

Chapter 2

Controlled-Release Systems

2.1 Engineering Concepts

2.1.1 Diffusion and Degradation

Why is there interest in the drug community in investing research time into the controlled drug release approach? Currently, the FDA estimates that approximately \$150 million is invested over a 10-year period in the design and implementation of new drug offerings [1]. These drug offerings typically have a narrow therapeutic index (i.e., the difference between toxic and therapeutic levels). Additionally, there is patient-related physiological fatigue from multiple injections, infection, and hemorrhages, while the danger from systemic toxicity limits the potency of the drug [2]. Each of these pitfalls indicates a narrow window of utility for which the drug is permitted. A drug company cannot simply flood the body with a large excess of drug in order to ensure some small percentage reaches its intended target. Think of it as throwing 100 darts simultaneously at a dartboard. You will be statistically likely to hit a bull's-eye, but you are also more likely to damage the wall as well! A controlled-release profile can allow for targeting of the delivery, improve the availability of the drugs (i.e., short half-lives), and can serve multiple functions within the system (i.e., release systems can be adjuvants as well). So referring back to the dartboard analogy, imagine the thrower tossing the darts individually, 1 through 100, while progressively moving closer to the target. Now, statistically, his or her chances of a bull's-eye will increase sans the wall damage!

Drug release systems can be separated into two distinct classes: **sustained release** and **controlled release**. *Sustained-release* systems are traditionally a mix of agents that affect the net rate of dissolution of the drug molecule. *Controlled-release* systems are comprised of a drug molecule (i.e., active agent) and a bioinert or biocompatible polymer. Polymeric systems are discussed in more detail in Sect. 2.2. The system also contains a functionality that can be free or tethered to the polymer chain, which allows for tailoring the release kinetics of the system or cell targeting.

Since there are inherent benefits for a controlled delivery approach, the next question to ask is

What is the desired location in the human physiology to which this treatment is going to be applied?

Controlled systems can be applied to a person through oral [3], ocular [4], parenteral [5], and sublingual [6] sites. Each site presents a series of challenges from both an engineering design and a medical treatment perspective, which we will evaluate throughout the remainder of Chap. 2.

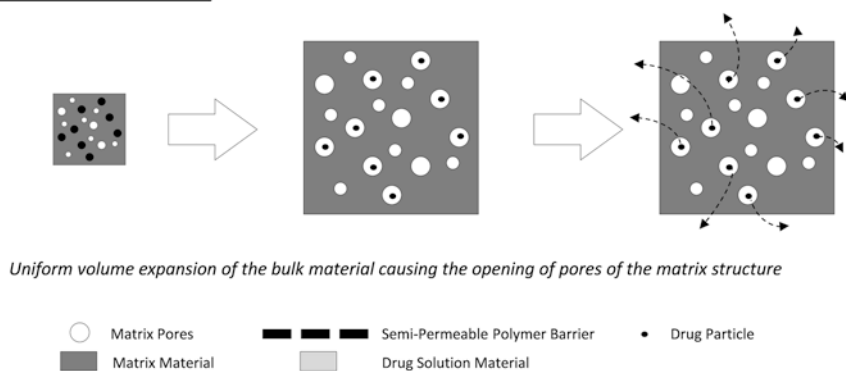
2.1.2 Diffusion-Controlled Systems

The process of drug release from an aqueous stimulus has several distinct advantages in terms of the timing of the control and response of the system. The speed at which water can swell the matrix of a crosslinked system is significantly more rapid than the degradation or dissolution rates described in the erosion section previously discussed. The term “diffusion” refers to the actions of the drug molecules upon exposure to stimuli affecting its external environment. The rate-limiting step of diffusion drug release systems is the diffusion through typically a water-insoluble barrier. Diffusion drug delivery systems are typically either **matrix-based** or **reservoir** diffusion systems. In matrix-based systems, the drug is combined with a polymer to form a composite matrix where water permeation leads to either swelling or osmotically controlled systems [7]. Since the matrix is composed of both polymer and drug molecules, the swelling effect is seen as a uniform volume expansion of the bulk polymeric material, causing the opening of pores throughout the matrix structure. This is conceptually not unlike a sponge that uniformly swells with water. In order for effective diffusion of drug molecules to occur, the pore size of the swelled matrix must greatly exceed the size of the hydrophilic drug molecule or hydrophobic drug particle. In reservoir systems, the drug solution is encapsulated within a polymer droplet, creating a permeable barrier between the drug solution environment and the surrounding environment [8]. Since the reservoir is composed of a permeable polymer barrier coating, the swelling effect is seen as a nonuniform volume expansion, where the barrier coating allows for water permeability and swells, while the internal components can diffuse out of the system. This is conceptually not unlike a dialysis bag, which allows free diffusion of water and size-selective permeability of its internal constituents. In order for effective diffusion of drug molecules to occur, the pore size of the swelled barrier must greatly exceed the size of the hydrophilic drug molecule or hydrophobic drug particle.

If we are designing a controlled-release drug delivery system to specifically exploit a diffusion-controlled mechanism, the next question we could ask is

What factors can we manipulate in order to allow for control over the swelling or permeability of the barriers utilized in matrix or reservoir systems?

Matrix Systems



Reservoir Systems

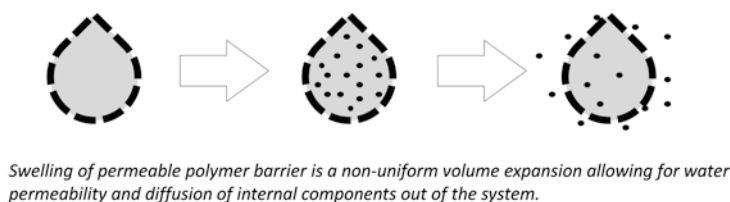


Fig. 2.1 Diagram of basic controlled-release systems for drug delivery

For the most part, the answer to this question lies in the chemistry of the polymer(s) used as either the matrix or permeable barrier. In matrix systems, the crosslinking of either a covalent or secondary bonding between, or within, polymer chains is used to stabilize the physical integrity while the system passively takes up water. In reservoir systems, crosslinking is also typically utilized with similar bonding as in matrix systems; however, the volumetric limitations of the swelling behavior are distinctly different. We engage in this discussion again in Sect. 2.2, where we look at the polymer characteristics and functionalities that contribute to the distinction between these two systems (Fig. 2.1).

2.1.3 Degradation-Controlled Systems

The primary modes of erosion-based drug delivery are through the release of the drug, typically from a bulk phase, which consists of a drug composite. Therefore, the rate-limiting step of degradation-controlled release systems is dissolution.

Table 2.1 Common erosion effects encountered by biomedical materials

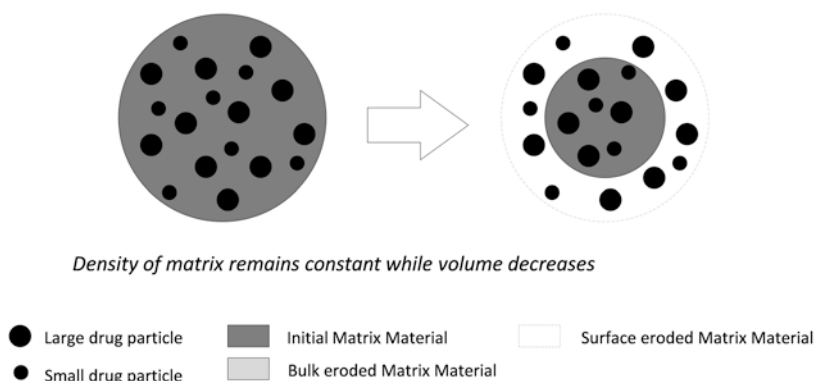
Erosion effects	
Adhesion	Physical interaction with another surface via friction causing displacement
Abrasion	Loss of material due to hard materials (i.e., particles) that are pressed against the surface
Fatigue	Surface is weakened by cyclical application of load
Fretting	Surface is weakened by cyclical rubbing
Cavitation	Physical interaction with another physical state
Corrosion	Wear created by chemical reactions with surface functionalities

The composite can consist of a polymer of a tailored degradation or deformation rate. The degradation or dissolution effects are measured as the erosion of the material over time in response to its immediate physiological environment. The erosion can occur through a number of mechanisms related to either the surface or the bulk of the material. Erosion on the surface causes displacement of surface features or regularity due to several common effects (Table 2.1).

