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Marion Paolini[a], Owen S. Fenton[a], Chandrabali Bhattacharya[a], Jason L. Andresen [a,b], Robert Langer[a,c]

a) Dr. M.S. Paolini, Dr. O.S. Fenton, Dr. C. Bhattacharya, J.L. Andresen, Prof. R. Langer

Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge MA 02142

Email: rlanger@mit.edu

b) J. L. Andresen

Department of Chemistry, Massachusetts Institute of Technology, Cambridge MA 02139

c) Prof. R. Langer

Department of Chemical Engineering, Massachusetts Institute of Technology, Cambridge, MA 02142

We would like to congratulate Professor Mauro Ferrari on the occasion of his 60th birthday for his impactful scientific career and his contributions to the field of bioengineering. Some of us were fortunate enough to have the opportunity to attend a lecture he gave at MIT in February 2018. Professor Ferrari's talk was creative and exciting, and his approach to science, management, and culture was truly inspiring. Congratulations Professor Ferrari and we wish you the happiest of birthdays.

Abstract

Developing strategies to deliver the required dose of therapeutics into target tissues and cell populations within the body is a principal aim of controlled release and drug delivery. Specifically, there is an interest in developing formulations that can achieve drug concentrations within the therapeutic window, for extended periods of time, with tunable release profiles, and with minimal complication and distress for the patient. To date, drug delivery systems have been developed to serve as depots, triggers, and carriers for therapeutics including small molecules, biologics, and cell-based therapies. Notably, the efficacy of these systems is intricately tied to the manner in which they are administered. For example, systemic and oral routes of administration are common, but both can result in rapid clearance from the organism. Towards this end, what formulation and administration route strategies are available to prolong the bioavailability of therapeutics? Here, we discuss historical and modern drug delivery systems, with the intention of exploring how properties including formulation, administration route and chemical structure influence the ability to achieve extended-release drug release profiles within the body.

Keywords

Controlled release system; drug delivery; extended release; polymer

Introduction

Worldwide prescription drug sales are forecasted to grow at an annual compound rate of 6.5 percent in the next five years and expected to reach US$1.06 trillion in 2022 (Deloitte, 2018). At the same time, and one probable cause of this growth, the population suffering from chronic diseases is also increasing. A recent study published by the RAND Corporation found that 60 percent of American adults live with at least one chronic condition, while 42 percent have more than one (Vogeli *et al.*, 2007; Buttorff, Ruder and Bauman, 2017). To treat their chronic condition(s) patients often need an increased, prolonged, and repeated intake of medication. Drug delivery systems (DDS) have been designed to alleviate tedious administration schedules and improve patient compliance. Another issue arising from the repeated intake of medication is the difficulty in staying within the specific active therapeutic window of the treatment. Indeed, if the drug concentration is too low, no therapeutic effect is observed; if a drug's concentration is too high, issues associated with toxicity can occur. Controlled release systems (CRS) have been developed to enable the administration of a drug, a small molecule or even a biologic in a single dose, with a preset release rate in the body (Figure 1), with optional triggered-release by physical, chemical or biological factors. Historically, there have been numerous attempts at creating materials capable of controlling the release of both small and large molecular weight drugs over a period of time. Early research was inspired by the diffusion of small molecular weight (< 300 g/mol) dyes through silicone tubing. Indeed, during these early studies, companies, including Alza, were formed and some of their early work focused on converting biocompatible and well-studied silicone tubing into materials that could deliver drugs including atropines, histamines, anesthetics, steroids, and antimalarial and antischistosomal agents. Following these research efforts and in tandem with the emergence of genetic engineering in the 1970s, interest in controlling the release of biologics developed. These efforts required preservation of the integrity and structure of proteins from degradation. Silicone and other traditional materials used for small molecule release, however, are impermeable to proteins given their hydrophobicity and, as a

consequence, additional materials and systems had to be designed (Hoffman, 2008; Kleiner, Wright and Wang, 2014).

CRS therapies have significant clinical and economic benefits. Such systems usually allow for reduced treatment-related toxicity, fewer medical visits (providing socioeconomic savings and improved access to health care), and also reduced treatment burden and improvement in compliance. Such systems indeed help to solve compliance issues, or even improve the feasibility of treatments. In particular, patients with chronic conditions, such as diabetes or human immunodeficiency virus (HIV) infection, could benefit from extended release systems to avoid the burden that daily intake of pills or daily injections represent. Requiring such burdensome treatments to treat these diseases often causes a lack of adherence in the treatment regimen for patients. For example, 35% to 50% of medication for chronic diseases are not taken as prescribed (Osterberg and Blaschke, 2005; Lauffenburger *et al.*, 2017). This non-adherence is due to multiple factors, including: *i.* difficulty to renew prescriptions, *ii.* inaccessibility to prescribed drugs, *iii.* inability to pay for treatment, *iv.* forgetting to take the treatment, and *iv.* psychological barriers against taking a treatment. The number of patients enduring chronic diseases is dramatically increasing, spurring the need for more convenient treatment options. Besides therapies for chronic diseases, some treatments such as contraceptive hormones or vaccines also require several repeated administrations. The need to inject vaccines at many different times cause feasibility issues in developing countries, where regular appointments with medical personnel cannot be easily guaranteed. On top of facilitating the access and the adherence to treatments for patients' population, CRS enable therapies targeted at difficult to reach areas of the body. Treatments in the joints, in the eye, or in the brain for instance can be either painful or technically difficult to realize. Implanting an CRS in these areas is a solution to prevent multiple interventions. CRS can therefore provide benefits to a vast number of patients, for many therapeutic indications.

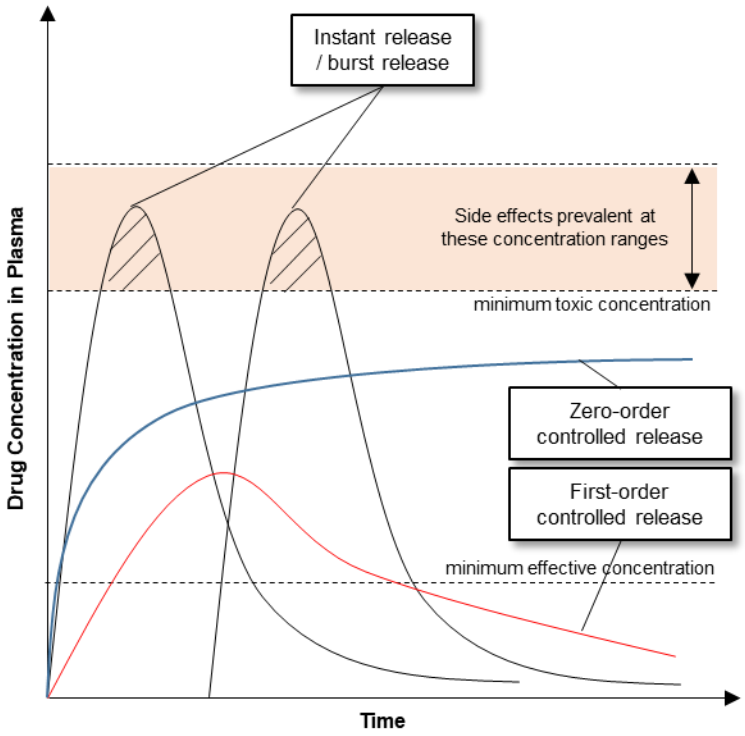

Figure 1. Extended release systems allow to keep the drug concentration in plasma stable, between the therapeutic level, or the minimum effective concentration (MEC) and the toxic level, or the minimum toxic concentration (MTC). Adapted with permission from (Fenton *et al.*, 2018)

Organic polymers in particular are an interesting option to design extended release systems because of their tunable mechanic properties, biocompatibility and biodegradability. Polymers, by definition, are molecules made of the repeat monomers. Polymers are the basis of some of the most fundamental materials of life. For example, proteins are polymers composed of chains of amino acids, and deoxyribonucleic acid (DNA) is also a polymer consisting of nucleotides. Organic polymers can also be synthetic, hydrophobic, hydrophilic, or amphiphilic, thermoplastics or thermosets. Polymers can also be tuned to have desired chemical and physical properties including molecular weight, elasticity, surface charge, and polarity can also be modified.

Here, we present (*i*) a brief summary of key theoretical rules to understand the mechanism of sustained delivery, as well as (*ii*) an overview of CRS, with triggered or passive release, and (*iii*) the limits of sustained delivery, in terms of difficulties of synthesis and biological responses.

Extended-release strategies – the chemistry behind it

Synthesis of sustained delivery devices and release mechanisms

Polymers as CRS can consist of hydrogels, i.e. hydrophilic matrices (such as hydroxypropyl methylcellulose (HPMC), sodium carboxymethylcellulose, alginates, hyaluronic acid, poly(hydroxyethyl methacrylate) or poly (HEMA), poly(ethylene glycol) (PEG), and poly(vinyl alcohol) (PVA)). Polymers can also form thermoplastics, thermosets, or hydrophobic matrices (such as polyethylene, polypropylene, ethylcellulose, polycaprolactone, poly(D, L-lactide), or poly(ethylene-co-vinyl acetate) (PEVA)).

Hydrogels are cross-linked hydrophilic polymers, which swell in water. Thermoplastics are usually high molecular weight hydrophobic polymers which soften with temperature and can be remolded upon heating. The arrangements between the polymer chains of thermoplastics are based on intermolecular forces, not chemical bonds. As a consequence, the intermolecular forces can be reversible. Thermosets, by contrast, are high molecular weight polymers, which are chemically bound together. They cannot melt and reform (Hatefi and Amsden, 2002; Sastri, 2010). Such differences in chemical and mechanical properties give the possibility to adapt to different routes of administration, to different targeted sites, and to different durations of treatment.

Polymeric matrices loaded with a drug of interest can be prepared either by mixing, by compressing, or by solvent swelling (Grassi and Grassi, 2005). Mixing or compressing are the simplest encapsulation methods: the drug is mixed with the pre-polymer or the polymer and added to the polymerization reactor, or compressed to afford a tablet. Solvent swelling techniques involve putting the pre-formed polymeric matrix in contact with a concentrated drug solution capable of swelling into the

matrix. The delicate step is to remove the solvent without disrupting the drug within the matrix. The solvent may be a supercritical fluid, dense as a liquid but viscous as gas for easy removal from the matrix.

The principles underlying extended release systems are based on physical mechanisms; they depend on the design of the polymeric release system as well as on the drug's properties. Because extended release is by definition a long process, it is fundamental to model this process theoretically as a function of time, in order to be able to choose early on the most appropriate design for the desired application.

Models focusing on drug release from systems made of non-degradable, non-swellable polymers, where the release of the drug depends solely on the diffusion of the drug out of the polymer have been developed (Fu and Kao, 2010; Siegel and Rathbone, 2012). This type of release mechanism is known as Fickian diffusion. Fickian diffusion is described by Fick's first and second laws (Equation 1). Solving Fick's second law with the relevant boundary limits is the simplest way to describe the Fickian diffusion of a drug from a polymer.

