locate the implant and concentrate the laser on the specific drug loaded reservoir, causing it to disintegrate and thereby releasing the drug into vitreous.

5.3. Magneto responsive release systems

Magnetic carriers such as magnetoliposomes, core-shell nanoparticles, and porous metallic nanocapsules used in magnetic field DDS are made by incorporating inorganic materials such as iron, cobalt, nickel etc. These materials are used for causing local hyperthermia or magnetic guidance which is achieved by focusing an extracorporeal magnetic field on the drug carrier. The magnetic field exerts a translational force together with the existing rotational torque on the drug carrier, thereby trapping it in the target site and pulling it toward the magnet [334,335]. Pulsatile release profile can be realized through the heat generated by an alternating magnetic field (AMF) due to hysteresis loss and/or Neel’s relaxation. A typical magnetic nanoparticle consists of a magnetic core coated with organic or inorganic materials and are attached to the targeting ligands by organic linkers (Fig. 11). Fig. 11 briefly describes the preparation of magnetic nanoparticles. Although magnetic field induced DDS have been studied for decades, they have numerous disadvantages such as there should be a relatively strong magnetic gradient and as soon as the drug is released from the magnetic carrier it is unresponsive to the applied magnetic field and adopts the pharmacokinetics and pharmacodynamics of the drug. This prevents precise local distribution of the drug and may cause systemic toxicity to an extent.

Hsieh et al. developed a controlled release system by incorporating magnetic steel beads in an ethylene vinyl acetate copolymer matrix using bovine serum albumin (BSA) as the payload to be released [336]. They concluded that on application of an external oscillating magnetic field, the release of BSA was increased by almost 100%. When
Fig. 11. Magnetic field-controlled drug delivery. (a) A typical magnetic nanoparticle, (b) pulsatile release profile for magnetic field controlled drug delivery, and (c) preparation of magnetic nanoparticles.

Fig. 12. (a) i. Schematic diagram of one reservoir of the polymeric microchip; ii. When subjected to a magnetic field directly above the device, the Fe$_2$O$_3$ particles jump up to fill the pores in the sealing membrane, hence the release of the drug is switched OFF; iii. When the magnetic field is applied at the bottom of the device, the Fe$_2$O$_3$ particles precipitated at the bottom of the reservoir, hence the release of the drug is switched ON. Reproduced from [338] with permission from Royal Society of Chemistry. (b) Magnetic field regulated MEMS ocular drug delivery implant. Reproduced from [342] with permission from Wiley-VCH. (c) Schematic illustration of the sandwich structure of the magnetic field actuated drug delivery device. Reproduced from [343] with permission from Elsevier.
subjected to the magnetic field, the magnet moves against the polymer causing alternating compression and tension shear [337]. This pulsatile stimulus acts as a pump, pushing out the encapsulated payload.

Pirmoradi et al. developed a magnetically regulated micro-electromechanical ocular implant that can be used to treat diabetic retinopathy (Fig. 12a) [338]. The prototype consists of a docetaxel loaded micro-reservoir, sealed by an elastic magnetic polydimethylsiloxane (PDMS) membrane, and a laser drilled opening. The device is proposed to be implanted in the posterior segment of the eye. When subjected to a magnetic gradient, the magnetic PDMS membrane deforms, releasing the contained drug.

NanoTherm therapy developed by MagForce Nanotechnologies AG is a novel treatment which involves introducing magnetic nanoparticles directly into the tumor [339]. These nanoparticles are then subjected to an alternating magnetic field causing local hyperthermia. These nanoparticles comprise of iron oxide core coated with aminosilane. They have also developed NanoPlan, a temperature simulation software which would help the physician to decide the treatment plan for NanoTherm therapy, such as estimating the treatment temperatures or magnetic field strength to be used.

Handy et al. developed a method in which single domain magnetic particles modified with a target specific ligand is contained in magnetic material composition which gets heated up when subjected to AMF [340]. In one embodiment, this method can be used to cause an apoptosis, necrosis or deactivation of the pathogen.

Ishikawa et al. developed a magnetic body and a drug delivery control device using the magnetic body [341]. The magnetic body consists of a magnet and a cover part made of a material with high magnetic permeability, attached to the edge of the magnet. Drug delivery control device consists of the magnetic body, head for supporting the magnetic body, and a drive mechanism for the head. It applies a magnetic field from the magnetic body to the specific location where the magnetic drug is administered.