The deformation rate is measured from a matrix swelling effect in response to the adsorption or flux of physiological, typically aqueous fluids within the body [9]. In these matrix, or monolith, systems, the drug is homogeneously dispersed throughout a matrix. The changes to the bulk phase can be segregated into two distinct categories: **bulk erosion** and **surface erosion** [10]. In the case of bulk erosion, the material degrades or deforms uniformly throughout the bulk of the material. As the deformation proceeds, the volume of the material remains constant while the mass of the material reduces, resulting in a decrease in the density of the degrading material. In the case of surface erosion, the material degrades from the outer surface inward uniformly only at the interface between the bulk of the material and the surrounding environment. As the deformation proceeds, the volume of the material decreases linearly with mass, which results in the density of the material remaining constant (Fig. 2.2).

This is a critical distinction between the two approaches that distinguishes their responses to physical stress and dictates their application. Materials that *retain volume but reduce density* become porous and brittle over time, with weaker mechanical integrity. This effect can occur with swelling or dissolution, covalent bond rupture, and secondary bond dissociation within the system [11]. Materials with brittle and porous structures resemble weak ceramics that can crumble or crack in response to shear, compression, or tensile pressure [12]. Materials where *density is constant* have a more predictable response to physical external stresses. If volume is lost, however, the function of the material may be compromised (i.e., see embolics [13]).

Surface Erosion



Bulk Erosion

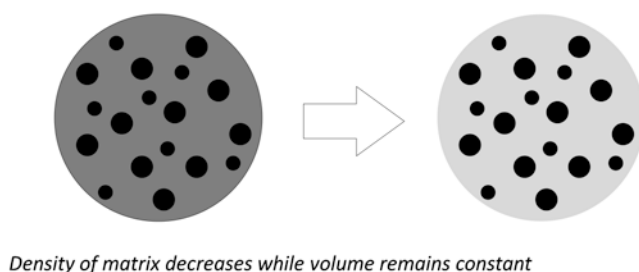


Fig. 2.2 Diagram of erosion mechanisms found in matrix systems

2.2 Material Design

2.2.1 Networked and Porous Structures

Given the different physiological environments possible for a controlled delivery approach, the next questions we can ask are

How can we predict when it is appropriate to select a bulk or surface erosion system?

How can we design a system to minimize or maximize its response to physical stimuli?

The simple answer is that it depends on two major characteristics: (1) the pharmacokinetics of the desired drug and (2) the function of the material construct being introduced into the physiological environment.

2.2.1.1 Pharmacokinetics

A majority of drugs in their base state display a first-order release, often referred to as “burst release,” followed by a steady decrease in drug concentration in the physiological environment [14]. The pharmacokinetics of this initial approach shows a series of peaks and troughs over time. These peaks and troughs represent multiple extreme minima and maxima and are the most nonideal in terms of limiting the potentially toxic overdosages of drug molecules. The ideal pharmacokinetic response curve is represented by a zero-order kinetic response over time [15], where the drug has a steady state of delivery over a fixed time. The drug molecule system with a zero-order response allows for the delivery of a consistent amount of drug over time in a kinetically controlled system according to Eq. (2.1):

$$\frac{\delta m}{\delta t} = \frac{DS}{Vh}(C_s - C_t), \quad (2.1)$$

where δm is the rate of dissolution, D is the diffusion coefficient of the compound, S is the surface area of the drug product, C_s is the concentration of the solid in the diffusion layer that surrounds the solid, C_t is the concentration of the solid in the bulk dissolution medium, V is the volume of the dissolution media, and h is the thickness of the diffusing film adjacent to the surface being dissolved. The release can also be analyzed using the Higuchi model [15] as a way of determining the dissolution of a drug from a matrix. The Higuchi model for the amount of drug released over time (Q_t) can be written in the form

$$Q_t = k_H t^{1/2}, \quad (2.2)$$

where k_H is the Higuchi model release rate constant and t is time. Similarly, the Korsmeyer–Peppas [15] equation can be used to determine the mechanism of drug release; it is written in the form

$$\left(\frac{M_t}{M_\infty} \right) = K t^n, \quad (2.3)$$

where M_t is the amount of drug released at time t , M_∞ is the total amount of drug present, K is the kinetic constant, and n is the diffusion exponent. This model allows for the mode of kinetics to be determined by the diffusion exponent value (n). Values of $n=0.5$ indicate Fickian diffusion, or drug release that is diffusion-controlled, as in the Higuchi model. If the diffusion exponent is in the range of $0.5 < n < 1$, it indicates anomalous diffusion, or drug release that is both diffusion-controlled and erosion-controlled. If $n=1$, it indicates case II transport, or drug release that is zero-order, where the release rate is constant and controlled by polymer relaxation. Finally, when $n > 1$, it indicates super case II transport, or drug release that is erosion-controlled.

The kinetic plot shown in Fig. 2.3 indicates a zero-order cumulative release of drug over time. This contrasts the sustained-release kinetic profile, which appears *first-order* in nature. The *first-order* release kinetics show a significantly slower, and consequently more variable, release rate over time (Fig. 2.3).

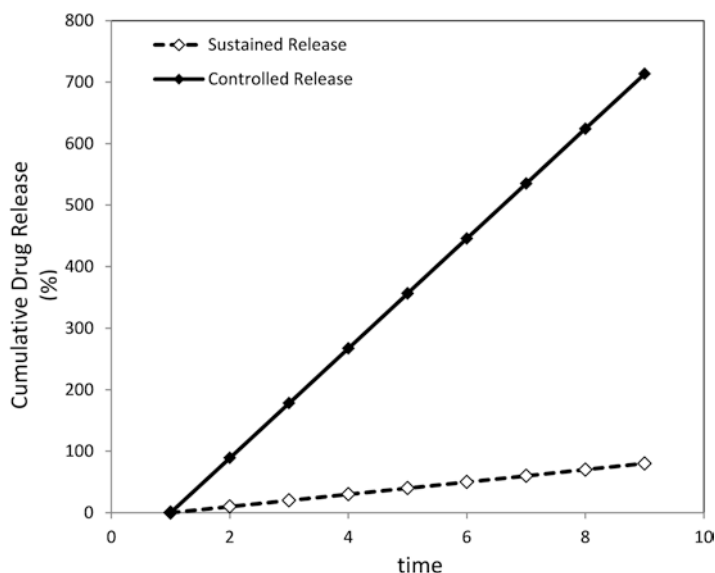


Fig. 2.3 Plot comparing zero-order and Fickian release kinetics (controlled release translates to zero-order release kinetics, while sustained release translates to first-order release kinetics)

The selection of the mode of release, zero- or first-order, relates to both the time required within the physiological system to reach the intended target and the desired dosage of drug to be delivered when it arrives.

2.2.1.2 Polymeric Materials

In order to effectively design a system to exploit the appropriate release kinetics, we need to discuss a basic grounding in polymer science. Polymers are commonly used as matrix or composite materials for controlled-release systems [16]. Polymers consist of a long chain of repetitive monomer segments, or mers, that are covalently bonded to one another. One does not have to look far to see examples of polymers in daily life. From plastic bottles (polyethylene) [17] to windows (polymethylmethacrylate) [18] to Blu-ray discs (polycarbonate) [19] to proteins (polyamide) [20], we see examples of polymeric materials, and it is critical to understand their benefits and limitations for applications in biological systems. In fact, our own DNA [21], to a material scientist, is considered an elaborate high-molecular-weight polymer chain!

The common structural nomenclature for polymer molecules is shown in Fig. 2.4; the bracketed area represents the repeat unit, or the repeated chemical domain, and the value n represents the **degree of polymerization (DP)**, or the number of repeated domains, of the polymer molecule. The theoretical molecular weight of a polymer can be calculated by multiplying the molecular weight of the repeating unit by the value n , or the DP.

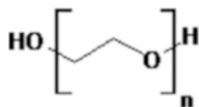


Fig. 2.4 Standard polymer structural nomenclature

Typically, polymers are described in terms of their **molecular weights** [22]. The molecular weight of a polymer is a unique property to this species of molecule since its physical properties of interest for our discussion include viscosity [23], degradation [24], and stimuli-responsiveness [25]. The glass transition temperature [26] (T_g) can be derived from this value.

Sample Problem 2a

In the case of two polymer molecules of polyethylene glycol with molecular weights of 1,000 Da and 20,000 Da dissolved in water, which polymer would you expect to have the higher viscosity?

We would expect that the polymer with the molecular weight of 20,000 Da would have a higher viscosity than the one with the molecular weight of 1,000 Da. Therefore, all domains being of equal functionality and concentrations, the higher molecular weight means the higher the viscosity. This, in fact, holds true.

While this reasoning appears to be fairly implicit, these properties become sufficiently more complicated, however, when looking at characteristics such as biodegradation, which will be addressed in examples throughout this text.