Equation 1. Fick's first and second Law

$$J = -D\nabla C \qquad (1)$$

$$\frac{\partial C}{\partial t} = D\Delta C \qquad (2)$$

Where

- *J is the "diffusion flux vector" of which the dimension is amount of substance per unit area per unit time, so it is expressed in such units as mol.m^{-2}.s^{-1}. J measures the amount of substance that will flow through a unit area during a unit time interval;*
- *D is the diffusion coefficient or diffusivity. Its dimension is area per unit time, so typical units for expressing it would be m^{2}.s^{-1};*
- *C is the concentration, of which the dimension is amount of substance per unit volume. It might be expressed in units of mol.m^{-3}.*

For such diffusion-driven drug delivery systems, the release rate of the drug will depend on the escape of the drug from the polymer, which relies on parameters such as the polymer's porosity and mesh size relative to the size of the drug, and the affinity of the drug to the matrix. Porosity depends on the nature of the polymer, the percentage of different polymers if it is a blend (e.g. L/G for PLGA), and also on the speed at which the solvent was removed (impacted by the solvent itself, and on the temperature used) (Pagels and Prud'Homme, 2015; Kasyapi, Dinesh Kumar and Bhowmick, 2017). Within the non-degradable category, a distinction is usually made between reservoirs and matrix-type systems (Figure 2) (Fung and Saltzman, 1997). Reservoirs are matrices coated with an inert material functioning as a rate-controlling membrane. As a consequence, the reservoir model is the simplest model of drug diffusion, viewed as solute released from a sphere. It assumes that drug is confined by a spherical shell of outer radius R and inner radius Ri; thus, the drug must diffuse through a layer of thickness (R−Ri) (Arifin, Lee and Wang, 2006). In this case, the solution of Fick's second law is the Zero order, or constant rate release model assuming a constant drug driving force (Equation 2), the cumulative amount of drug release is linear in time (Table 1).

Equation 2. Zero order release model.

$$M_t = M_0 + K_0 t$$

Where

- *M_t is the amount of drug released until time t, in mol;*
- *M_0 is the initial amount of drug, in mol;*
- *K_0 is the zero order release constant, in mol.s^{-1};*
- *t is the time in seconds.*

In particular, for a spherical matrix, $K_0 = 4\pi \frac{RR_i}{R-R_i} DC_i$

Where

- *R is the outer radius R and R_i is the inner radius, both in m;*

- *D is the diffusion coefficient in the polymer matrix in $m^2.s^{-1}$*
- *C is the drug concentration inside the reservoir, in $mol.m^{-3}$.*

In the case of matrix-type devices, there is no diffusion rate-controlling membrane and the drug release is dependent on a non-constant drug concentration gradient (Fickian diffusion). Consequently, release is associated with concentration gradient, diffusion distance, and the degree of swelling of the polymer, which may be null in the simplest case (Equation 1) (Fu and Kao, 2010). Fickian diffusion refers to the solute transport process in which the polymer relaxation time (t_r) is much greater than the characteristic solvent diffusion time (t_d), and vice-versa when the characteristic solvent diffusion time (t_d) is much greater than the polymer relaxation time (t_r) (Peppas and Khare, 1993; Grassi and Grassi, 2005; Fu and Kao, 2010). Mathematical models for matrix systems are often valid for DDS where the drug is assumed to be in high amount inside the non-biodegradable polymer matrix the system (constant source) and uniformly distributed. Here, we will consider dispersed drug system, meaning that the initial drug loading is higher than the solubility of the drug inside the polymer matrix ($C_0 > C_s$).

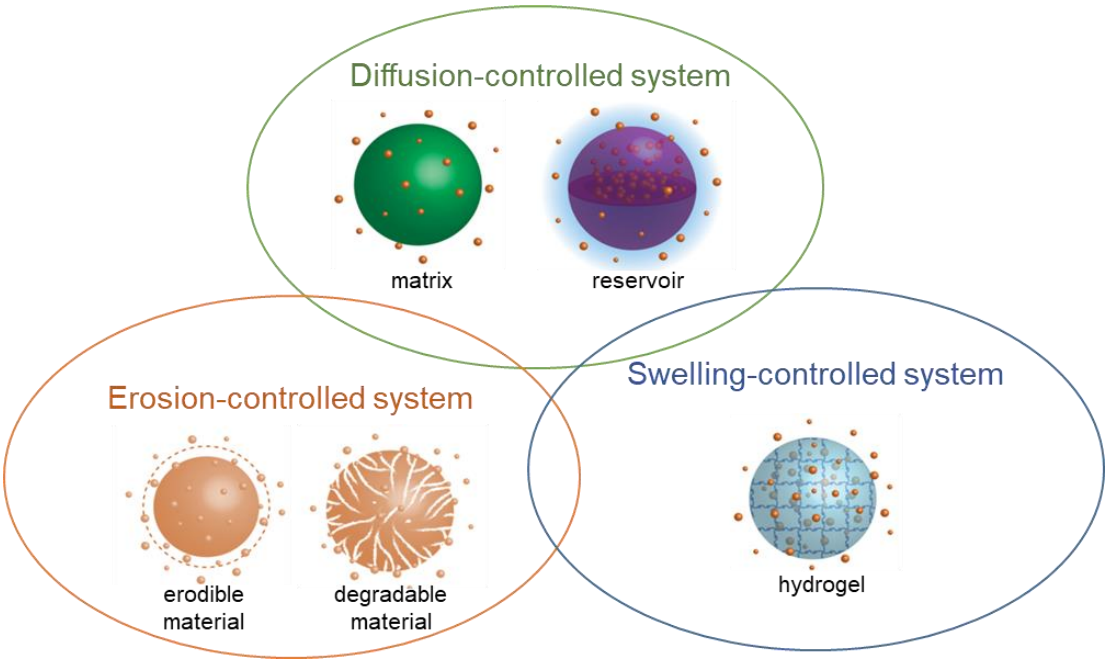

Figure 2. Schematic representation of erodible, swellable or diffusion-controlled sustained drug delivery devices. Adapted with permission from (Tibbitt, Dahlman and Langer, 2016)

The diffusion-controlled mathematical model for dispersed drug system ($C_0 > C_s$) in a planar sheet and a sphere was initiated by Higuchi. Higuchi's model to describe the diffusion based on Fick's law, which is square root time dependent (Equation 3, Table 1) (Higuchi, 1963).

Equation 3. Higuchi's equation.

$$M_t = A\sqrt{D(2C_0 - C_s)C_s t}$$

Where

- *M_t is the amount of drug released until time t, in mol;*
- *A is the release area, in m^2;*
- *D is the drug diffusion coefficient, in $m^2.s^{-1}$;*
- *C_0 is the initial drug concentration in the matrix, it is expressed in $mol.m^{-3}$;*
- *C_s is drug solubility, in $mol.m^{-3}$ as well;*
- *t is the time in seconds.*

For reservoirs, the rate of diffusion mainly relies on the permeability of the polymeric membrane. Matrices or reservoirs may be made of polymers that are erodible or biodegradable, either by passive degradation or triggered by an external stimulus. The release of the drug they encapsulate will depend on erosion of the polymer itself (Figure 2).

To model the release of a drug from a reservoir (that has a membrane) or from a degradable or erodible material, intrinsic parameters of the material must be considered. The Camera-Roda and Sarti equation (Equation 4) models non-Fickian diffusion effects on macroscopic swelling kinetics (Camera-Roda and Sarti, 1990). The authors assume that the swelling fluid flux J may be expressed as the sum of two terms: J_f, characterized by a zero relaxation time and representing the Fickian contribution to the global flux, and J_r, characterized by a non-zero relaxation time and representing the non-Fickian contribution to the global flux, respectively. Accordingly, the global flux can be expressed as:

Equation 4. Camera-Roda and Sarti equations

$$J = J_f + J_r$$

$$J_f = -D_f \times \nabla C$$

$$J_r = -D_r \times \nabla C - \tau \times \frac{\partial J_r}{\partial t}$$

Where

- *J is the total swelling fluid flux, in mol.m^{-2}.s^{-1};*
- *J_f, is the Fickian contribution to the global flux, in mol.m^{-2}.s^{-1};*
- *J_r, is the non-Fickian contribution to the global flux, in mol.m^{-2}.s^{-1};*
- *C is the swelling fluid concentration; it is expressed in such units as mol.m^{-3};*
- *τ is the relaxation time of the given polymer/swelling fluid system, in s;*
- *D_f is the diffusion coefficient relative to the Fickian flux; it would be expressed in m^2.s^{-1};*
- *D_r is the diffusion coefficient relative to the non-Fickian flux; expressed in m^2.s^{-1} as well;*
- *t is time in s.*

From these equations are derived the power law equations for modeling release kinetics. Such equations are particularly interesting in studying extended release as they represent the cumulative drug release as a function of time and are straightforward. Several commonly used power law equations for modeling release kinetics are summarized (Table 1).

Table 1. Commonly used power law equations describing the release of drugs from polymeric matrices.

Model	**Expression**	**Application**	**Time dependence**	**Ref.**
Ritger-Peppas	$\frac{M_t}{M_\infty} = Kt^n$	$n = 1/2$, Fickian diffusion (Higuchi model, see Equation 3)	$f(t^{1/2})$	(Ritger and Peppas, 1987), (Higuchi, 1963), (Serra, Doménech and Peppas, 2006)
		$n = 1$, swelling controlled, case II transport (Zero order model)	$f(t)$	

		$1/2 < n < 1$, Non-Fickian diffusion: dependent on diffusion and swelling (First order model).	$f(t^n)$	
Peppas-Sahlin	$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m}$	Non-Fickian diffusion		(Peppas and Sahlin, 1989), (Alfrey, Gurnee and Lloyd, 1966)

Where

- *M_∞ is the amount of drug released after an infinite time;*
- *K is a constant;*
- *n is the exponent characterizing the release process.*

In the case of Fickian diffusion, *n* is equal to 0.5, 0.45 and 0.43 for a thin film, a cylinder and a sphere, respectively (Siepmann and Peppas, 2001). When *n* exceeds these thresholds, non-Fickian release occurs.

Release from most polymers follows Fickian diffusion and the release rate falls as the concentration of drug in the polymer decreases. However, a zero-order release rate (i.e. a release rate that is constant over time) is desired for drug delivery applications. This is the reason why a lot of sustained release delivery systems are coated with a non-permeable membrane. In the case of hydrogels, prolonged zero-order release kinetics may be obtained if the reduction in the driving force for diffusion matches the decrease in the resistance to diffusion due to the polymer degradation (Pagels and Prud'Homme, 2015).

Triggered drug release

Both small and large molecules have been studied for sustained release application by exploiting the fact that the material properties of the delivery system influence drug diffusion (Figure 2). Matrix and reservoir diffusion are united by the fact that the user commonly has only passive control over drug elution (Peppas *et al.*, 1980; Kim, Bae and Okano, 1992; Peppas and Wright, 1998; Freiberg and Zhu,

2004). Indeed, upon impregnation of the material, the drug will release without a trigger. Accordingly, some challenges associated with these systems include burst release phenomena (wherein initial implantation would result in large amounts of the drug being released into the surroundings) and limited tunability of the sustained release profile (Lee, 1985; Gupta, Vermani and Garg, 2002; Mullarney, Seery and Weiss, 2006). As an alternative, the concept behind triggered drug release is to still use a single administration of the therapeutic, but to control the drug's release using chemical, biological or physical cues (Jeong and Gutowska, 2002; De Las Heras Alarcón, Pennadam and Alexander, 2005; Hoare and Kohane, 2008; Liu and Urban, 2010; Aghabegi Moghanjoughi, Khoshnevis and Zarrabi, 2016).