Cai et al. developed a magnetically actuated biodegradable polymeric multi-reservoir microchip device for the pulsatile release of vitamin B2 and DNA by incorporating magnetic Fe3O4 particles as switch carriers and poly-(D,L-lactic acid) as the polymer substrate (Fig. 12b) [342]. When the device is subjected to the magnetic field, the magnetic Fe3O4 particles move toward the pores of the polycarbonate membrane which is filled or emptied depending on the position of the magnetic field with respect to the membrane. Huang et al. developed a similar magnetic field-controlled device by electrodepositing core-shell Fe3O4/SiO2 nanoparticles carrying anti-epileptic drug ethosuximide on an electrically conductive polyethylene terephthalate (PET) substrate (Fig. 12c) [343].

5.4. Electro-responsive release systems

Electro-responsive pulsatile release profiles can be obtained by application and removal of electrical field. The magnitude of the electric current, the interval between pulses and direction of the current flow can be precisely controlled, making electric field triggered DDS a promising candidate for innovative research in the future. Electro-responsive hydrogels are developed from polyelectrolytes, which are polymers that have many ionizable functional groups attached to its backbone chain, and hence exhibit pH responsiveness as well [344]. When subjected to an electric field, they bend or deswell depending on the shape of the gel and its position with respect to the electrodes. Iontophoresis is a non-invasive and needle free technique which involves the application a small external electrical potential gradient that drives the charged molecules across the membrane (Fig. 13).

EyeGate® II Delivery System developed by Eyegate Pharmaceutical, Inc. (Waltham, MA, US) is a device which utilizes transscleral iontophoresis for delivering optimal dosage of drug to the targeted ocular tissue (Fig. 14a). It is used to deliver EGP – 437, which is used to treat anterior uveitis, dry eye syndrome, macular edema and to control post-cataract surgery inflammation. It involves placing a small electrode on the patient’s forehead and loading the ocular applicator with the drug. The drug delivery process begins when a very small preset electric current is applied using the handheld generator to the electrode embedded

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Fig. 13. (a) Pulsatile release profile for electric field-controlled drug delivery. (b) Iontophoresis. (c) Various ultrasound triggers. (d) Schematic representation of cavitation property of microbubbles.
within the applicator. At the electrode, the current electrolyzes water molecules within the applicator converting them to either hydronium or hydroxide molecules depending on whether anodic or cathodic polarity is employed. The electro-repulsion between the newly created ions and like charged drug molecules drives the drug molecules into the targeted ocular tissue. Iontophoresis is limited to drug molecules of ionic nature, small size and low molecular weight; hence the drug should be reformulated to confer an electric charge which may affect its bioactivity.

Iontocaine is a device developed by IOMED Inc. in 1995 to deliver lignocaine by iontophoresis. However, the company stopped its production in 2005. IontoPatch is an electronic transdermal drug delivery medical device developed by Travanti Medical. It consists of a built-in battery which provides the small electric current required to carry the drugs through the skin into the subcutaneous layer. It shuts off when the preset dosage of the drug has been delivered. It is single use and disposable.

IsisIQ™ is a programmable iontophoretic patch developed by Isis Biopolymer, Providence, Rhode Island. It consists of polymer thick electrodes, a drug loaded hydrogel layer, and a permeable membrane which can selectively facilitate or prevent the transport of drugs (Fig. 14b). It has been studied for delivery of cefazolin, methylphenidate, L-Dopa and ibuprofen.

NuPathé's Zecuity is an iontophoretic transdermal system and was the first FDA-approved migraine patch. It is a battery powered patch which delivers sumatriptan by using a mild electrical current merely by pressing a button (Fig. 14c) [345]. Recently, its sales and distribution have been stopped after reports of it causing severe skin reactions such as redness, blistering etc.

The Medicines Company developed IONSYS®, a pre-programmed fentanyl delivery system to treat acute post-operative surgical pain instead of administering an opioid analgesic, by employing an imperceptible electric current [Fig. 14d] [346]. LidoSite® developed by Vyteris, is another technology that utilizes iontophoresis. It is an active transdermal patch used for topical delivery of lidocaine to act as an analgesic for venipuncture [347]. Similarly, Alza Corporation developed E-TRANS® fentanyl HCL, an electronic transdermal patch to deliver fentanyl [348].