The molecular weights of polymer molecules differ relative to the method of their creation. For biologically created or synthesized polymers, such as proteins and DNA, the polymers have perfectly uniform chain length, molecular weight, and DP. This is somewhat of a relief since this specificity is tied to their physiological function, and the slightest imperfection of even one monomer unit may lead to significant repercussions in nature [27]. In synthetic systems, however, polymer chains are not all the same DP, but instead are a distribution of chain lengths. This is due to a number of factors that are tied to the organic chemistry of the monomer reactions. As a synthetic reaction proceeds, a few factors can predominate in the creation of a polymer. Generally, as the reaction propagates, the viscosity will increase, while the number of reactive monomers will simultaneously decrease since they are being consumed to form the polymer. As the reaction moves to a higher viscosity, the mobility of molecules in the system slows while the number of monomers that remain significantly decreases (Fig. 2.5).

This leads to a distribution of molecular weights and a percentage of the reaction that remains incomplete. The broadening and narrowing of this distribution can be tied to the synthetic method used to make the desired polymer molecule.

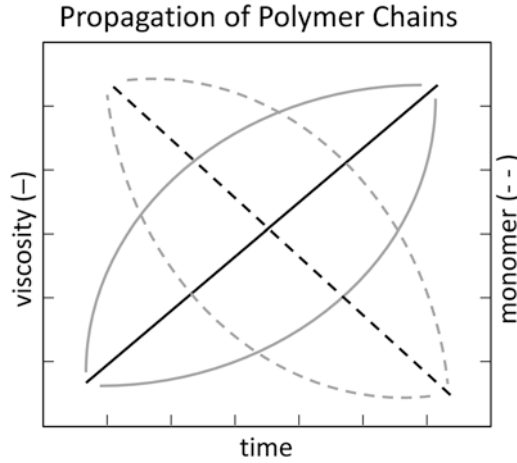


Fig. 2.5 Diagram of viscosity behavior with propagation of polymerization

Traditionally, molecular weights are described in terms of their number average molecular weight (M_n) [Eq. (2.4)], their weight average molecular weight (M_w) [Eq. (2.5)], and their molecular weight distribution or polydispersity index (M_w/M_n or PDI or MWD) [Eq. (2.6)] [28]:

$$\sum M_n = \sum (n_i M_i), \quad (2.4)$$

$$\sum M_w = \sum (w_i M_i), \quad (2.5)$$

$$\text{MWD} = \text{PDI} = \frac{M_w}{M_n}. \quad (2.6)$$

In the case of the molecular weight distribution, the M_w and M_n represent statistical overestimates and underestimates, respectively, of the actual molecular weight. The M_n is a summation of the number of molecular weights at each discrete chain length.

Sample Problem 2b

If a polyethylene glycol polymerization has five polymer chains with molecular weight 1,000 Da, three with 15,000 Da, and two with 50,000 Da, what would be the number average molecular weight?

The M_n would be $(5 \times 1,000) + (3 \times 15,000) + (2 \times 50,000)$ all divided by the total n , which in this case would be 10. Therefore, M_n for this example would be 15,000 Da.

The M_w is a summation of the weight fraction of molecules of each respective molecular weight.

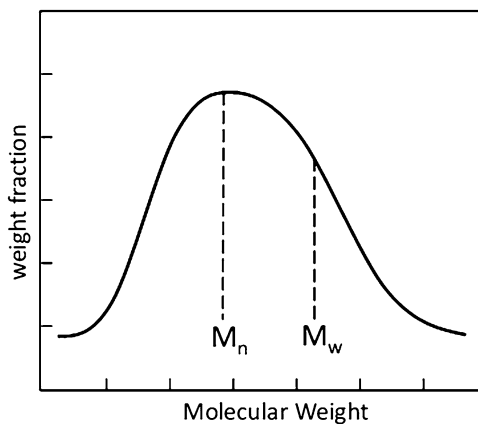


Fig. 2.6 Diagram of the molecular weight distribution as described in terms of M_n and M_w

Sample Problem 2c

If the same polyethylene glycol polymerization has five polymer chains with molecular weight 1,000 Da, three with 15,000 Da, and two with 50,000 Da, what would be the weight average molecular weight?

The M_w would be $(5 \times 1,000^2) + (3 \times 15,000^2) + (2 \times 50,000^2)$ all divided by the total weight fraction, which in this case would be $(5 \times 1,000) + (3 \times 15,000) + (2 \times 50,000)$ or 150,000. Therefore, M_w for this example would be 37,867 Da.

The molecular weight distribution (PDI) is a ratio of the weight average (M_w) and number average (M_n) molecular weights (Fig. 2.6).

Sample Problem 2d

For the same polyethylene glycol polymerization with an M_w of 37,867 Da and M_n of 15,000 Da, what would be the molecular weight distribution?

The molecular weight distribution would be M_w/M_n . Therefore, M_w/M_n for this example would be 2.52.

There are three PDI ranges that define the molecular weight uniformity [29] of a polymer molecule. The first range consists of perfect uniformity of molecular weights, which is defined as when M_n is equal to every individual M_i . The second range consists of polymers with a PDI of 1.0–1.5. These polymers are statistically uniform, contain highly predictable properties, and typically are run to a high degree of conversion of monomer to polymer. The third range consists of polymers with

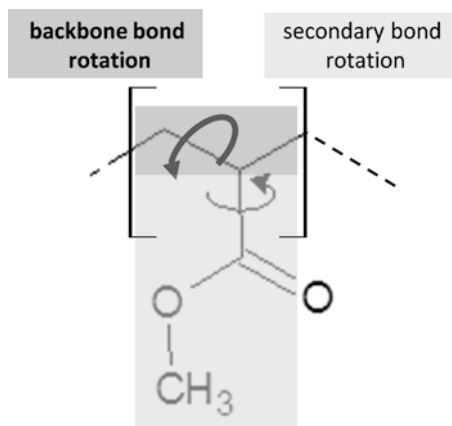


Fig. 2.7 Diagram of rotational modes of common polymers

$PDI > 2.0$. These polymers are statistically disperse and typically consist of a number of competing side reactions that can act to complicate their use in biological applications by introducing an undesirable chemistry to the human physiology unless otherwise addressed. Current examples of controlled-release systems use polymers that fall in the second or third range, whereby special attention is required to mitigate undesirable side effects.

We have discussed that the molecular weight can influence the properties of the matrix or surface used in a controlled-release system by the method of synthesis, the magnitude of the M_n or DP, and the values of the molecular weight distribution. The molecular weight is also integrated with the glass transition temperature (T_g) as well. The T_g is described as the temperature above which an amorphous polymer behaves like a viscous fluid or rubber and below which it behaves like a glass or brittle solid. The molecular weight can act either to shift the value of the T_g or to increase the rate at which the transition effects occur. If we look closer at T_g on the molecular level, it is also described by Adams and Gibbs [30] to be the temperature below which polymer backbone rotation slows or ceases while secondary molecular bond rotation remains (Fig. 2.7).

The Adams and Gibbs [30] definition provides a perspective on the effects that T_g can have on the matrix of controlled-release systems. Until this point, we have discussed controlled-release systems (matrix or reservoir) releasing via either surface or bulk erosion. In selecting your polymeric material for either of these systems, it is important to verify that the T_g of that polymer is amenable to the properties (i.e., density, volume, porosity) of that system [31]. We can ask, for example, what is occurring in this system with respect to its volume and density characteristics? For a matrix system with a bulk erosion release mechanism, the density is decreasing while the volume remains constant. Since it is a matrix system, there needs to be a base level of physical integrity to sustain the shape and function, and this needs to be maintained while the density of the system is decreasing. For this reason, the

design requires a polymer with a $T_g > 37^\circ\text{C}$, and likely in a stable temperature regime $> 60^\circ\text{C}$.

This example accounts for more rigid systems. Special care should be taken as $T_g > 100^\circ\text{C}$ since those polymers tend to be more brittle. What is occurring in systems that swell, with respect to their volume and density characteristics? For a reservoir system with a nonuniform volume expansion release mechanism, the volume is increasing with no net material loss other than the release of your drug. This system requires that the polymeric material be elastic in response to the volume expansion or swelling behavior. For this reason, the design requires a polymer with $T_g < 37^\circ\text{C}$, and likely in a stable temperature regime $0^\circ\text{C} < T_g < 37^\circ\text{C}$.

This example accounts for more elastic systems. Special care should be taken as $T_g < 0^\circ\text{C}$ since those polymers tend to have a higher degree of viscous flow.

As T_g is shifted between higher and lower levels, the view of these systems in terms of molecular motions aids in determining the upper and lower thresholds of each temperature regime. For systems requiring elasticity for swelling, the lower T_g limit is established. While the T_g in this case can refer to the temperature at which the secondary molecular motion starts or stops, a low T_g (i.e., $< 0^\circ\text{C}$) under physiological temperatures could lead to mobility of polymer chains past one another, or viscous flow. Viscous flow acts to destabilize an elastic network and subsequently change the release characteristics. For applications in physiological systems, the general rule of thumb is the operational temperature range of interest is 37°C ($\pm 37^\circ\text{C}$).