Toward this end, interest arose in using stimuli responsive materials to control and extend the release of drugs, while also avoiding issues associated with burst release (Okano *et al.*, 1990; Huang and Brazel, 2001; Min *et al.*, 2010). Stimuli responsive materials represent promising platforms for controlled drug delivery and biomaterials application. By definition, stimuli responsive materials are those whose physical properties can be altered upon exposure to specific cues. These cues can include chemical signals (in the form of small molecules) (Bajpai *et al.*, 2008; Dong *et al.*, 2011; Lee *et al.*, 2011; Yan *et al.*, 2012; Schattling, Jochum and Theato, 2014), pH (Peppas *et al.*, 1999; Uhrich *et al.*, 1999; Stuart *et al.*, 2010; Gao *et al.*, 2012), or alterations in chemical gradients including ion concentration (Sui, King and Murphy, 2008)), biological signals (including proteins, enzymes, and antibodies) (Fischel-Ghodsian *et al.*, 1988; Sui, King and Murphy, 2008; Bawa *et al.*, 2009; Maitz *et al.*, 2013), and physical signals (including photonic (Lee *et al.*, 2011; Azagarsamy *et al.*, 2012; Han, Tong and Zhao, 2012; Yan *et al.*, 2012), electronic (Bawa *et al.*, 2009), magnetic (Kost, Wolfrum and Langer, 1987; Satarkar and Zach Hilt, 2008; Bawa *et al.*, 2009), and ultrasonic (Mitragotri, Blankschtein and Langer, 1995; Bawa *et al.*, 2009)), amongst others.

From a molecular design standpoint, stimuli responsive materials can be engineered from the bottom up to afford differential architectures of responsive polymers (Figure 3). For example, some systems consist of block copolymers linked by degradable functional groups. Upon exposure to a specific

cue, the degradable linkage can break to liberate the individual blocks. By contrast, other systems can have therapeutics appended directly to the main polymer chain, and these drugs can be release into the surroundings. Still other DDS consist of polymer chains synthesized from responsive monomers. Finally, cross-linking bonds can also be incorporated to join together with polymers to form responsive networks (Manouras and Vamvakaki, 2017). Each of these architectural paradigms has been exploited in drug delivery research, highlighting the importance of unifying chemistry and materials design for biomaterials science. Overall release can therefore be extended through administration of a DDS with release occurring once or multiple times upon exposure to the designed signal. These responsive polymer architectures can be manipulated for triggered drug release ability and certain systems have been further engineered to utilize these cues for an extended release compared to a bolus administration of various drugs.

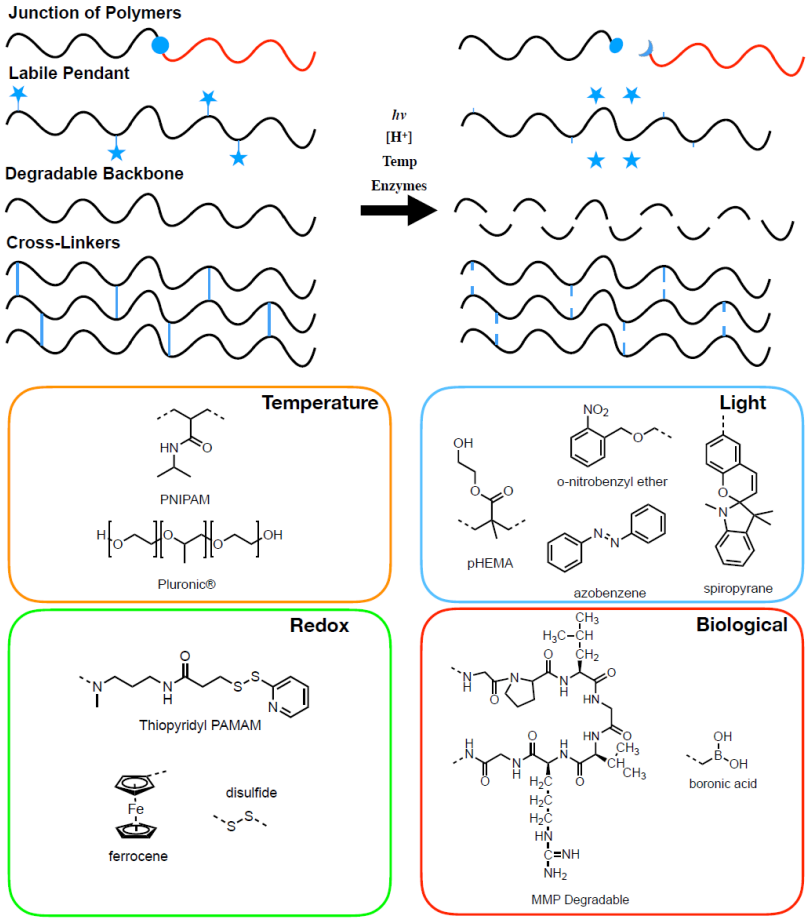

Figure 3. Triggered extended release strategies. (A) Design of triggered release polymers: release mechanism after stimulus. (B) Selection of important polymers and functional groups exhibiting stimuli responsive behavior. Adapted with permission from (Schattling, Jochum and Theato, 2014; Manouras and Vamvakaki, 2017).

Chemical

To date, chemical cues are commonly employed to generate smart materials capable of extended release of drugs *in vitro* and *in vivo*. Chemically-responsive materials are those that can change in property (whether shape, stiffness, rheological property, chemical composition, molecular weight, etc.) upon interacting with a molecule in the environment (Culver, Clegg and Peppas, 2017). Chemical cues bear a number of strengths in creating responsive materials. For example, both nature and synthetic chemists have created materials replete with analyte-specific responsive functional groups (Bajpai *et al.*, 2008; Bawa *et al.*, 2009; Schattling, Jochum and Theato, 2014). Towards that end, polymers that are either synthesized from responsive monomers, or are accessed using post-polymerization modification strategies, have been exploited for the development of extended release signals (Huang *et al.*, 2000; Bawa *et al.*, 2009; Wang *et al.*, 2009; Mura, Nicolas and Couvreur, 2013; Yesilyurt *et al.*, 2016).

From a strategic standpoint, chemically-responsive materials have a number of advantages. First, small molecules can be both implemented and studied with relative ease. Indeed, molecular characterization techniques including liquid chromatography mass spectrometry, nuclear magnetic resonance, infrared spectrometry, and gas chromatography ensure that we have chemical cues of precise and defined molecular structure. Nevertheless, chemical cues can be difficult to work with because of issues including diffusion, local concentration gradients, and imperfect chemical reactivity. For example, for an implanted material to be responsive to a small molecule, it is dependent both on the kinetics and thermodynamics of binding to the responsive functional group of interest (Hoffman and Stayton, 2007). Therefore, many current materials were developed to target a naturally occurring cue that demonstrates elevated levels as a cause or symptom of a disease, such as blood glucose concentration in diabetes or glutathione levels both intracellularly and in certain cancers (Huang *et al.*, 2000; Bawa *et al.*, 2009; Mura,

Nicolas and Couvreur, 2013). Many systems designed for insulin release have taken advantage of glucose-sensitive polymers containing terminal functional groups like concanavalin A (conA) or phenylboronic acid (PBA) that form reversible bonds with glucose, leading to release of insulin from the matrix (Wang *et al.*, 2009; Lu *et al.*, 2016; Yesilyurt *et al.*, 2016).

pH

In pH-mediated release systems, a local change in pH can cause both chemical and mechanical changes in the polymeric material. Decreased pH can lead to the cleavage of acid-labile linkers connecting the polymer network or directly induce the cleavage of a covalently-bonded pendant drug molecule (Mura, Nicolas and Couvreur, 2013; Lu *et al.*, 2016). Acid-degradable linkers or polymer chains are frequently utilized in hydrogel formation, where the cleavage of these bonds will lead to further swelling or degradation of the hydrogel, effectively triggering increased release kinetics of the encapsulated drug (Peppas *et al.*, 1999; Schmaljohann, 2006). These changes in pH can occur naturally in the surroundings of the polymeric system as they progress through the digestive system or encounter an acidic tumor microenvironment. Alternatively, pH changes can be produced internally through encapsulated enzymes (Hasan *et al.*, 2007; Dai, Ravi and Tam, 2008; Min *et al.*, 2010). One commonly used enzymatic trigger is glucose oxidase, catalyzing the conversion of glucose into gluconic acid, decreasing pH to enhance the solubility of lysine-modified insulin as well as to trigger the swelling or collapse of hydrogels (Fischel-Ghodsian *et al.*, 1988; Podual, Doyle and Peppas, 2000b, 2000a; Z. Gu *et al.*, 2013). A nanonetwork of chitosan and alginate coated dextran particles impregnated with glucose oxidase and catalase was able to achieve extended release of insulin to induce glycemic control for two weeks in diabetic mouse models (Z. Gu *et al.*, 2013). One FDA approved polymer used as a pH-sensitive release trigger is Eudragit®, a taste-masking agent composed of methacrylic acid and cellulose esters (Hoy and Roche, 1993). Eudragit® coatings of polymeric particles can be used for oral medicines to prevent burst release, as the polymer is unaffected by the neutral pH of saliva whereas degradation occurs upon entering the highly acidic gastric fluid (Moustafine, Zaharov and Kemenova, 2006; Hasan *et al.*,

2007). Multiple delivery vehicles triggered by the slightly acidic conditions surrounding tumors have been explored to release a payload of doxorubicin (DOX) from polymeric particles (Car *et al.*, 2014; Liu *et al.*, 2016; Xu *et al.*, 2016). A DOX-prodrug nanoparticle utilizing a pH-sensitive hydrazone linker to connect DOX to poly(L-glutamic acid) for targeted release to tumors was detectable up to one week after administration in mouse models (Xu *et al.*, 2016).

Redox

Some DDS incorporate redox sensitive functional groups (ex. disulfides, ferrocenes, etc). These functional groups can respond to changes in redox potential which can alter the overarching polymeric structure. Naturally occurring reducing agents, such as glutathione, or the presence of reactive oxygen species, such as hydrogen peroxide, can be used to trigger the release of encapsulated or covalently modified drugs from polymeric carriers(Staff *et al.*, 2012). One study explored the use of poly(amidoamine) (PAMAM) with thiopyridyl terminal groups to form disulfide crosslinks with an 8-armed thiol-terminated PEG subsequently loaded with antibiotics where the release was monitored over 72 hours *in vivo* in the vaginal cavity of pregnant guinea pigs (Navath *et al.*, 2011). Exposure to glutathione in the vaginal secretions caused a reductive cleavage of the disulfide crosslinks leading to degradation of the gel and release of amoxicillin. In another example, oxidative hydrogen peroxide was used as a trigger to initiate the production of carbon dioxide bubbles through an iron-mediated oxidation of ethanol. These bubbles ultimately could disrupt the barrier of PLGA microspheres, allowing the release of encapsulated dexamethasone sodium phosphate over 48 hours (Chung *et al.*, 2015).