Reversible valves prepared from polymer actuators, which are also called ‘artificial muscles’ can control the release of the contained drug from the ‘smart pill’ single reservoir implant. The implant contains polymer rings of micrometer size, which when subjected to an electric current through a conducting polymer, modulates the flow of the drug from the reservoir [349].

Macroesis is another drug delivery method developed by Buckeye Pharmaceuticals, Beachwood, Ohio that uses alternating current to deliver the therapeutic payload to the targeted tissues. Singh et al. conducted the feasibility studies for using macroesis to deliver triamcinolone acetonide and ranibizumab to ocular tissues [350]. Both iontophoresis and macroesis have numerous advantages compared to intravitreal injections. However, they concluded that macroesis is a more viable method compared to DC iontophoresis as it does not involve heat generation and the drug molecules need not be reformulated.

This technique has been used to deliver anti-fungal drugs for a condition called onychomycosis. It has shown promising results in the treatment of other conditions such as herpes labialis and catheter infections.

Uhland et al. patented a drug delivery device using electrothermal ablation [351]. The reservoir cap in the device used to contain the
reservoir contents is electrically conductive. The electrical input lead and the electrical output lead are connected to the same reservoir cap, and when subjected to an electrical potential gradient, the reservoir cap heats up and ruptures, thereby releasing the reservoir contents.

5.5. Ultrasound regulated release systems

Ultrasound is often used as an enhancer to facilitate drug permeation through biological barriers such as blood vessels, skin etc. Ultrasound can be used to attain spatiotemporal control of the drug release by regulating its tissue penetration depth by altering its duty cycles, power density, frequency, and time of exposure. Pulsatile release profiles can be realized by on/off application of ultrasound. Ultrasound can trigger the release of the encapsulated drug from the carrier by increase in temperature due to absorption of ultrasound or growth and oscillation of gaseous activities, known as cavitation. Fig. 13 illustrates the two types of cavitation effects, namely, stable cavitation and inertial cavitation.

Sonoprep is a low frequency ultrasonic skin permeation device developed by Sontra for topical lidocaine delivery and continuous transdermal glucose monitoring. It consists of a hand piece containing an ultrasonic probe, return electrode, coupling medium disposable cartridge and battery-operated power and control unit. The ultrasonic probe vibrates at 55 kHz to apply a low frequency ultrasound to the skin through the liquid coupling medium for 30 s. This causes cavitation bubbles to oscillate and disorder the lipid bilayer of the stratum corneum, forming reversible micro-channels in the skin through which drugs can be delivered or interstitial fluids can be extracted for diagnostic purposes such as glucose monitoring. The current moving through the return electrode measures the reduction in skin impedance and once the level of skin permeation is attained, the device automatically switches off. Extensive research is being conducted on using ultrasound to improve drug transport via transdermal patch [358].

So far, the basic principles associated with each of the external triggers and their recent advancements in terms of their clinical translational potential have been presented. Although the preparation of stimuli-responsive carriers has a long history, there are a few products approved by FDA (Table 7).

6. Advances in the design of drug delivery systems

In the previous sections, we have described the different technologies for fabricating drug carriers with different release profiles. Each of these technologies, however, can usually fabricate only a type of drug carrier that provide only one specific type of release profile. It is important to construct a single platform for fabricating customizable drug carriers (e.g., particles or tablets), such as for designing drug tablets that flexibly deliver any type of release profiles. In the field of personalized medicine, the medical needs of each and every individual are recognized to be different: individuals may have different biological characteristics (e.g., age, sex, size, and genome), working/living environment, dietary habits, and/or variations of a similar type of illness [359,360]. Despite knowing that the medical needs of every individual are different, it is currently still technologically challenging to be able to create a single platform for fabricating customizable carriers that can be programmed to release any type of profile. Fabrication of unique types of drug tablets of any shape and size for customizable release may be possible through many advanced methods (e.g., micromachining and photolithography); however, the challenge lies in the cost and logistics of preparing the customizable tablets for mass populations of people.