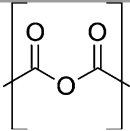
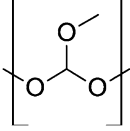
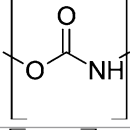
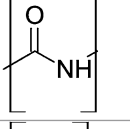
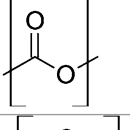
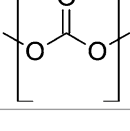
2.2.1.3 Biodegradation

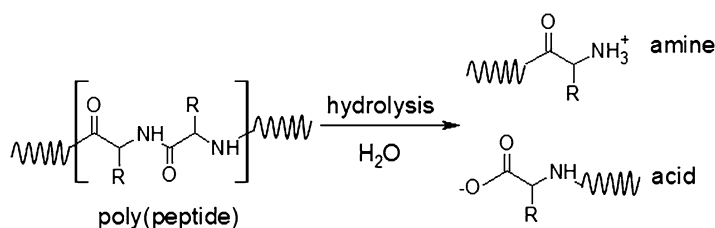
Up to this point, the discussion has been abstract in its description of the chemical functionalities that are appropriate for the design of controlled-release systems. While the basic physical principles of polymer chains and structures have been discussed, the specific functionalities provide information regarding response to physiologically relevant stimuli. The degradation or, more specifically, biodegradation can govern a number of the major characteristics discussed thus far. Biodegradable polymers are composed from a pool of several common bonding types [32] (Table 2.2).

The mode of degradation behavior of polymeric materials can be separated into the following categories: oxidative, chemical, radiation, biological, and stress-induced [33]. For the purposes of biodegradation, we will limit our discussion to chemical and biological modes since the other modes do not represent a reasonable level of occurrence in drug delivery applications. The chemical mode is often the hydrolysis of a labile covalent linkage in either the backbone of the polymer or the pendant (i.e., side group) functionality. For example, if a polyamide undergoes hydrolysis, the peptide bond is cleaved to give amino acid products (Fig. 2.8).

Often this level of chemical hydrolysis can occur in different organs of the body, such as the stomach, where levels of (H^+) ions are high (i.e., pH 2) [34]. Chemical hydrolysis can also occur outside the body, where a diagnostic test may be exposed to aqueous conditions. The biological mode [35] is commonly referred to as the

Table 2.2 Examples of common degradable polymers used in controlled-release applications

Polymer	Degradable bond	Biodegradation	Examples
Polyanhydride		Hydrolysis	Poly(sebacic anhydride), poly(adipic anhydride)
Polyorthoester		Hydrolysis	Dioxolane-based diketene acetals
Polyurethane		Hydrolysis- or enzymatic-mediated degradation	Chronoflex®, Pellethane™, Bionate®
Polyamide		Hydrolysis- or enzymatic-mediated degradation	Poly(hexamethylene adipamide), poly(peptide)
Polyester		Hydrolysis- or enzyme-mediated degradation	Poly(lactide), poly(caprolactone)
Polycarbonate		Hydrolysis- or enzymatic-mediated degradation	Lexan®, Apec®

**Fig. 2.8** Scheme of the general mechanism for the chemical hydrolysis of a polypeptide

enzymatic-mediated degradation mode, where an enzyme acts to activate a peptide bond, typically in a select location within the peptide sequence, for bond cleavage reactions. The enzymatic route [36] relies on a peptide being of a specific, stereochemical, geometry (i.e., tertiary structure) to fit into a catalytically active site on the enzyme. Once occupying this site, the peptide is activated for hydrolysis typically by a nucleophilic attack followed by a regeneration of the active enzymatic

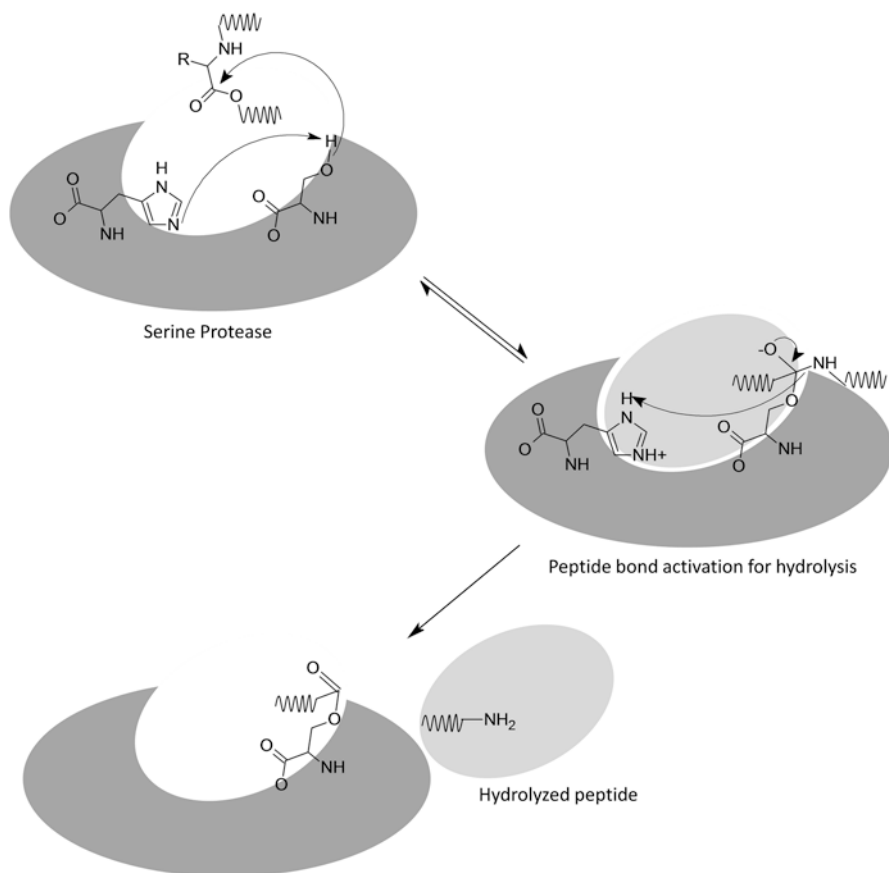


Fig. 2.9 Scheme of the general mechanism for the enzymatic hydrolysis of a polypeptide

site. For example, the case of serine protease enzyme acts to hydrolyze a peptide bond by nucleophilic attack of the peptide carboxylate by a serine residue that is stabilized by proton transfer between the histidine and serine residues of the catalytic binding domain. The rearrangement of electron density of the bound state leads to the release part of the cleaved peptide chain, leaving the remaining portion bound to the serine residue, which then is released, leaving the regenerated catalytic domain (Fig. 2.9).

What is commonly seen, however, is a combination of the chemical hydrolysis mode with the enzymatic-mediated degradation mode [37]. Some polymers, such as polyorthoesters, are in a majority of cases chemically hydrolyzed, while polyamides are degraded through both routes described here.

To frame this in our discussion thus far, we know that the erosion or degradation mode of the polymeric material can dictate whether the system hollows bulk or surface release kinetics and whether it would function as a matrix or reservoir

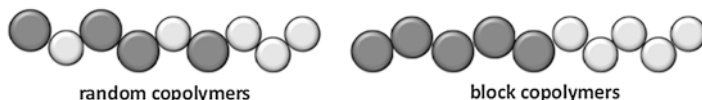


Fig. 2.10 Diagram of the random and block domain morphologies

system. The selection of the appropriate biodegradable material must follow the appropriate, predictable, rate of degradation. In the discussions regarding the mode of biodegradation, it is important to distinguish both the dominant mode of degradation and whether a desirable mode is present in the area of physiological release. What would you expect the degradation mode and T_g to be for a flexible poly(lactic-co-glycolic acid) polymer molecule? A matrix system comprised of poly(lactic-co-glycolic acid) (PLGA) typically takes on a bulk degradation whereby the rate of hydration into the matrix is greater than the rate at which the PLGA polymer is solubilized. This hydration also causes a polymer relaxation, shifting the T_g to a lower value, which increases the degradation rate.

In addition to the mode of biodegradation, the release kinetics are affected by the composition and molecular weight of the polymeric species used. Up to this point, we have assumed that our molecular weights of biodegradable species remain unchanged and our polymeric systems were homogeneous in nature. In fact, a majority of biodegradable systems for drug delivery are copolymers composed of two or more domains of degradable bond types. We will go into copolymers in more detail in the remaining chapters of this book. As a cursory view for this discussion, however, imagine copolymers as two or more functional monomers, which in our case are degradable bond types, grouped within a single polymer in one of two ways: either randomly distributed throughout the polymer chain (i.e., random copolymer) or grouped into discrete homogeneous domains next to another different homogeneous domain (Fig. 2.10) within the same polymer chain (i.e., block copolymer).