Biological

Materials that are biologically responsive, that is, responsive to proteins or enzymes, have also been posited and explored given their high specificity. These systems overcome some of the limitations of small molecules – namely, enzymes are extremely specific, can be created using genetic engineering approaches, and can also be administered into the body or are found endogenously (Bajpai *et al.*, 2008;

Dai, Ravi and Tam, 2008; S. Zhang *et al.*, 2015; Lu *et al.*, 2016). Nevertheless, the stability, cost, and long circulation times of many antibodies and enzymes can limit their application. Chemical sequences degradable by esterases or peptides degradable by matrix metalloproteinases (MMPs) are often incorporated into polymeric materials for eventual biological cleavage and release (Dong *et al.*, 2010; Zhu, Kate and Torchilin, 2012; G. Gu *et al.*, 2013; Amer and Bryant, 2016). These enzymatic triggers can help to delay the release of therapeutics from hydrogels or polymeric vesicles compared to a bolus injection of the free drug. SDS may include multi-step triggers, such as the release of DOX-loaded quantum dots from a gelatin-based nanoparticle degraded by gelatinases (Wong *et al.*, 2011). Certain SDS take advantage of overexpression or changes in activity levels of enzymes that occur in certain disease sates. Injection of a hyaluronic acid-dextran sulphate network containing MMP-cleavable peptide sequences was impregnated with an MMP-inhibitor TIMP3 thereby reducing the activity levels of overexpressed MMPs caused by myocardial infarction in a pig model. After 14 days, inhibitor levels were still detectable in plasma and the activity of the MMP in the myocardial infarction site was significantly decreased compared to control animals (Purcell *et al.*, 2014). Other polymeric materials display a binding affinity for circulating biological molecules, including antibodies and glucose, thereby triggering a change in the binding preference or structure of the polymeric system. A poly(ethylene-co-vinyl acetate) chain functionalized with isocyanate groups to conjugate different haptens has been developed, initiating future antibody production causing competitive binding that could lead to the release of a narcotic antagonist from the polymer (Pitt *et al.*, 1985).

Some systems are capable of interacting with receptors and antigens present on certain cell membranes. Such interactions allow both targeting a specific cell population as well as triggering release in a certain environment, enabling extended release of therapeutics through selective release conditions (Y. Zhang *et al.*, 2015). A “virus-mimetic” nanoparticle comprised of poly(L-histidine-co-phenyalanine) and PEG-linked bovine serum albumin presenting folate ligands was shown to focus release of doxorubicin to the slightly acidic tumor microenvironment upon binding to folate receptors overexpressed

in an ovarian carcinoma model (Lee *et al.*, 2008). Certain targeting approaches that deliver to specific antigen-presenting cells are currently being explored in clinical trials. The safety and efficacy of a product composed of PEG-PLA polymeric nanoparticles modified with a small molecule ligand found to bind to the prostate specific membrane antigen (PSMA) is being investigated in order to target and deliver docetaxel to tumors that overexpress PSMA (Hrkach *et al.*, 2012). Though the parent company recently went bankrupt and was purchased by Pfizer, a recent Phase II clinical trial indicated that BIND-014, a product utilizing this targeted release technology may be beneficial in treating patients with metastatic cancers that present circulating tumor cells (Autio *et al.*, 2018).

Photodegradable

Light represents one of the most commonly employed cues used to trigger responsive materials. The advantages of using light as a trigger are myriad; for example, light can offer exquisite spatio-temporal control over reactive substrates – this is because the response of a polymer can be controlled using the wavelength, the intensity, and the duration of exposure to the light (Azagarsamy *et al.*, 2012; Han, Tong and Zhao, 2012; Yan *et al.*, 2012). Moreover, light-based systems are often relatively affordable – indeed, lamps can be purchased with removable bulbs of different wavelength, and the versatility of these systems is one reason why light-based systems have become particularly pervasive in the scientific literature. Despite these advantages, light-based systems can also suffer from a variety of disadvantages. Some of these limitations include inability to penetrate deep enough into the system, uneven response across/throughout the surface, and inaccessibility of some wavelengths necessary for photoresponsivity (Tibbitt *et al.*, 2012).

To create each of these architectures, specific chemical functional groups must be incorporated into each polymer to imbue photo-responsivity into the network. In choosing a photoresponsive functional group, several parameters must be considered. First, the wavelength of absorbance must be carefully selected – in many cases, it can be ideal to have functional groups that can selectively absorb the wavelength of absorbance. In this way, side processes including unwanted degradation of the polymer can

be circumvented (Klinger and Landfester, 2011). Additionally, the intensity of the light source must be considered which can affect the kinetics of degradation of the system. The intensity of the light source also has a delicate balance with the quantum yield of the functional group. Quantum yield is defined as the number of times a specific event occurs per photon absorbed by the system (Zhang *et al.*, 2008). This property is functional group specific, and accordingly should be considered in deciding upon the polymer substrate design. Several photoactive functional group combinations have been incorporated into polymeric controlled release systems. These functional groups include, but are not limited to ortho-nitrobenzyl ethers, azobenzene, spiropyrans, spirooxazines, diarylethene, cinnamic esters, and coumarins, amongst others (Figure 3) (Mura, Nicolas and Couvreur, 2013; Lee *et al.*, 2014; Kamaly *et al.*, 2016; Liu *et al.*, 2016).

To date, several light responsive materials have been utilized for controlled release applications. These gels remain in place upon implantation or injection and can be triggered at a desired time to release their payload. Some of these systems are even capable of being triggered multiple times, extending the release of drugs compared to single administrations. Specifically, microparticles containing a photocleavable ortho-nitrobenzyl ether linker have been explored for the triggered release of proteins (Azagarsamy *et al.*, 2012). These systems have been engineered to release growth factors from a PEG-diphotodegradable-diacrylate/PEG-thiol based network *in vitro* upon exposure to single photon UV light or multiphoton light at higher wavelengths (Tibbitt *et al.*, 2012). Other DDS have used multiresponsive polymers sensitive to both pH and light triggers. One microgel composed of a poly(2-hydroxyethyl)methacrylate (pHEMA) and methacrylic acid demonstrated reversible swelling behavior that led to changes in release rates of myoglobin *in vitro* before irradiation with UV light led to complete release and degradation of the gel through the incorporation ortho-nitrobenzyl ether linkers (Klinger and Landfester, 2011). Another study explored the conjugation of different moieties to an ortho-nitrobenzyl ether-PEG-methacrylate linker in order to conjugate growth factors, specific peptides or model proteins into a hydrogel scaffold for triggered UV initiated release (Griffin *et al.*, 2013).

Magnetic

Magneto-responsive materials are an emerging material platform that is characterized by their ability to interact with externally applied magnetic fields. Magnetic responsive materials are becoming considerably more attractive with time for several reasons. First, magnetic responsive materials bear considerable amounts of orthogonality with respect to other more traditionally employed triggers. For example, unlike chemical or biological cues which are diffusion dependent, and unlike other physical cues, including light, which are exposure dependent and can have overlap with other UV-absorbing functionalities, magnetic responsive materials are quite specific (Li and Keller, 2009; Esser-Kahn *et al.*, 2011; Mura, Nicolas and Couvreur, 2013). What also makes magnetic responsive materials so attractive is that they can be multimodal in nature. For example, magnetic cues can be used for controlled release applications to release therapeutics with spatial and temporal control (Ling *et al.*, 2014); additionally, these materials can be used for imaging purposes which provides an additional handle for achieving drug delivery goals. Despite these advantages, magnetic responsive materials can be quite challenging to implement within the drug delivery field. There are two predominant driving factors behind this difficulty which are in part tied to one another: the first is magnetic strength, and the second is cost. For example, to implement function, a magnetic field must be strong enough to interact with the magneto-responsive material. This can be challenging when devices are implanted into the body, or are located in difficult to reach areas that may be too far outside of the magnetic field. Although clinically we have access to strong magnets, particularly in the form of MR-based technologies, these instruments are extremely expensive and can only be operated by trained professionals, both of which limits their function for traditional materials.

From a synthesis and design standpoint, several classes of magnetic-responsive materials have been investigated. Magnetic gels are hydrogels that can respond to alterations in magnetic field. Recent efforts have demonstrated that hydrogels can be made magneto-responsive by either covalent modification of magnetic-responsive functionality into the polymer chains, or, more simply, by direct

mixing of magnetic particles including iron or cobalt into the hydrogel system (Satarkar and Zach Hilt, 2008). To date, these materials have found widespread use in drug delivery, including for the delivery of cancer therapeutics such as doxorubicin (Widder *et al.*, 1981; Sanson *et al.*, 2011). Another study demonstrated magnetic control of insulin release from an ethylene-vinyl acetate copolymer depot containing a small magnet that led to triggered decreases in blood glucose over a 50 day study in diabetic mouse models (Kost, Wolfrum and Langer, 1987). It is also important to note that from an atomic standpoint, the majority of these materials are imbued with their properties by combining iron, ferrocene, cobalt, modified PEGs, or folates – effectively, many of these processes are most commonly governed by free radical molecules with unequal spin quantum numbers and a large density of crosslinks, ultimately allowing for large net quantum values for either ferromagnetic or anti-ferromagnetic exchange coupling between the molecules. The administration of a constant low voltage as an electronic release trigger has also been previously explored (Yan *et al.*, 2010; Kim, Jeong and Park, 2011).

Temperature

The solubility and mechanical properties of polymeric networks are affected by changes in temperature, allowing for systems to be developed with thermoresponsive release. Some polymers demonstrate a lower critical solution temperature (LCST), above which the polymers can undergo a phase transition from a solid gel to a liquid solution where the polymer will become miscible or the network will degrade (Zhang *et al.*, 2008). The desired increase in temperature can be achieved through the placement of hot water bottles, a heating blanket, or a directed heat lamp for systems designed for subcutaneous delivery. The LCST of the polymer network can be manipulated through combinations of different polymer backbones as well as through the addition of hydrophobic groups. For example, a study varying the amount of acrylamide in a poly(N-isopropylacrylamide-co-acrylamide) (PNIPA-co-AAm) demonstrated different LCST properties resulting in varying levels of encapsulation and release of near-infrared dyes for *in vivo* imaging studies (Zhang *et al.*, 2008).

Polymeric hydrogels can therefore be designed for drug delivery and extended release with the physiological temperature of 37ºC in mind, or systems can be tuned to promote release at slightly higher temperature as found in the tumor microenvironment. A polymeric hydrogel consisting of acrylamide-co-acrylic acid was designed with an upper critical solution temperature (UCST) slightly above 37ºC to promote the swelling of the gel and release of cisplatin (Shirakura *et al.*, 2014). Another system utilized nanoparticles comprised of poly{γ-2-[2-(2-methoxyethoxy)-ethoxy]ethoxy-ε-caprolactone}-b-poly(γ-octyloxy-ε-caprolactone) (PMEEECL-b-POCTCL) that were engineered to achieve an LCST of 38ºC, resulting in the controlled *in vitro* release of doxorubicin and a fluorescent molecule with potential for release over 48 hours (Cheng *et al.*, 2012). A Pluronic® (poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide)) based gel loaded with vascular endothelial growth factor (VEGF)-laden nanoparticles demonstrated different LCST properties depending on the weight percentage of Pluronic® used. These gels were further encapsulated in a porcine bladder acellular matrix and the VEGF release was extended to 60 days *in vitro* (Geng *et al.*, 2011).