There is a need to devise a technological simple and low-cost platform that can allow the customization of drug carriers to be conducted in a typical setting (e.g., a drug store or clinic) for the drugs to be as widely accessible to the public as possible.

In this section, new technologies that enable drugs to be released with customized release profiles will be described. These technologies

Table 7
Exogenous stimuli-responsive DDSs which are FDA approved or in clinical trials.

<table>
<thead>
<tr>
<th>Triggering signal</th>
<th>Product name</th>
<th>Drug</th>
<th>Particle type/Device</th>
<th>Route of administration</th>
<th>Application/Indication</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>Rysmon® TG</td>
<td>Timolol Maleate</td>
<td>Liposome</td>
<td>Intraocular</td>
<td>Glaucoma</td>
<td>Approved in Japan</td>
</tr>
<tr>
<td></td>
<td>Thermodox</td>
<td>Doxorubicin</td>
<td>Liposome</td>
<td>Intravenous</td>
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<tr>
<td></td>
<td></td>
<td>–</td>
<td>Gold nanoshell</td>
<td>Intravenous</td>
<td>Macular degeneration</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>EGP – 437</td>
<td>Ocular device</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>Visudyne</td>
<td>Verteopin</td>
<td>Liposome</td>
<td>Intravenous</td>
<td>–</td>
<td></td>
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<tr>
<td></td>
<td>AuroLase</td>
<td>Lignocaine</td>
<td>Transdermal patch</td>
<td>–</td>
<td>Pain management</td>
<td></td>
</tr>
<tr>
<td>Electric field</td>
<td>EyeGate® II</td>
<td>Dexamethasone</td>
<td>Transdermal patch</td>
<td>–</td>
<td>Pain management</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Delivery System</td>
<td>Fentanyl</td>
<td>Transdermal device</td>
<td>–</td>
<td>Pain management</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lidocaine</td>
<td>Iron-oxide magnetic nanoparticles</td>
<td>Intratumoral</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Magnetic field</td>
<td>Iontocaine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>IontoPatch</td>
<td>–</td>
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<tr>
<td></td>
<td>IONSYS</td>
<td>–</td>
<td>–</td>
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<tr>
<td></td>
<td>Nanotherm</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Sonoprep</td>
<td>Lidocaine</td>
<td>Skin permeation device</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

a https://clinicaltrials.gov/ct2/show/NCT02536183
b https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process
c https://clinicaltrials.gov/ct2/show/NCT01679470
d https://clinicaltrials.gov/ct2/show/NCT00698425
e https://www.accessdata.fda.gov

include microchips technology, mixtures of particles with different sizes, inkjet printing technology, and 3D printing technology. Through these technologies, different types of release profiles have been demonstrated; they include constant, pulsatile, and linear.

6.1. Microchip technology

One flexible way of controlling the release of drug was proposed by Robert Langer and coworkers using microchips [361]. The microchip is a device with several small (i.e. micron-sized) reservoirs loaded with the drugs to be released (Fig. 15a). The reservoirs are sealed with a polymeric membrane for controlling the release of the drug [361]. In their study, PLGA was the material of choice for the membrane because of its long degradation time and biocompatibility. Through the use of PLGA with different molecular weights, the rate of degradation of the membrane can be tuned. Four types of PLGA were chosen in their study: PLGA4.4 (molecular weight: 4.4 kDa), PLGA11 (molecular weight: 11 kDa), PLGA28 (molecular weight: 28 kDa), and PLGA64 (molecular weight: 64 kDa). Higher molecular weight PLGA has a slower degradation rate. Therefore, by sealing the micro-reservoirs with these four types of PLGA, it is possible to release the drug with four pulses (Fig. 15b). Due to the long degradation time of PLGA, the duration of release can last as long as a few months. The polymeric microchip is proposed to be implanted into a patient’s body via surgery for providing sustained release of drug [361].

Recently, a more advanced type of microchip which allows the release of drug to be controlled wirelessly or in a programmed manner [362,363] was reported. The drug can be released immediately upon receipt of a command from an operator. In this design, the devices with many small reservoirs are sealed by an impermeable, thin metallic membrane instead of the previously mentioned polymeric membranes. This metallic membrane can be removed electrothermally via an internal electronic circuit. The images of the microchip are shown in Fig. 15c, d [362,364].