Looking closer at polymer composition, we can see that the weight fractions of different biodegradable groups and their molecular weights can influence both the rate of biodegradation (or erosion) and the percentage of the total material degraded [38]. For the purposes of this initial discussion, we will assume that all fabricated biodegradable species are in the same geometric conformation (i.e., tablet, disc) with the same dimensions. The erosion rate profiles of all species follow the same pattern. Initially, there is an induction period, which is dimensionless, or no change in rate of erosion based on the dimensions of the material. There is then a peak in erosion rate, followed by a sharp decrease. Both the timing of the peak and the duration of peak time prior to the decrease will stratify materials based on dimension and geometry. For example, in the case of drug discs, the thickness is approximately directly proportional to the time of the peak rate before reaching the decrease. For thicker discs, one would expect a longer erosion at the peak rate. For thinner discs, the erosion at the peak rate would be expected to be shorter. This is true for either bulk erosion or surface erosion cases (Fig. 2.11).

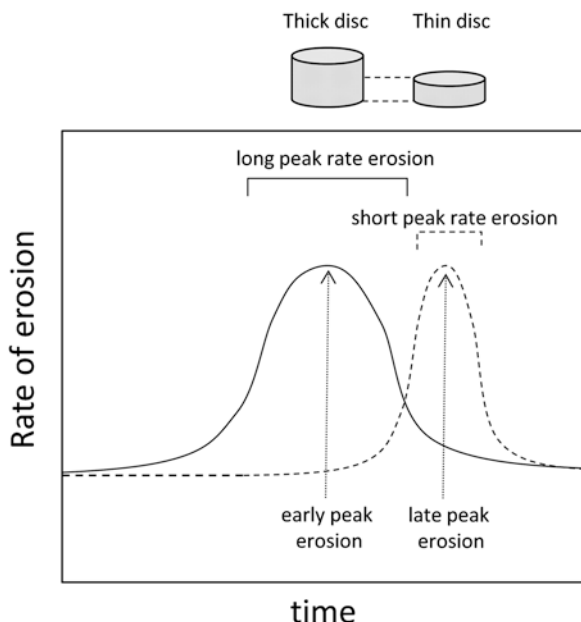


Fig. 2.11 Plot of the changes in the rate of erosion with changes to geometric shape

What if we now move into systems composed of two distinct erosion regimes? This could include a copolymer system, with each domain composed of a polymer with its own distinct erosion regime, or mixture of two polymer systems with different erosion regimes. This approach is commonly used to fabricate systems with multiple release phases. For example, in a layered system that undergoes surface erosion, the outer layer could dissolve at a faster rate than the inner surface. This method could be used to provide the delivery of a two-component system in a time-controlled method, predicted through the use of surface erosion properties.

For systems with a mixture of materials with two distinct erosion regimes, the amount of eroded material over time will show different degradation kinetics with each component. Both the kinetic differences and the positioning of the biodegradable polymer within the system help to dictate the overall shape and threshold of the kinetic curve. For example, in the case of a surface release system with multiple layers, if the outer layer is rapidly degradable relative to the inner layer, the percentage of eroded polymer will begin at a higher rate and will plateau over time. The inner layer would show a more gradual degradation over time due to unimpeded, slow degradation kinetics (Fig. 2.12).

Another way of looking at the system is by observing the weight fractions of each biodegradable domain of either the copolymer or polymer mixture. This will provide information regarding the change in the weight fraction of biodegradable species with the movement of the *erosion zone*, or mode of erosion, through the system [39]. In systems that are spherical or disclike in geometry, this would

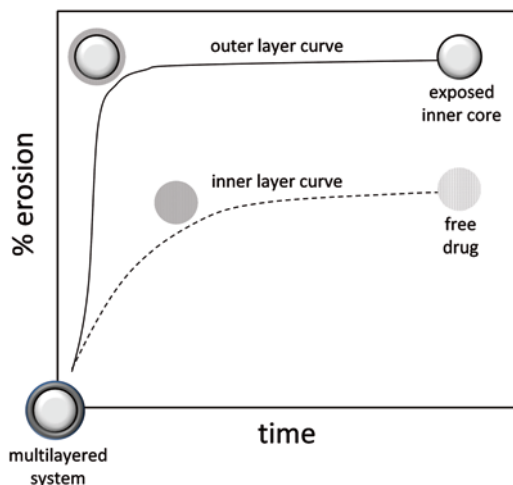


Fig. 2.12 Plot of the percent erosion with changes to the layering of a core-shell material

translate into the movement of the erosion zone uniformly from the outside surface toward the core. Let's look at a specific system comprised of a block copolymer with a polymer domain A, which is an 80:20 weight fraction of polymer functionality A to polymer functionality B, and polymer domain B, which is an 50:50 weight fraction of polymer functionality A to polymer functionality B. What would the system look like as it degrades? We would expect that the outer zone shows a rapid decrease in initial polymer domain A content relative to polymer domain B, whereas the inner zone retains the initial composition for a longer time. Therefore, polymer domain A is degraded from the erosion zone as it moves from outside to inside the system. The shell would then be polymer domain B material.

We have seen the changes to erosion and degradation due primarily to composition. One can infer that molecular weight would then act to change the rate of degradation (Fig. 2.13). A simple way of thinking about this would be cutting spaghetti. It would take less time to cut a plate of short spaghetti into small pieces than it would a plate of long spaghetti. As we move through subsequent chapters of this text, we will revisit erosion and degradation and highlight the effects of shape (Chap. 3), chemical functionality (Chap. 7), and morphology (Chap. 4).

2.2.1.4 Crosslinked-Networked Systems

The perspective of controlled-release materials becomes more complete when we look at crosslinked systems. **Crosslinked**, or **networked**, systems are comprised of any structure that is joined in a three-dimensional lattice of polymeric materials by covalent or secondary bonds. The premise of this approach is to induce the formation of a lattice surrounding drug molecules, in essence encapsulating them in a

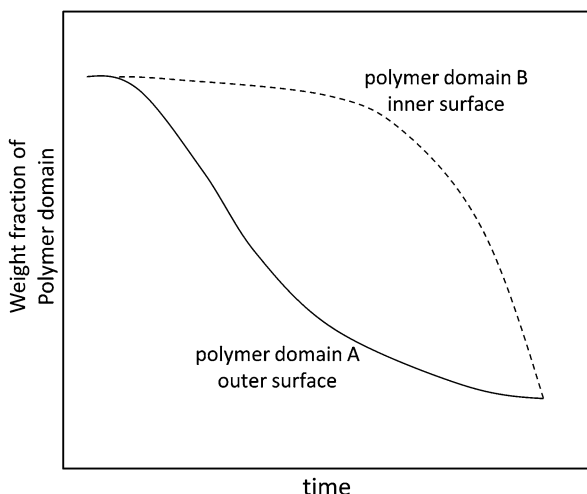


Fig. 2.13 Plot of the weight loss of a multilayered material due to degradation with time

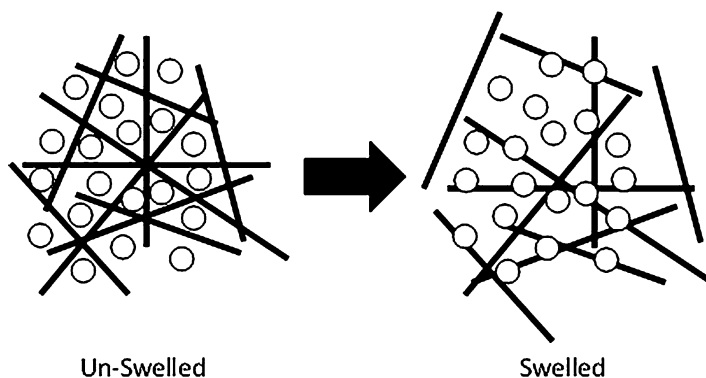


Fig. 2.14 Diagram of crosslinked systems in swelled and unswelled states

matrix [40]. The properties of the lattice typically are similar to those of the matrix systems discussed earlier in this chapter, whereby degradation or swelling drives drug release (Fig. 2.14).