Visudyne, a liposomal non-polymeric nanomedicine for photodynamic therapy, is the only nanomedicine with stimuli-responsive nanoplatform concept approved by Food and Drug Administration (FDA). Other stimuli-responsive drug delivery systems, including polymeric ones, are still at clinical stage. The potential of these promising clinical carriers for successful clinical trials and for market approval relies on the simplicity of their formulation. However, in order to obtain "smart" properties, most of stimuli-responsive drug delivery systems in development were designed with sophisticated features, difficult to scale up for industrial production. Therefore, the design simplicity is still one of the key properties for successful drug carrier translation (Liu *et al.*, 2016).

Formulation of polymers as CRS: implants, gels and particles.

Polymers can be used to deliver therapeutics over a long period in different forms. Implants, either pure polymeric implants, or ones coated with polymers can be placed in the body for prolonged therapeutics

release. Hydrogels, may be injected or implanted to sustain the administration of therapeutics. Lastly, the encapsulation of therapeutics within microparticles or nanoparticles, administered in gels or as depots, may prolong their release.

Achieving the sustained delivery of therapeutics with polymeric implants

Implants are man-made medical devices placed in the body to replace or support a biological structure. They may be hard implants, made of metal or ceramic, coated with polymers, entirely polymeric implants, or even cells artificially put in a polymeric envelope (Sabel *et al.*, 1990; Elstad and Fowers, 2009; Gershanik and Jenner, 2012; Weaver *et al.*, 2014; Cho and Kwon, 2014; Appel *et al.*, 2015; Blanco, Shen and Ferrari, 2015; Vegas *et al.*, 2016; Bellinger *et al.*, 2016; Kamaly *et al.*, 2016; Ball, Bajaj and Whitehead, 2018; Tzeng *et al.*, 2018; Fenton *et al.*, 2018).

Routes of administration of sustained delivery implants

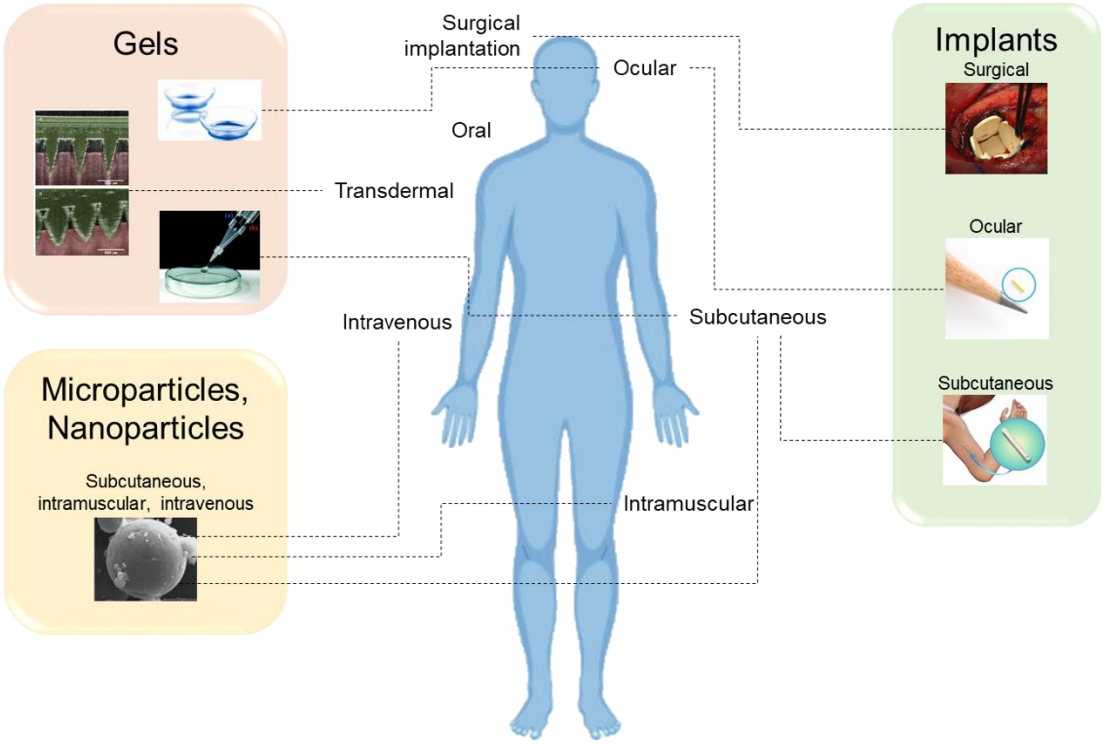

Figure 4. Example of routes of administration by type of sustained release polymeric device. Adapted with permission from (Lesniak and Brem, 2004; Park *et al.*, 2011; Caffarel-Salvador *et al.*, 2015; Lee, Yun and Park, 2016; Fenton *et al.*, 2018).

Implants can be placed close to the zone to be treated, or in a more accessible area for practical administration or explantation (Sussman *et al.*, 2014). Implants can be subcutaneous, intraperitoneal, oral, intracranial, intraocular, mucosal, or transdermal with microneedles (Figure 4). One issue with oral administration is that it encounters the hepatic first-pass metabolism. Hepatic first-pass metabolism reduces the effective dose of drug by metabolizing it rapidly and can have harmful effects on the liver (Pond and Tozer, 1984; Lalka, Griffith and Cronenberger, 1993). Even intravenously injected drugs tend to be catabolized very rapidly, eliminated from circulation by the liver or the kidneys (Paolini *et al.*, 2017; Germain *et al.*, 2018). Placed subcutaneously, DDS may be injected as hard implants or in the form of depots. A depot consists in the deposition of a drug in a localized volume, from which the drug is gradually absorbed by surrounding tissue. Depot injections are usually either solid (hydrophobic drug aggregates) or oil-based. Although subcutaneous administration results in high dose variations from one injection to the other and may cause pain, it is still a very common route for most extended-release depots (Kim, Park and Lee, 2017).

Approved implants for sustained delivery

Table 2. Examples of approved polymeric implants allowing the sustained delivery of therapeutics.

Brand	**Company**	**FDA Approval**	**Active Pharmaceutical Ingredient (API)**	**Composition of the implant**	**Indication**	**Dosing (months)**
Jadelle®	Population Council / Bayer	1996	levonorgestrel	silicone	contraception	60
Zoladex®	AstraZeneca	1998	goserelin	poly(lactic-co-glycolic acid)	Prostate cancer, breast cancer, endometriosis	1 or 3
Eligard	QLT Inc.	2002	leuprolide	poly(lactic-co-	Prostate cancer	1, 3, 4 or

				glycolic acid)		6
Gliadel®	Eisai inc.	2003	carmustine	polyanhydride	glioma and glioblastoma	N/A
Cypher™	Cordis, J&J	2003	sirolimus	poly(butyl methacrylate) (PBMA)	coronary stent	N/A
Taxus Express	Boston Scientific	2004	paclitaxel	poly (styrene-bisobutylene-b-styrene) (SIBS)	coronary stent	N/A
Implanon®, Nexplanon®	Organon / Merck	2006	etonogestrel	ethylene vinyl acetate	contraception	36
Ozurdex®	Allergan	2009	dexamethasone	poly(lactic-co-glycolic acid)	diabetic macular edema, uveitis	6
Propel™	Intersect ENT	2012	mometasone furoate	poly(lactic-co-glycolic acid)	Post-surgical inflammation	N/A
Iluvien®	pSivida Corp / Alimera Sciences	2014	fluocinole acetonide	Polyimide and polyvinyl alcohol	diabetic macular edema	36
Probuphine®	Titan Pharmaceuticals	2016	buprenorphine	ethylene vinyl acetate (EVA)	opioid dependence	6

Norplant® was the first extended-release polymeric implant approved by the Food and Drug Administration (FDA) in the US, in 1990. It was discontinued in the early 2000s and replaced by the Jadelle® (Norplant® II) implant (Table 2) consisting of two rods of a dimethylsiloxane /

methylvinylsiloxane copolymer core enclosed in thin-walled silicone tubing (Diaz *et al.*, 1982; Segal, 1987). The original Norplant consisted of a set of six rods. Each rod is a cylindrical reservoir, placed subcutaneously, releasing levonorgestrel over 5 years. The outer membrane, as well as the cylindrical shape enable a zero-order release of the hormone. Other birth control implants were later approved by the FDA, such as the etonogestrel implants Implanon and Nexplanon (Blumenthal, Gemzell-Danielsson and Marintcheva-Petrova, 2008). Implanon and Nexplanon are made of ethylene vinyl acetate copolymer, a nonabsorbable material, and Nexplanon contains 15 mg of barium sulfate. Nexplanon was originally marketed under the brand name Implanon, but was subsequently modified and marketed as Nexplanon/Implanon NXT. The presence of barium sulfate in Nexplanon makes it visible via X-ray, differentiating it from Implanon (Pedroso *et al.*, 2015).

Contraceptive implants are placed subcutaneously for systemic diffusion, but other implants are designed to be implanted directly at their therapeutic sites. Implants such as ocular implants, designed to slowly release drugs in the vitreous chamber, present the opportunity to reach this organ protected by the so-called blood-ocular barrier (Bradbury and Lightman, 1990). The eye is subject to conditions such as glaucoma, age-related macular degeneration (AMD), diabetic macular edema (DME), and retinal vein occlusions (RVOs). Since the commercialization of Vitrasert, the 1st generation of intravitreal implant, in 1996, several successive generations were designed and approved to treat different disorders (Figure 5). Vitrasert, a ganciclovir implant (Bausch + Lomb), was approved by the FDA for the treatment of cytomegalovirus (CMV) retinitis in AIDS patients. It consisted of a pelleted form of ganciclovir (4.5mg) coated with polyvinyl alcohol (PVA) and ethylene vinyl acetate (EVA) layers to control the release of the drug, for up to 8 months (Martin *et al.*, 1994). This mode of delivery reduced morbidity from systemic use of ganciclovir and immunosuppressive drugs such as steroids, while alleviating the patients' eye disease. The marketing authorization in Europe was voluntarily withdrawn in 2002 due to a lack of demand. Furthermore, the implant only provides local protection against CMV, so oral ganciclovir must be taken by people with implants to prevent the disease from arising elsewhere in the body (Martin *et al.*,

1999). Following Vitrasert, FDA approved polymeric implants for intravitreal drug delivery include Retisert (for uveitis), Iluvien (for DME) and Ozurdex (for DME). Retisert is based on the same delivery platform as Vitrasert but with Retisert being slightly smaller in size. In the case of Retisert, a pelleted form of fluocinolone acetonide (0.59mg) is attached to a PVA suture tab and coated with additional PVA and silicon layers with a drug diffusion port. It can release the drug for up to 2.5 years (Jaffe *et al.*, 2006; Callanan *et al.*, 2008; Hazirolan and Pleyer, 2013). Both implants require a sclerotomy at the pars plana region for implantation. On the other hand, Iluvien and Ozurdex are injected into the vitreous cavity *via* a 23–25-gauge needle (Cabrera, Yeh and Albini, 2014). Illuvien is composed of a small cylindrical polyimide tube with drug release membrane caps on either end of the tube, in which fluocinolone acetonide is loaded within a PVA matrix (Ghasemi Falavarjani, 2009; Wang *et al.*, 2013). These systems enable near zero order drug release of effective drug concentrations over extended periods of time (Kaji *et al.*, 2017). Since Vitrasert, Retisert and Iluvien are non-biodegradable, the drug-depleted devices need to be surgically removed or may accumulate in the vitreous cavity as in the case of Iluvien. However, the influence of the residual device left in the vitreous cavity is still unclear (Kaji *et al.*, 2017; Mandal *et al.*, 2017). Other than the eye, arteries are another site where implants are placed directly to release drugs. Since the approval of Cypher™, a sirolimus-eluting coronary stent in 2003, different generations of drug-eluting stents (DES), loaded with anticoagulant, immunosuppressant, anti-inflammatory and antiproliferative agents have been approved. As a whole, they demonstrated significant improvements compared to classical coronary stents in reducing in-stent restenosis, target lesion revascularization (TLR) and major adverse cardiac events (MACE) (Zilberman *et al.*, 2010).