This technology is useful for patients with conditions that require frequent administration of drug (e.g., chronic diseases, or regular pain-management needs). For example, these programmable chips can change the treatment for many kinds of diseases, such as cancer, osteoporosis and multiple sclerosis. These diseases usually require patients to have a strict regimen of taking pills at regular periods of time, which can be inconvenient or impossible to maintain for certain patients (e.g., patients with disabilities). Through implanting the microchip into the patient’s body, the drug can be programmed to be released at the desired times automatically for a duration of several months; hence, the patient will be able to benefit from the release of drug without effort from their part [361,362,365].

reported in which the device was implanted in human subjects for delivering drugs in vivo.

6.2. Mixtures of uniform-sized microspheres

Methods of fabricating microspheres with uniform size had been reported for many years, using techniques such as microfluidic [366], spraying [367, 368], and emulsion [369]. Although drug-containing microspheres can only release drugs with a decreasing release profile as mentioned in the previous sections, it is possible to release drugs with customizable release profiles by mixing uniformly-sized microspheres with different size and properties [370]. Basically, the release profiles that can be achieved through mixing these microspheres is the superposition of the release profiles resulting from the individual type of microspheres. For example, Kyekyoon et al. combined uniformly-sized microspheres of different sizes to produce zeroth-order release ofnorepinephrine and piroxicam. The uniform microspheres were generated by the precision particle fabrication (PPF) method (Fig. 16a). This PPF technology breaks a stream of polymer into a continuous series of uniformly-sized droplets by an acoustic wave along the liquid jet [370]. The size of the droplets was controlled by various process parameters, such as flow rates and acoustic frequency. Different release profiles are obtained by controlling the ratio of two types of microspheres (e.g., combinations 10 and 50 μm piroxicam-containing microspheres; Fig. 16b) [370].

These results showed that mixing microspheres with uniform sizes can be a general method for controlling drug release rates [371–373]. The method, however, may depend greatly on the type of release profile desired. For example, if a complex release profile is required, it may be needed to select and mix many different types of microspheres together; a task that can be challenging to implement.

6.3. Inkjet printing technology

Conceptually, the perception of the technology that involves inkjet printing of drug is similar to that of inkjet printers commonly found in offices and homes. The printer is usually loaded with a reservoir of liquid that contains the drug. When in demand, the printer dispenses small volumes (e.g., nano-liter or pico-liter) of drug-containing liquid droplets onto a substrate [374]. Through this method, the release of the drug can be customized through various means. For example, the dosage of the drug in the droplet can be varied [375]. Another example involves using different substrates or an additional polymeric coating of different thickness on the droplets after they are dispensed on the substrates [376]. Genina et al. reported a customized oral dosage forms by combining inkjet and flexographic printing technology together. In this study, the release of drug can be tuned by the coating layer and substrates. Riboflavin sodium phosphate was used as the model drug. The tablets with different ethyl cellulose (EC) coating layer were printed onto three different substrates, including uncoated wood-free paper, triple-coated inkjet paper and double-coated sheet fed offset paper. Results showed that the release profiles were different when different substrates were used. In addition, the release can differ from decreasing to constant depending on the number of layers of the coating. (Fig. 17) [376]. Because of the various flexibility to print the drug-containing droplets, inkjet printing has been proposed to be an inexpensive method for customizing drug dosage and release profiles [377]. This method also has the advantage that it can accurately print small volumes of fluids with high throughput.