In crosslinked systems, the key design characteristics are (1) crosslink density, (2) type of bonding, (3) molecular weight, (4) rigidity, and (5) T_g [41]. The **cross-link density** dictates the size of the drug species being encapsulated, or vice versa, and relates to the amount of drug that can be released at any given time. It also provides an indication of the structural integrity of the system. Materials with high crosslink densities tend to be stronger materials due to their having a higher number of points to dissipate stresses to the system. Think of it as denser scaffolding on a building. The higher crosslink density also allows for the tighter hold over smaller drug species. In order for release to occur via a crosslink density mechanism, the

crosslink point must be either reversible, as in secondary bonding, or responsive, as in degradation or another stimulus. The **type of bonding** at crosslink points dictates the energy, type, or magnitude, required for the collapse of the system. The collapse of the system induces release of drug species [42]. The system can be designed to have covalent, secondary, or labile bonds that are responsive to swelling, temperature, concentration, light, or sound, among others. The **molecular weight** [43] of constituent polymers can indicate the degree of swelling, when coupled with the crosslink density, or the rate of degradation. The values for M_n , M_w , and PDI are important for determining the extent of control the polymer molecular weight has on these behaviors. The **rigidity** [43], or *structural rigidity of the polymer chain*, ties into the functionality of the polymer and the degrees of bond rotation. As a general rule, the higher the number of bond rotations within the polymer structure, the greater the chain flexibility. The chain flexibility is correlated to the rate and threshold of swelling of the system. The more flexible the system, the higher the swelling, assuming the molecular weight is constant among compared species of polymer. The T_g [43] of constituent polymers also has implications relative to the rigidity of the polymer molecules. Higher bond rotations typically correlate with lower T_g materials since more energy—in this case, temperature—must be removed from the polymer system in order to allow for the slowing of the more numerous bond rotations. While the rigidity provides information regarding the swelling and release kinetics, the T_g provides information regarding the structural integrity of the swelled and unswelled species. In order to fabricate a successful controlled-release system, the designer wants to have either a stable structure upon release or a collapsed one. For a matrix system whose release is based on polymer swelling, one would want the swelled system to have some structural or mechanical integrity. This would lead to a balance between the rigidity of the polymer system and the T_g . For a matrix system whose release is based on biodegradable bulk erosion, the structural integrity is not a required property, and the selection of the polymer system is less restricted (Fig. 2.15).

2.2.1.5 Drug–Polymer Conjugates

To this point in our discussion, we have identified a number of design properties to exploit degradation, erosion, system shape, and release of encapsulated drug cargo. There are a number of drug delivery systems that can take advantage of any single property or combination of these properties [44]. Another approach works on the general premise that drug molecules can be made more physically durable, chemically stable, soluble, and amenable to processing by conjugating the drug to a polymer molecule. These conjugate systems can consist of the following isolated or combined design elements from our previous discussion in this chapter: molecular weight, polydispersity, biodegradation, swelling, crosslinking, chemical functionality, composition, and release kinetics [44] (Fig. 2.16).

The **chemical functionality** is perhaps the most critical point to address related to conjugate systems. The polymer is chosen, in part, to deliver a conjugated molecule

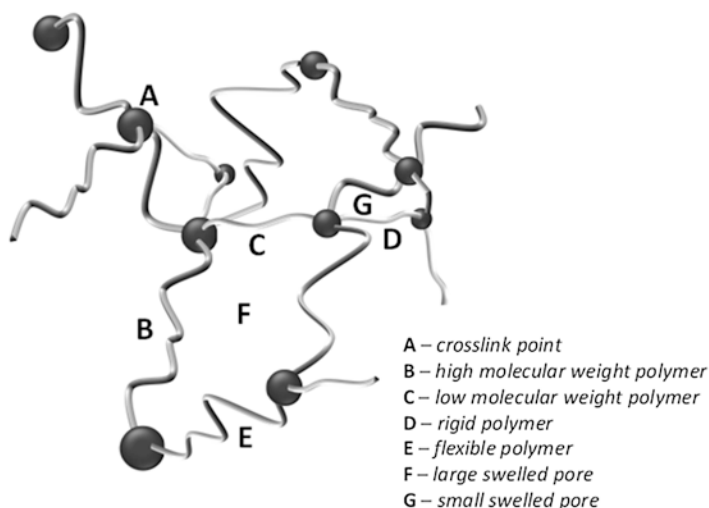


Fig. 2.15 Diagram of the components of crosslinked systems

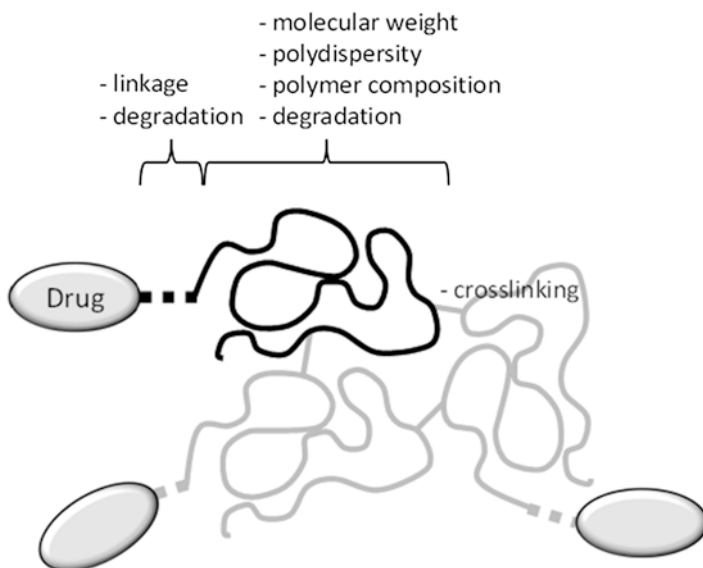


Fig. 2.16 Diagram of the components of drug-polymer conjugate systems

with more favorable aqueous solubility [45]. Care must be taken not to chemically degrade the drug molecule or protein molecule. Typically, the list of polymer candidates consists of the biodegradable polymer systems discussed in this chapter with the addition of PEG as a bioinert polymer. Each candidate is appropriate for the purposes of imparting favorable solubility to the system. In addition to functionality,

the **molecular weight** and polydispersity become relevant as well. The rate or threshold solubility is dictated by molecular weight [46]. The higher the molecular weight of a water-soluble species, or any species for that matter, the longer it takes for that molecule to solvate. Think of it from another perspective. In order for a polymer to be soluble in water, it must hydrogen-bond with water; therefore, the polymer chain must be entirely accessible to water molecules in the system. The larger the molecular weight, the slower the mobility of the polymer chain and the more *sterically* shielded the hydrogen bonding groups on the polymer chain to water. This is, for the most part, a time-dependent phenomenon whereby the polymer chain will eventually become fully solvated provided enough time has elapsed. The **polydispersity** simply allows for insight into the predictability of the behavior. We learned previously that a larger PDI indicates a broader distribution ($\text{PDI} > 2$) of molecular weights within the system. If the system being designed requires specific control over viscosity or degradation, then one would benefit from a narrower PDI ($\text{PDI } 1.0\text{--}1.5$).

The **biodegradation** encompasses two regimes of the design: the backbone polymer and the linkage. The backbone polymer may or may not be desired to be a degradable species. In this case, the degradation of the polymer system would lead to a marked reduction in the localized viscosity, potential change in the solubility of the system, and exposure of the drug to its immediate environment [47]. Care must also be taken that biodegradation conditions do not compromise the drug function themselves or yield degradation products that compromise drug function. The linkage could be one of the degradable functional groups discussed earlier in the *Biodegradation* section in this chapter, or it could be a stimuli-responsive group triggered by temperature [48], light [49], sound [50], magnetic field [51], or electric current [51]. The stimuli-responsive linkages are discussed in greater detail in Sect. 7.2.1. The linkages typically occupy either the end groups of the polymer chain or the side chain (i.e., pendant) groups.

The design of a conjugate system can break into two general classes: particle systems or **crosslink** systems. It should be noted that there are a number of examples for systems comprising both properties (i.e., hydrogel particles); however, for simplicity, we'll start with these two classes here. *Particle systems* are those described earlier in this chapter referring to erodible or degradable matrix systems driven by bulk or surface erosion. *Crosslinked systems* refer to matrix systems whose release is dependent on **swelling** and changes to void volume with the addition of water [52]. Drug–polymer conjugate particle systems typically form 2–5-nm species that can be aggregated to form larger agglomerated microspheres for drug delivery applications [53] (Fig. 2.17). Drug–polymer conjugate crosslinked species can form gelled microsphere or fabricated surfaces for implantation (i.e., embolics).