Eligard is a more classic implant: it is a subcutaneous depot of poly(lactic-co-glycolic acid) (PLGA) filled with leuprolide. Different formulations altering release durations are achieved notably by varying the ratio of of D,L-lactide to glycolide. In the 1-month formulation the PLGA has a 50:50 molar ratio of D,L-lactide to glycolide with carboxyl end groups, the 3-month formulation has a molar ratio of

75:25 of D,L-lactide to glycolide with hexanediol, and the 6-month formulation has a molar ratio of 85:15 (Cox, Scripture and Figg, 2005; Sartor, 2006).

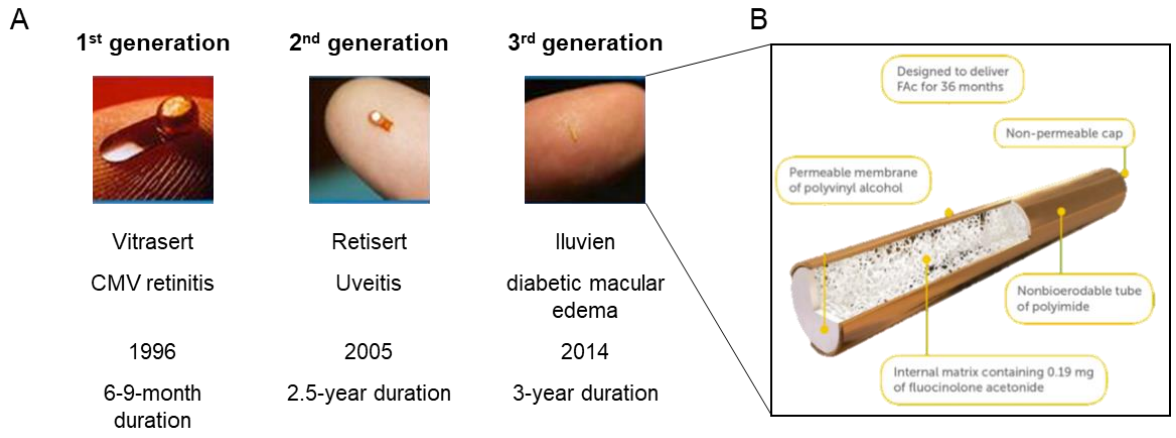

Figure 5. (A) Evolution of hard implants for intravitreal delivery. (B) Details of the composition of Iluvien, 3rd generation of intravitreal implant

Sustained delivery implants in clinical or preclinical trials

Another type of intravitreal implant is in trials, the ECT cell capsule, Renexus® (NT-501), developed by Neurotech Pharmaceuticals (Figure 6). It contains cells genetically engineered to produce ciliary neurotrophic factor and already completed a phase II clinical trial for Macular Telangiectasia type 2 (MacTel) in addition to evaluating a current phase II clinical trial for glaucoma (Smith *et al.*, 2015). In NT-501's phase I safety trial, researchers implanted the cells in 10 eyes of 10 patients with retinitis pigmentosa for six months. When the implants were removed at the six-month mark, all implants still contained viable cells, exhibited minimal cell loss, and were secreting CNTF at levels shown to be therapeutic towards retinal degeneration in dogs (Sieving *et al.*, 2006; Chew *et al.*, 2015; Birch *et al.*, 2016).

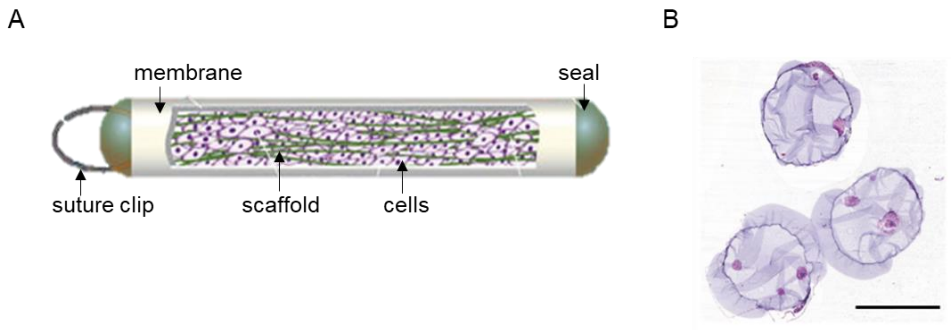

Figure 6. Cell implants (A) The NT-501 implant puts genetically engineered cells into the retina (B) Synthetic pancreas: images of implants retrieved from the STZ-treated C57BL/6J mice presented in a–c that were implanted with SC-β cells encapsulated with TMTD alginate at a dose of 250 SC-β clusters/mouse. Scale bar, 400 µm. Adapted with permission from (Vegas *et al.*, 2016)

This idea of implanting functional cells producing the therapeutics for an prolonged period of time has also been investigated to treat diabetes, this time encapsulating cells within a hydrogel (Figure 6) (Köllmer *et al.*, 2015; Vegas *et al.*, 2016; An *et al.*, 2018).

Another difficult area to access is the brain. The current gold standard to treat patients with Parkinson's disease is oral levodopa (L-dopa), the precursor of dopamine. However, the short half-life of L-dopa and its variable absorption through the gastro-intestinal tract and the blood-brain barrier limit the efficacy of this treatment. Moreover, the efficiency of L-dopa relies on the enzyme L-amino acid decarboxylase, which declines with the disease progression (Laloux *et al.*, 2017). Solutions that are currently being investigated include a continuous administration of L-dopa, L-dopa implants in the duodenum, and neurostimulating electrodes for deep-brain stimulation in the brain (Sabel *et al.*, 1990; Gershanik and Jenner, 2012; Weaver *et al.*, 2014; Laloux *et al.*, 2017).

More classical subcutaneous or retinal implants are being redesigned in order to become refillable in order to extend their period of drug release. One example is a refillable microfabricated PDMS drug delivery device for the treatment of ocular diseases (Lo *et al.*, 2008). This DDS consists of a reservoir and cannula with support structures to be secured to the sclera of the eye. Release is activated by applying mechanical pressure to the reservoir to force medication through the cannula. The device can be refilled

by using a syringe and needle up to 24 times, with an expected refill frequency of 3 months at one delivery per day, meaning that the device will have a lifetime of approximately 6 years. Therefore, one surgery to implant the device and insert the cannula spares the patient from over 2000 injections into the eye (Koch *et al.*, 2016). Refillable devices are also being developed for subcutaneous implants. To avoid the explantation and replacement of such devices, transcutaneously refillable implant are being developed. Notably, implants filled with antiretroviral drugs to achieve pre-exposure prophylaxis and avoid HIV transmission have been designed to be refilled after approximately 70 days of drug release (Chua *et al.*, 2018).

Implants may also be designed to be administered in a less invasive manner: to be placed in the lumen of some organs, for instance, in the gastrointestinal (GI) tract or in the bladder. In the GI, star-shaped orally delivered capsules have been designed to unfold in the stomach and allow an extended drug delivery (Bellinger *et al.*, 2016). After a single administration of the implant, a sustained delivery of mosquitocidal ivermectin has been achieved for up to 10 to 14 days. After this period, the polymers forming the capsule dissolve and allow the release of the remaining parts from the stomach to the intestine (Bellinger *et al.*, 2016). To deliver lidocaine in the bladder for a similar period of time (about 14 days), the LiRIS (i.e., Lidocaine-Releasing Intravesical System, TARIS Biomedical, Lexington, MA, USA), a silicone tube with shape-memory was designed (Cima *et al.*, 2014; Lee and Choy, 2016). This tube is inserted through the ureter and coils once in the bladder cavity. It releases lidocaine by zero-order release for the first 24 hours, followed by a first-order release for the rest of the 14-day period (Cima *et al.*, 2014; Lee and Choy, 2016).

Even less invasive implant options include microneedle patches. Microneedle patches have been developed for the release of flu vaccine or contraceptive hormones (Chu and Prausnitz, 2011; Prausnitz, 2017; Rouphael *et al.*, 2017). Microneedles can be made of metal, silicon or polymers. The ideal shape for polymeric microneedles is a wide base to a sharp tip, which increases the mechanical strength. Nondissolving polymeric microneedles are often made of polycarbonate, polymethyl methacrylate, and

silicon. Microneedles may also be made of swellable hydrogels that release the encapsulated drug upon gel hydration. Such designs have been realized with materials such as poly(methyl vinyl ether-comaleic acid) crosslinked with PEG. Work has also been done to develop microneedles as slow-release devices made out of biodegradable polymers such as PLGA and silk (Prausnitz, 2017).

Using hydrogels as extended-release vehicles

Hydrogels are a macromolecular three-dimensional hydrophilic network of polymers formed by crosslinking through various mechanisms including hydrophobic association, electrostatic interactions, thermally induced entanglement, and covalent chemical crosslinking. Hydrogels are remarkably tunable, biocompatible, and have the ability to retain high water content which makes them extremely valuable biomaterial scaffolds for drug delivery, tissue engineering, soft electronics, and regenerative medicine. Additionally, hydrogels can be formed in aqueous solution, minimizing the denaturation and aggregation risks of biologic cargo (Pagels and Prud'Homme, 2015; Tong *et al.*, 2015; Li, Wang and Cui, 2016). Traditional hydrogels can break easily due to a lack of mechanical strength (Langer and Peppas, 1981). However, engineered hydrogels with improved stability and structural complexities have provided enhanced spatial and temporal control over the extended release of various therapeutics (Li and Mooney, 2016; Tibbitt, Dahlman and Langer, 2016). Various advancements have also been made to improve the shear-thinning, self-healing, and responsive nature of hydrogels (Guvendiren, Lu and Burdick, 2012; Hozumi *et al.*, 2018; Leach *et al.*, 2018).