6.4. 3D printing technology

Three-dimensional (3D) printing has recently gained much of interest in the scientific community due to its versatility in fabricating customizable drug tablets, including customizable release profiles [378–380]. In addition, 3D printing has recently been approved by the Food and Drug Administration (FDA) in the United States for fabricating drug tablets [381]. One of common methods to print drug tablets involves two main steps. First, a layer of powder is spread out on a platform for printing the tablets. Subsequently, a drug-containing liquid is ejected onto the powder through the nozzle of the 3D printer; this liquid binds the powder together to form the tablet. The cycle then continues: another layer of powder is spread again on top of the previous layer of powder, followed by the ejection of the drug-containing binder until the whole 3D structure of the drug tablet is formed. In order to customize the release profiles, many parameters (e.g., the dimensions, materials, and the design of the tablets) can be changed [66]. One of the earliest designs involved constructing the geometry of the tablet as illustrated in Fig. 18a [378]. Hydroxypropyl methylcellulose (HPMC) and lactose monohydrate were used for this study. Basically, it consists of an innermost circular core surrounded by multiple concentric annular regions. The top and bottom surfaces of the tablet were coated with an impermeable layer of coating such that the tablet releases drug only via the radial direction. By fabricating each region with a specific concentration of the drug, it was possible to customize the desired type of release profile. For example, if a constant (zero-order) profile is desired, the concentration of the drug of each region is calculated. As an illustration, if a tablet consists of a circular core and four outer annular regions (Fig. 18a), the cumulative amount of drug, Q, can be calculated using

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Fig. 16. a) Scheme of the dual-nozzle precision particle fabrication (PPF) technology for producing uniformly-sized microsphere, b) In-vitro release of piroxicam from mixtures of 10-μm and 50-μm diameter PLG microspheres. Reproduced from [370] with permission from Springer Nature.

Eq. (25). In this equation, \( Q_{\text{Total}} \) is the total amount of drug in the tablet, \( k_{r,\text{region}} \) is the rate of erosion of that region, \( C_{\text{region}} \) is the concentration of drug of that region, and \( t \) refers to the time of release. Each term in the square bracket on the right side of the equation represents the release of each respective region. This equation thus illustrates that by varying the concentrations, \( C_{\text{region}} \), in the different regions from zero to a high concentration, it is possible to achieve many different types of profiles. The experimental results with different ratios (Lactose to HPMC = 70:30 and 80:20) and the theoretically predicted curves for the constant release profile is shown in Fig. 18b.

Another type of 3D printing technology is filament-based printing. This method involves first fabricating a filament that contains the drug.
and then extruding the filament through the nozzle of the printer. The tablet is formed after directly printing the material onto a planar substrate layer by layer [382]. The filament containing the drug can be prepared by melting a polymer with the drug and other excipients; alternatively, the drug can be impregnated directly into the polymeric filaments by soaking the polymer filaments in highly concentrated drug solutions. Alvaro et al. reported that the release of drug can be controlled by the geometry of the tablets (Fig. 18c). Model drug and polymer (polyvinyl alcohol, PVA) were mixed by dissolving both in an aqueous solution. The mixed liquid was then extruded through a filament extruder for preparation of the drug loaded polymer filament. The tablets with different geometries were printed using the filament-

Fig. 19. (a) Scheme of the tablet. Redrawn from [385]. (b) The images of dye-containing surface-erosing polymers of different shapes. (c) Release rates of dye-loaded tablets with different shapes. (d) Simultaneous release of two drugs, each with a different release profile. The plot on the left shows the case in which one dye released according to an increasing profile, while the other dye released according to a decreasing profile. The plot on the right shows the case in which both dyes released with pulsatile profiles. The pulsed profiles, however, are out of phase for both drugs. Reproduced from [385] with permission from Wiley-VCH.

based printer. The release profiles of tablets with different geometries are shown in Fig. 18d.

\[
\frac{Q}{Q_{\text{Total}}} = \left[1 - \left(1 - \frac{k_{\text{region}1}}{C_{\text{region}1} T_1}\right)^2\right] + \left[1 - \left(1 - \frac{k_{\text{region}2}}{C_{\text{region}2} T_2}\right)^2\right] + \left[1 - \left(1 - \frac{k_{\text{region}3}}{C_{\text{region}3} T_3}\right)^2\right] + \left[1 - \left(1 - \frac{k_{\text{region}4}}{C_{\text{region}4} T_4}\right)^2\right] + \left[1 - \left(1 - \frac{k_{\text{region}5}}{C_{\text{region}5} T_5}\right)^2\right]
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(25)