The mode of **release kinetics** (i.e., zero-order or first-order) will depend on the degradation mode and rate, the swelling rate and absorption threshold (i.e., the maximum amount of water it can hold), crosslink density, polymer molecular weight, and polymer composition [54]. The polymer **composition** refers to the ratio of one polymer functionality to another different polymer functionality expressed in the same polymer molecule. Not only the ratio matters. The positioning within the polymer chain can influence the *self-assembly* of the polymer system in aqueous

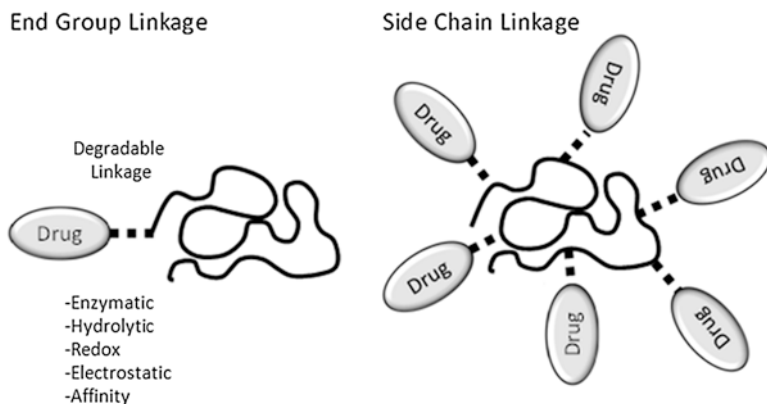


Fig. 2.17 Diagram of design strategies for drug-polymer conjugate systems

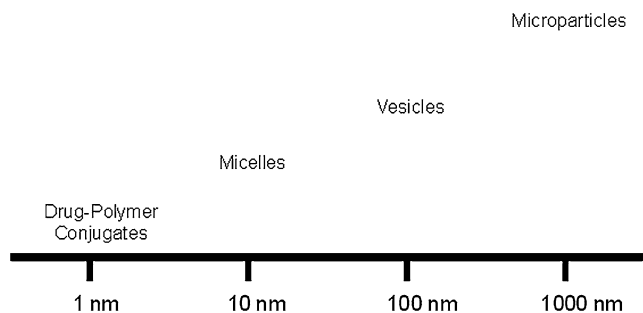


Fig. 2.18 Relationship between size and drug delivery system

environments. Self-assembly is discussed in more detail in Chap. 4. For the purposes of our discussions in this section, the polymer composition is strictly for the determination of degradation and release kinetics.

The drug-polymer conjugate process has a number of advantages over conventional controlled-release methods for several reasons. The size of these conjugate systems falls in the 1–5-nm regime [55], which is significantly smaller than traditional nanoparticles (Chap. 5), micelles (Chap. 4), vesicles (Chap. 4), and microparticles (Chap. 2). The size advantage is strictly application-dependent. The enhanced permeability and retention effect [56] (EPR), which is discussed in more detail in Chap. 4, imparts a size restriction for circulation through physiological systems to be possible. The smaller size regime for the conjugate materials allows for a number of biological modes of evacuation to be circumvented (Fig. 2.18).

Generally, conjugation of a polymer chain to a desired drug molecule or protein allows for adjustment of the dissolution or degradation of the drug complex. Polymer-drug conjugates, or as we will see later in Chap. 5 as **nanocarriers**, function as a drug molecule coupled to a polymer via some degradable or labile linkage [57]. This conjugate system can be fabricated in a number of ways to form

controlled-release materials with perhaps the widest range of applications currently known [58].

In each of our sections, we will deconstruct several critical characteristics of each of the approaches and show examples of the design criteria associated with each. It is important to keep in mind that the rational design of each of these methods relies on a substantially longer list of specific criteria; however, the approach taken here will ground the reader in the major fundamental properties governing the behavior we are seeing.

2.3 Implementation

2.3.1 *Microspheres, Drug–Polymer Conjugates, and Biodegradable Particles*

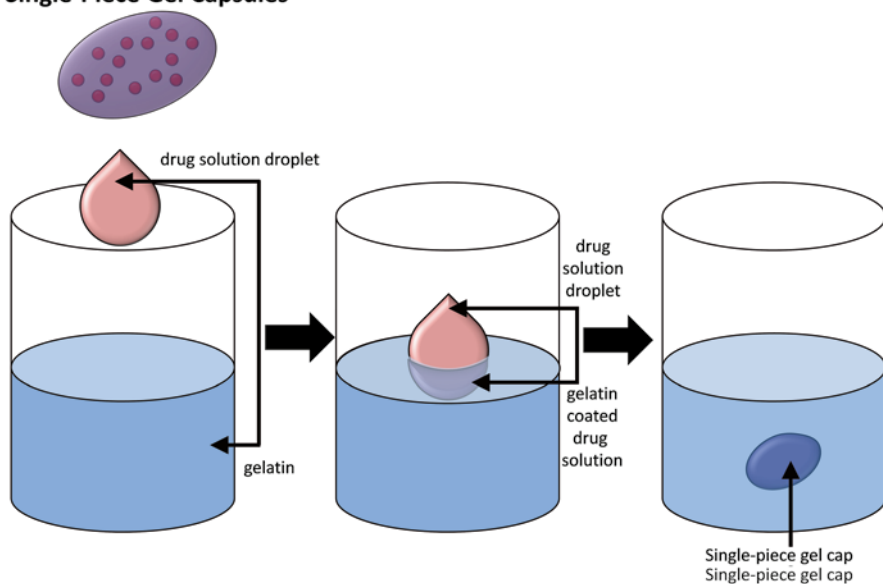
Traditionally, when one is approached with the task of identifying a controlled-release system, the term “gel caps” often arises. This may, in part, be due to the volume of sales, or the media attention in the late 1990s associated with “fast-acting” over-the-counter pain relief [59]. This typical example can be a good foundation to begin the discussion of fabricating a controlled drug release system. Gel capsules traditionally fall into one of two categories: single-piece [60] and two-piece [61] systems. Both are formed from aqueous solutions of gelling agents such as polysaccharides, gelatin, starch, xanthan gum, or a form of cellulose. The single-piece systems are formed when a drop of drug solution is sealed within a drop of the gelling agent, essentially creating a balloonlike structure where the gelatin functions as the barrier network between the drug environment and the surrounding physiological environment. This is an example of a **reservoir system**, which was described earlier in this chapter. The two-piece systems are formed by forming a film layer of gelling agent in the cavities from metal pins. The resulting cavities are blanketed with gelling agent, which looks similar to a hollow bullet casing. Two halves of casing are then filled with drug powder and compressed together to form the capsule (Fig. 2.19).

Based on the fabrication on the macroscale, we can see the influence on the constitution of the drug (i.e., liquid, powder) and its stability. What if we now move from this macroscopic view of the drug delivery to one where we can apply the fundamentals we have talked about in Sects. 2.1 and 2.2 to enhance the efficiency of drug release and delivery?

2.3.1.1 Microspheres

The term **microsphere** refers to spherical particles, typically consisting of polymeric or ceramic materials, in the size regime of 1–1,000 μm in diameter [62]. A more in-depth discussion involving nanoparticles, in the size regime $<200\text{ nm}$,

Single-Piece Gel Capsules



Two-Piece Gel Capsules

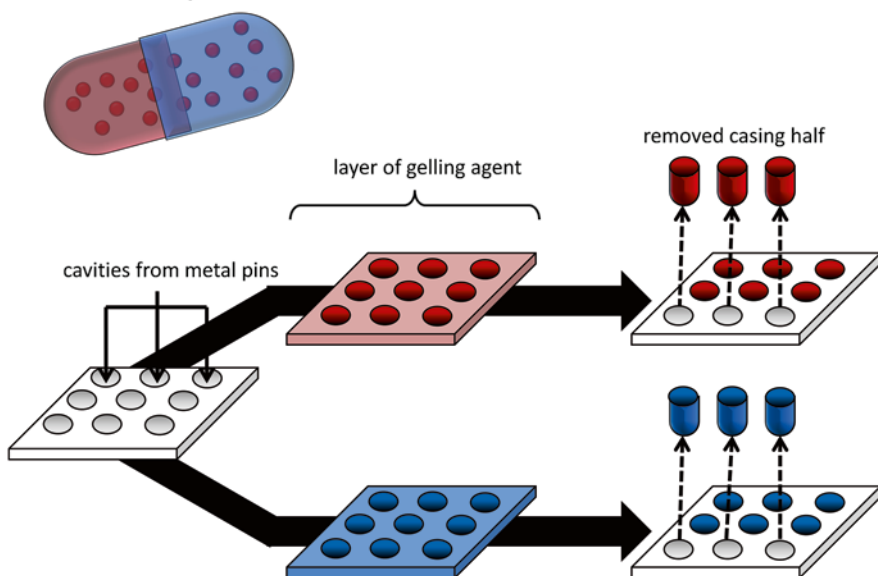


Fig. 2.19 Diagram of the common commercial controlled-release systems

appears in Chap. 5. A microcapsule is similar to a microsphere in that the size regimes are the same; however, the latter is hollow, whereas the former is not necessarily. So a microcapsule is always a microsphere, but a microsphere is not necessarily a microcapsule. The size regime can dictate the location and function of the material. In cases where the particle size is small enough (i.e., $1\ \mu\text{m}$), they are

capable of flow within a physiological system. In cases where the particle size is larger (i.e., 1,000 μm), they are typically stationary. To the designer, the size will tie into the function, where for small particles with flow, the controlled release of systemic drugs may be the goal, and for large particles that are too large for systemic flow, they are implanted at the site of infection. The fabrication of the correct particle size looks not unlike the two gel case examples discussed earlier. The advantages of the microsphere approach are increased active circulation, improved drug delivery, reduced side effects and toxicity, and injectability. There are a number of methods to successfully fabricate microspheres for drug delivery applications. A few of the more relevant methods at they pertain to drug delivery are the emulsion method [63], phase separation coacervation [64], spray drying [65], air suspension [66], solvent extraction [67], and particle replication in nonwetting templates PRINT[®] method(s) [68].