Routes of administration of hydrogels as CRS

Hydrogels may be administered through different routes. These include but are not limited to: oral, nasal, rectal, epidermal, vaginal, subcutaneous, intraperitoneal, intraocular, deposited on mucosa, etc. Gels present the advantage to be delivered through standard gauge needles, offering minimally invasive administration. Depending on the requirement of the delivery method, hydrogels can be developed into any size and shape, the major challenges being the efficiency of release and patient compliance. Hence, they are classified into macro, micro and nano gels (Figure 7). Macrogels are

typically millimeters to centimeters in size and are either transdermally administered (Tiwari *et al.*, 2012) or surgically implanted, which is invasive and may result in patient discomfort (Yu and Ding, 2008). To address this limitation,progress has been accomplished in the development of injectable alternatives designed to form the gel in the body (*in situ* hydrogels), outside the body but that transition to solution state under shear stress (shear-thinning hydrogels), or prepared externally but readily collapse and undergo shape recovery in the body (shape-memory hydrogels). In the case of *in situ* hydrogels, the sol-gel transition process is very slow and the solution solidifies after reaching the body. The various strategies of gelation applied in this case include click reactions, Michael addition, or charge complexation (Hiemstra *et al.*, 2007; Silva and Mooney, 2007; Silva *et al.*, 2008; Jin *et al.*, 2010). Another interesting class of hydrogels developed to bridge the gap between *in situ* sol-gel transition and biomaterial design is the exploration of temperature-responsive systems. Moreover, certain shear-thinning hydrogels transform into low-viscosity solutions under the mechanical stress exerted during injection and gelate quickly after removal of the force: self-healing polymers enable gels to resist the strain caused by an injection (Appel *et al.*, 2015). This behavior is mainly due to hydrophobic and electrostatic interactions (Guvendiren, Lu and Burdick, 2012). An alternative approach to using larger invasive hydrogels is to use micro- and nanogels.

Controlled release of a drug from the hydrogel is governed among other factors by the pore size of the polymeric network. The diffusion can be caused by degradation, swelling, mechanical deformation, or stimuli-responsive release. Hydrogels should also be biodegradable in a controllable manner after the drug is exhausted to avoid surgical removal.

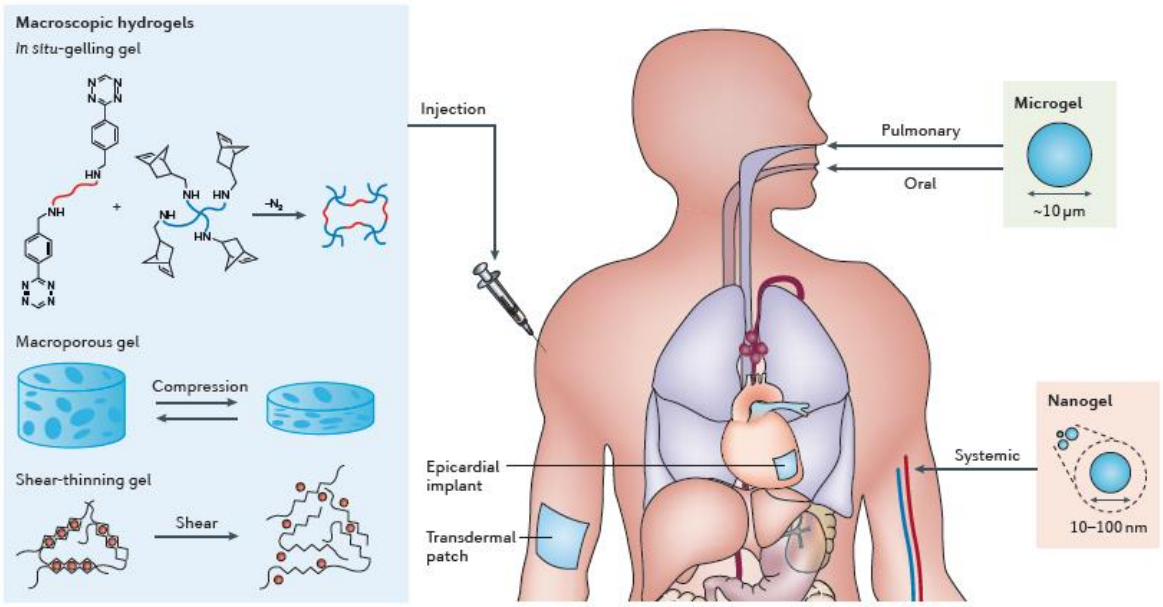

Figure 7. Different hydrogel delivery systems (macroscopic hydrogels, microgels and nanogels) determines the route of administration. Adapted with permission from (Li and Mooney, 2016)

Approved sustained release hydrogels

Table 3. Examples of approved gels allowing the sustained delivery of therapeutics. Adapted with permission from (Li and Mooney, 2016)

Brand	**Company**	**FDA Approval**	**Active Pharmaceutical Ingredient (API)**	**Composition of the implant**	**Indication**	**Dosing (months)**
Cervidil	Ferring Pharmaceut-icals	1995	dinoprostone	PEG or urethane polymer	Vaginal insert for cervical ripening to induce labor	12 hours
AndroGel	AbbVie	2000	testosterone	Carbomer 980	Topical gel for hypogonadism treatment	N/A

INFUSE	Medtronic	2002	recombinant human bone morphogenetic protein 2 (BMP2)	Collagen	bone regeneration	
Vantas®	Endo International	2004	histrelin acetate	acrylic co-polymer (Poly(2-hydroxyethyl methacrylate), poly(2-hydroxypropyl methacrylate))	prostate cancer	12
Supprelin LA®	Endo International	2007	histrelin acetate	Poly(2-hydroxyethyl methacrylate)	central precocious puberty	12
AzaSite	Akorn	2007	azithromycin	Poly(acrylic acid)	Bacterial conjunctivitis	7 days
MASTER GRAFT	Medtronic	2009	BMP2	Calcium phosphate and collagen	Spinal fusion	
Besivance	Bausch & Lomb	2009	Besifloxacin	Poly(acrylic acid)	Bacterial conjunctivitis	5 days

Medtronic's INFUSE, a collagen-based hydrogel, has been used to deliver recombinant human bone morphogenetic protein 2 (BMP2) for regeneration of bone and cartilage. Excitingly, in a different application, the approval of Vantas hydrogel in the clinic for controlled and sustained release of histrelin

in prostate cancer patients, opened the path to fuel further developments in cancer hydrogel therapy. A major drawback of the extended release formulation of hydrogels is the challenge of sterilization due to their high-water content. Hence, the cost of commercialization is often significantly high for hydrogel-based delivery systems.

In clinical trials / preclinical

In a clinical research study on the regeneration of bone and cartilage, a scaffold made of both hydrogel and porous hard material was used. In this scaffold, the atelocollagen gel promoted the production of cartilage matrix and PLGA or PGA served as porous support to build the bone on (Takato *et al.*, 2014). In another example of hydrogels used as scaffolds, an alginate hydrogel was implanted as a prosthetic scaffold into LV heart muscle (Anker *et al.*, 2015).

For ophthalmic conditions, drug-modified medicated contact lenses are being developed for use in prolonged and controlled release of drugs for the treatment of glaucoma (Carvalho *et al.*, 2015). Contact lenses can be classified into two groups, namely rigid lenses consisting of poly (methylmethacrylate) (PMMA) and soft (gelatinous) lenses consisting mainly of polymers of hydroxyethyl methacrylate (pHEMA).

Hydrogels have also helped in suppressing immune responses. In this context, Vegas et. al. developed a combinatorial library of alginate hydrogels having chemical modifications for encapsulation and protection of pancreatic islet cells from the host's immune system. In this study, triazole modified alginate showed anti-fibrotic and anti-inflammatory properties and helped in providing sufficient nutrient supply to the implanted insulin-producing cells up to six months, thereby maintaining normoglycemia in rodents and non-human primates (Vegas *et al.*, 2016). Further work is still being conducted to improve the polymer encapsulating the cell islets (nature of the alginate, size and shape of the formulation), especially to mitigate the immune response. As An et al. pointed out, one major problem with alginate capsules is that it is almost impossible to remove or replace the implant due to the complicated organ

structures and the large capsule number required (i.e., ~100,000 capsules needed for a human patient) (An *et al.*, 2018). To address this hurdle, the authors designed an implant they call TRAFFIC (thread-reinforced alginate fiber for islets encapsulation), consisting of an alginate hydrogel with *in situ* cross-links to a nanoporous, wettable, Ca2+-releasing polymer thread.

More recently, Liu et al. engineered a novel set of materials that demonstrated prolonged stability of the hydrogel in the stomach and provided safe delivery of the active drug through gastrointestinal tract in a large animal model (Liu *et al.*, 2017).

Oncogel, an injectable hydrogel for extended release of the chemotherapy drug paclitaxel, made it to phase II clinical trials (Elstad and Fowers, 2009). In a similar fashion, the French company MedinCell is developing a platform for the extended release of drugs based on the biodegradable DB PEG-PLA and TB PLA-PEG-PLA copolymers dissolved in a bio-compatible solvent, tripropionin (Leconet *et al.*, 2018). Their most advanced product, an extended treatment for schizophrenia, is currently in phase III clinical trials.

Microparticles and nanoparticles as CRS

The difficulty in slowing the release of therapeutics from hydrogels is the limiting factor in their success as a controlled delivery platform. Controlled release of small drugs from hydrogels requires correspondingly small mesh sizes. This has led to approaches which increase the effective size of small therapeutics by first encapsulating them in nanoparticles, microparticles, or charge complexes in order to prolong their release from hydrogels (Stenekes *et al.*, 2000; Park *et al.*, 2010; Seo *et al.*, 2011; Pinkerton *et al.*, 2014; Pagels and Prud'Homme, 2015). Even without being embedded or bound into a gel, nanoparticles, microparticles or drug aggregates can be delivered as depots.

Routes of administration of microparticles and nanoparticles for extended release of therapeutics

It has been shown that microparticles and nanoparticles often undergo accelerated clearance and fail to accumulate in target tissues and deliver their payload for an extended period of time (Tsoi *et al.*, 2016; Wilhelm *et al.*, 2016; Zhang *et al.*, 2016). Particles, of different sizes and shapes, combined to a gel formulation or not, may be administered through different routes: intravenous, subcutaneous, intraperitoneal, intraocular, mucosal, intra-tumoral, intra-cardiac, etc. The advantage of subcutaneous, intraperitoneal, or intraocular injection depots is an added distance from the blood circulation, resulting in a slower diffusion and elimination. Nanoparticle-based drug delivery to the heart has also been explored previously through intra-myocardial administration for the treatment of infarcts, intracoronary administration for the treatment of in-stent restenosis, as well as through injection into the pericardial space (Segura-Ibarra *et al.*, 2017). Nanoparticles injected into the pericardial space showed a prolonged presence in the heart, with a half-life of approximately 2.5 days (Segura-Ibarra *et al.*, 2017).