This technology, however, have several disadvantages [66,384]. Examples include clogged nozzles, low dosage of drugs, uncontrollable initial burst release, poor mechanical property, and/or complex structures that need to be printed for the different types of release profiles. It also requires complex mathematical modeling and/or iterative algorithms in order to obtain a specific release profile, and may involve the fabrication of complex (e.g., layer-by-layer) structures [378,384]. Because of the difficulties related to printing of drug tablets using the 3D printer, an alternative method was developed [385]. Instead of printing the drug tablets directly using the 3D printer, the 3D printer was used to print the molds of unique shapes. A dye and a surface-eroding polymer for controlling the release of the dye were used in this development. Briefly, the procedure involved first printing the mold of a desired shape using a 3D printer. The liquid that contained the dye and the pre-polymer liquid is then poured into the mold. After polymerization, the dye-containing polymeric matrix is extracted from the mold and coated with a layer of impermeable polymer on all but one side. The remaining void space was subsequently filled with the same surface-eroding polymer that does not contain the dye. Hence, the tablet consisted of three main components: the dye-containing polymer with the desired shape, the polymer that did not contain the dye, and the impermeable coating (Fig. 19a, b). Because the tablet was coated on all but one side, the release of the dye is only in a single direction (i.e., the uncoated side). This one-dimensional degradation of the surface-eroding polymer and the release of dye ensured that the rate of release is directly proportional to the shape of the dye-containing polymer. This approach has been demonstrated to work for a variety of release profiles, including constant, increasing, decreasing, pulsatile, and an arbitrary profile (Fig. 19c and d). These release profiles correspond directly to the shape of the dye-containing polymer. In addition to the release of a single type of drug, it was demonstrated that the concept could be extended for the release of multiple drugs. By stacking the polymers of different shapes into the tablet, it is possible to customize the release profile of each of the drug in the tablet. The rate of degradation (i.e., the total duration of release) can be tuned by varying the properties of the surface-eroding polymer. Hence, this approach allows a range of customization of the drug tablets, including the customization of release profiles, dosage (i.e., as a direct consequence of the ability to customize release profiles), duration of release, and release of multiple drugs. Further work will be needed to demonstrate that the technology can be used for drug molecules and biocompatible polymeric matrices.

7. Conclusions and perspective remarks

Many of the available delivery systems cannot provide an accurate dosage of a therapeutic compound at a target organ over a specific period. The unacceptable or sub-optimal performance of these delivery systems may be due to poor drug biodistribution (physicochemical properties), underestimating the effects of physiological barriers and surrounding tissue on biodistribution of the drug, limitations in material selections and fabrication technologies, and/or miss-matching between an optimal therapy (i.e. predefined drug administration intervals) and the release behavior of commercial DDSs. To address all abovementioned obstacles, scientists can first describe the required properties of a DDS and work backward to find out what they should do and how they should direct their research toward that goal. With the translation of a number of polymeric DDSs to clinic, the development of smarter carriers with more precise and tunable release profiles is indispensable. Therefore, based on our entire discussion in this review article, the future DDSs should have a sophisticated architecture and controllers (e.g. sensors), which can precisely regulate the release of drugs on “On-Off” manner as prescribed by clinicians.

Although the practical experience in the use of real DDSs is helpful for optimization of new devices, the mechanistic studies and mathematical modeling can greatly improve our understanding of drug release mechanisms and predict the distribution of the compound in vivo, which consequently accelerate the preparation of an optimal depot. It will be highly beneficial if scientists can theoretically predict the favorite parameters of release profiles via mathematical models or computer-based simulations. This information can then be used for evaluating the appropriateness of a payload for a DDS and further optimization of size, shape, therapeutic dose required, and in vivo biodegradation of a carrier.

In addition, the compatibility of materials with new manufacturing technologies such as 3D-printing will be a key for greater miniaturization of drug delivery devices and implants with a specific functionality. As the ultimate goal is to develop personalized DDSs comprising a closed-loop diagnosis controller for long-term drug delivery, new devices should employ biocompatible materials with long-term stability, which can continuously monitor physiological changes and release a sufficient amount of therapeutic agent. However, not only manufacturing and reproducibility is a highly challenging step, the in-vivo assessment of stimuli-responsive materials and the highly variable conditions of patients or even the site of a disease may adversely affect the standardization and commercialization of a new product.

Despite numerous challenges in full utilization of available technologies and materials in healthcare and pharmaceutical products, the drug delivery products have had a considerable impact on enhancing medical therapies and are bringing new hopes for the treatment of life-threatening diseases.

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