The size and shape of particles influence their opsonisation (their mechanical exit from the bloodstream through noncontinuous endothelia with vascular fenestrations) as well as the diffusion kinetics of their content (Blanco, Shen and Ferrari, 2015). Their size and shape are fundamental parameters in their bioavailability and kinetics of elimination, especially when considering intravenously injected particles. To benefit from the so called and debated enhanced permeability and retention (EPR) effect and accumulate at the vicinity of solid tumors for instance, nanoparticles have to have defined mechanical properties such as size, shape, surface charge, and even elasticity (Blanco, Shen and Ferrari, 2015; Guo *et al.*, 2018). To overcome barriers to achieve an optimal release in time and place after intravenous administration, new designs have been developed, such as the multistage vector (MSV) platform, combining objects on the micron scale and nanoparticles, or the injectable nanoparticle generators (Venuta *et al.*, 2017).

Oral delivery of microparticles or nanoparticles is typically limited because the epithelium of the GI tract is not porous enough to let these objects through. However, oral administration of particles is still currently investigated, especially to deliver therapeutics to these epithelial GI cells (Ball, Bajaj and Whitehead, 2018).

Approved microparticles for sustained drug delivery

Table 4. Examples of approved depots and microparticles designed for sustained release of proteins and peptides

Brand	**Company**	**FDA Approval**	**Active Pharmaceutical Ingredient (API)**	**Composition of the implant**	**Route of administration**	**Indication**	**Dosing (months)**
Lupron Depot®	TAP	1989	leuprolide	PLGA microparticles	intramuscular	Prostate cancer, endometriosis	1, 3 or 4
Sandostatin® LAR®	Novartis	1998	octreotide	PLGA microparticles	intramuscular	Acromegaly	1
Somatuline® LA	Ipsen	1998	lantreotide	PLGA microparticles	intramuscular	Acromegaly	0.5
Trelstar Depot®	Debiopharm	2000	triptorelin	PLGA microparticles	intramuscular	Prostate cancer	1 or 3
Risperidal® Consta®	Alkermes/Janssen	2003	risperidone	PLGA microparticles	intramuscular	Schizophrenia	0.5
Vivitrex®/Vivitrol®	Alkermes Inc. / Cephalon Inc.	2006	naltrexone	PLGA microparticles	intramuscular	Alcohol dependence	1

Lutrate Depot®	G P Pharm	2010	leuprolide acetate	PLGA microparticles	intramuscular	Prostate cancer	1 or 3
Bydureon®	Amylin Pharmaceuticals Inc.	2012	exenatide	PLGA microparticles	subcutaneous	Type 2 diabetes	0.25
Lupaneta Pack	AbbVie	2012	leuprolide acetate / norethindrone acetate	polylactic acid microparticles	intramuscular	Prostate cancer, endometriosis	1 or 3

Some hormones have a very short half-life and may be used as chronic treatments, either to supplement a hormonal deficiency, or in the context of hormone therapy to treat hormone-dependent cancers, such as some prostate cancers. Lupron Depot is a depot of leuprolide acetate, a hormone in the gonadotropin-releasing hormone (GnRH) analogue family of medications. GnRH agonists are hydrophilic small peptides with poor absorption and relatively short half-lives, so they were developed for daily injections (Periti, Mazzei and Mini, 2002). In the case of Lupron Depot, the hormone is formulated into biodegradable PLGA polymer microspheres, injected intramuscularly, which degrade and release drug over one, three or four months. Trelstar is another example of approved extended release of a GnRH agonist encapsulated in PLGA microparticles for treating prostate cancer. Yet another hormone based therapy, on the market in 1999 and later removed, Nutropin Depot was a growth hormone for children formulated in PLGA microparticles. It was withdrawn because of manufacturing issues, but also potentially because of adverse events such as pain at injection site (Yuen, Miller and Biller, 2018).

Vivitrex®/Vivitrol® contain naltrexone formulated into injectable microspheres of PLGA of approximately 100 μm in diameter, which contain other proprietary active moieties that lead to its extended-release properties lasting for several weeks (Anderson and Shive, 1997; Johnson, 2007). In this

way, Vivitrex delivers 337 mg of Naltrexone per gram of microspheres in a monthly depot injection to control opioid abuse (Johnson, 2007).

In clinical trials / preclinical

Innovative single injection vaccines are in development to facilitate the vaccination process in areas where access to medical care is difficult. Some of these single injection vaccines have been designed as spherical PLGA microparticles filled with inactivated polio vaccine (IPV) antigens. Formulations release two bursts of IPV 1 month apart, reproducing a typical vaccination schedule for those in developing countries (Tzeng *et al.*, 2016, 2018). Fillable cubic microparticles are also being developed to deliver proteins during an extended period of time: for example at 0-16 weeks after injection (McHugh *et al.*, 2017).

For ocular delivery, several nanosized micelles, for direct injection into the eye, or encapsulated into hydrogels, have been designed or are in development. As an example, cross-linked methoxy(polyethylene glycol)-block poly(ε-caprolactone) (mPEG-b-PCL) nanosized micelles, coated with silica and incorporated into a pHEMA hydrogel were developed and tested for sustained delivery of dexamethasone acetate (DMSA) into the eye. The *in vitro* drug release profile from DMSA-loaded SSCMs showed a biphasic distribution with a burst release over the first 8 h followed by a release of 6% per day over 6 days. In contrast, hydrogel containing DMSA-loaded SSCMs provided sustained release of the drug for periods up to 30 days (Lu *et al.*, 2012; Mandal *et al.*, 2017). This example of micelles embedded in a hydrogel, along with the multistage vector platform in development described previously, illustrate the nesting strategy to design optimized, long lasting drug delivery systems.

In addition to therapeutics, extended release can also be used to deliver probes, for continuous *in vivo* monitoring. For instance to monitor glucose concentration in blood, glucose-responsive fluorescent probes were designed to be slowly released: packed in microbeads, themselves formulated in an injectable hydrogel (Shibata *et al.*, 2010).

Challenges in extended-release

Synthesis and formulation challenges

An important aspect in the design and development of CRS is avoiding burst release. Burst release leads to uncontrolled variations in dose, which can result in toxicity for the patient. Burst release also limits the amount of encapsulated therapeutics left available to be released over time.

Apart from burst release, some CRS present low or variable encapsulation rates and loading volumes (Tng *et al.*, 2012; Markwalter and Prud'homme, 2018), as well as issues regarding the stability of the encapsulated therapeutics. Difficulties in synthesis and development may indeed arise from the encapsulated therapeutics: their physical characteristics such as size, or their stability. For instance, cells cannot be encapsulated in any vehicle as they require specific circumstances to remain viable. Another example is that of proteins or peptides encapsulated in aliphatic polyesters, which may be degraded by the acidic products of these polymers (Park, Lu and Crotts, 1995; Fu *et al.*, 2000).

Body reaction to CRS

The biological reactions triggered by the implementation of extended-release systems pose a potential hurdle when designing these DDS. Such biological reactions may be local, such as an inflammation, and fibrosis around the foreign body, or result in a systemic inflammation or allergy. In a clinical trial for Vivitrex®, an intramuscular injection of PLGA microparticles filled with naltrexone, involving 25 individuals, one participant dropped out due to induration at the injection site, and another was discontinued because of an allergic reaction that resulted in angioedema, which resolved soon after the participant stopped taking the medication (Johnson, 2007). After a local inflammation, a so-called foreign body reaction may occur: the end-stage response of the inflammatory and wound healing responses following implantation of a medical device or biomaterial (Anderson, Rodriguez and Chang, 2008). On top of local and systemic reactions directly due to the implant, gel or depot, issues can arise from the mode of administration: complications after surgery or injection via large gauge needles. For

instance, with Implanon and Nexplanon implants, implant site complications were reported by 3.6% of subjects during assessments in clinical trials. Pain during or after insertion was the most frequent implant site complication, occurring in 2.9% of subjects. Additionally, haematoma, redness and swelling were reported by 0.1%, 0.3% and 0.3% of patients, respectively (Pedroso *et al.*, 2015). Local reactions, such as inflammation may also be sought because they are beneficial to the treatment: the recruitment of immune cells is useful for vaccines for instance. In such cases, inflammation caused by microneedle patches are turned into an advantage (Prausnitz, 2017).

Systemic reactions consist mostly in systemic inflammation with allergy-like symptoms. For instance, the so-called CARPA syndrome due to the complement activation after the injection of liposomes (Nilsson *et al.*, 2007; Szebeni *et al.*, 2011). In the case of Nexplanon implants, which contain barium sulfate, although extremely rare, patients may present an allergic reaction to barium sulfate. To date, only two cases associated with Nexplanon have been reported in the literature (Sullivan, 2012; Chaudhry, 2013; Pedroso *et al.*, 2015).

Because of their extended release purpose, the drug delivery systems may stay in the body for a prolonged period of time and cause not only a local or systemic inflammation, but also a chronic inflammation. Consequences of chronic inflammation include fibrosis (Kastellorizios, Papadimitrakopoulos and Burgess, 2015) and even tumors, such as implant-associated anaplastic large cell lymphomas. Another long-term consequence of extended release drug delivery devices shared with any other chronic treatment is the induced tolerance to the extended released drug.

Solutions to decrease implant-site reactions and inflammations consist in using approved polymers known to minimize such reactions or adjusting other parameters such as shape, size, charge, and hydrophobicity of the biomaterials used (Veiseh *et al.*, 2015; Vegas *et al.*, 2016; Fenton *et al.*, 2018). The use of PLGA-based devices may lead to an inflammatory response in the vitreous space due to the acidic degradation products of PLGA. Consequently, Graybug Vision, Inc. has developed a proprietary technology to reduce the inflammation related to PLGA degradation (Kaji *et al.*, 2017). Another strategy

involves encapsulation of inflammation resolution agonists, such as resolving D1 (RvD1), an ω-3 derived lipid mediator. Resolvin D1 (RvD1) loaded in Pluronic gels or PLGA films can significantly decrease arterial inflammation after sterile injury (Fenton *et al.*, 2018).

Drug delivery devices may be explanted, either upon completion of the treatment or because of an unexpected reaction. The process of explantation may be difficult because of the material's degradation, movement inside the body, or because of the body's reaction around the device (Kleiner, Wright and Wang, 2014). Implanon rods can be located only through high-frequency ultrasound, or magnetic resonance imaging (MRI). Nexplanon can be located using traditional X-ray or CT-scan because of the inclusion of barium sulphate. There have been rare reports of Nexplanon implants having reached the lung via the pulmonary artery (D'Journo, Vidal and Agostini, 2015; Rowlands, Mansour and Walling, 2017).

For the past 30 years, many CRS have been approved to treat chronic conditions and alleviate patients' treatment burden. Specific challenges to CRS such as burst release, stability, invasiveness and inflammation have been addressed in newer generations of approved CRS or in CRS in development. New materials, smaller objects, and different routes of administrations have also been explored. In order to control the release kinetics more precisely, triggered release features are being investigated, making more sophisticated, or "smart" CRS. With the increasing prevalence of chronic diseases and concern towards patients' quality of life, CRS development holds a promising future.

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