The selection of the drug and polymeric material(s) is of the utmost importance. The polymer must have controlled-release properties, water solubility, stability, low toxicity, drug shielding, long systemic circulation, and biocompatibility. The particle size of the fabrication process is also of critical importance and must tie into the function of the material.

The **emulsion method** [63] consists of single- or double-emulsion techniques. The single-emulsion technique involves solubilizing or dispersing a polymeric component within the aqueous phase of a mixture followed by the addition of an oil phase composed of the drug. Upon addition of the two components, the system is rapidly stirred and crosslinking of either the polymeric component or the oil phase by means of heat or covalent linkages occurs. The double-emulsion technique involves multiple emulsions within one another. The case of a water-in-oil-in-water (w/o/w) emulsion allows for the drug to be contained in either the aqueous phase, oil phase, or both. This is achieved by dispersing an aqueous drug solution in an organic hydrophobic continuous phase containing a soluble polymer, which also may contain drug constituents. The polymer in the hydrophobic phase will encapsulate the drug in the aqueous phase, which is an inverse of what occurs in the single-emulsion case. The solution is then exposed to homogenization to break up the emulsified particulates, followed by the addition of an aqueous polymer solution to stabilize the emulsion particulates formed. The final step involves the evaporation of the organic phase, yielding the last phase of a w/o/w emulsion.

The **phase separation coacervation** [64] method typically involves aqueous drugs but can involve hydrophobic drugs, to form a **reservoir** delivery system. This method involves two phases: a polymer-rich organic phase and an aqueous (or in the hydrophobic case simply) drug phase. The drug phase is added continuously to the organic phase, causing the polymer to be steadily exposed to an unfavorable solvent environment and form a coacervate with the aqueous drug particles (or drug particles) under high stirring to aid in the control of the particle size. The phase separation causing the formation of the coacervate can be accelerated or stabilized using salt, pH, or incompatible polymer.

The **spray-drying** [65] method involves the drying and stabilization of atomized polymer particles of drug molecules. This is achieved by dissolving the drug and polymer in a volatile organic solvent such as tetrahydrofuran, acetone, or methylene

chloride. The solution is homogenized in the event that it is not fully soluble. The polymer–drug solution is then flowed through an orifice that is attenuated through an atomization tip. This process can also be done using the process of electrospinning. In the electrospinning application of this process, the polymer–drug solution would be attenuated through a charged tip, and nitrogen flow coupled with a voltage differential relative to a grounded collection plate leads to the formation of sprayed microparticles.

The **air suspension** [66] method involves the drying and suspension of drug particles in an air stream. The suspended particles are then spray-coated with a rapidly drying polymer solution. Because the particles are consistently cycling through the system, the process allows for sequential coating or layered coating. While solid particles are typically used in this process, liquid particles and emulsions are also possible.

The **solvent extraction** [67] method involves the quenching of particle formation by the extraction of the organic miscible solvent in an aqueous phase. The organic phase is composed of polymer and is chosen to be miscible in water. The drug particles are added to the organic phase, which is then extracted using an aqueous solution. The size of the precipitated microspheres can be controlled by the temperature of the water, the solubility of the polymer, and the ratio of the polymer to water and organic phases.

The **PRINT**[®] [68] method was developed by DeSimone et al. and involves the top-down fabrication of microparticles of differing size, shape, strength, and surface functionality to drive a variety of applications, which include drug delivery. The process involves several steps borrowed from the electronics, materials, and chemical industries. The process begins by creating a master template using common lithographic etching techniques used in the semiconductor industry. A liquid fluoropolymer is then poured into the master template and set by the photocrosslinking process. Once the material is solidified after the crosslinking process, it is removed from the master template, resulting in the precise mold that is used for the remainder of the process. A liquid solution of drug and polymeric material is then poured into the template, pressed by a roller to ensure complete template filling without bleedover, and allowed to set. The solidified material is then transferred to a harvesting film that allows for facile removal of cast materials (Fig. 2.20).

Currently, at the time of drafting this text, **PRINT**[®] materials are not typically referred to as microspheres, due in part to their size (1–3 μm) being on the low end of the size regime commonly used and their ever-changing shape as a driver for their fabrication method. Instead, they are referred to somewhat anomalously as **microparticles**, given the lack of reference to shape. It is becoming ever more accepted within the biomaterials community, however, that shape can be a factor contributing to the enhanced cellular internalization and intracellular trafficking of drug molecules.

The specified internalization of microparticles as large as 3 μm was recently demonstrated in nonphagocytotic HeLa cells by nonspecific endocytosis. The microparticles were poly(ethylene glycol)- (PEG) based hydrogels fabricated using the **PRINT**[®] system with fluorescent probes as intracellular markers. The microparticles

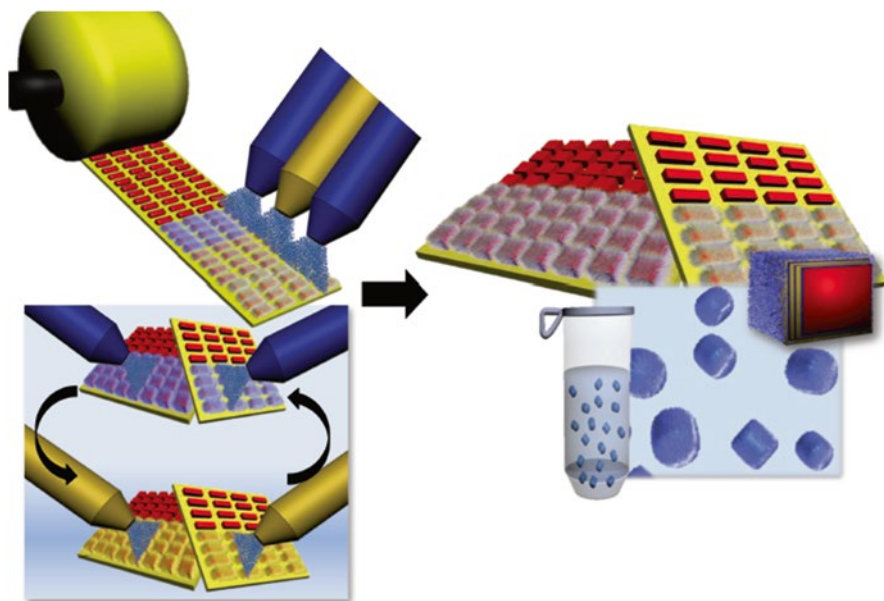


Fig. 2.20 Spray-LbL on PRINT nanoparticles. PRINT particles were fabricated and stored as particle arrays on the harvesting layer. Arrays were subsequently crosslinked under vapor-phase glutaraldehyde/concentrated acid conditions, followed by spray-LbL application (sequential deposition of polycation/wash/polyanion/wash comprising one bilayer). Functionalized particles were harvested by sonication of the arrays in water and purified by filtration and ultracentrifugation [68]

were cubic, cylindrical, and rod-like in shape and fabricated to different sizes and aspect ratios. It is a widely held belief that the upper size threshold for nonspecific internalization of particles is in the 150-nm size regime. Therefore, the particles fabricated using the PRINT[®] process highlight the additional importance of shape in addition to size to dictate preferential internalized drug delivery materials. There was also a benefit within the shape itself, where rodlike particles with a high aspect ratio appeared to internalize more than their cylindrical analogs (Fig. 2.21).

It would be appropriate to take what we have learned to this point in terms of controlled-release materials and apply those learnings to the microspheres developed using the PRINT[®] system. These PRINT[®] microparticles are designed as a **matrix** system. The drugs are to be loaded via the absorption of molecules with water within the PEG-based hydrogel matrix. Similar to how a sponge absorbs water, these hydrogels form in situ with drug molecules. The hydrogel system allows for a **bulk erosion** mechanism in the sense that the swelling of the matrix causes a net decrease in the density of the system since the volume is increasing with decreasing mass. Note that this is *not* bulk erosion in the classical sense since the volume does not remain constant with mass loss. This is in part due to the fact that the system is not undergoing any true erosion but rather a structural fluctuation that is reversible. In other words, one can oscillate the swelling and deswelling of

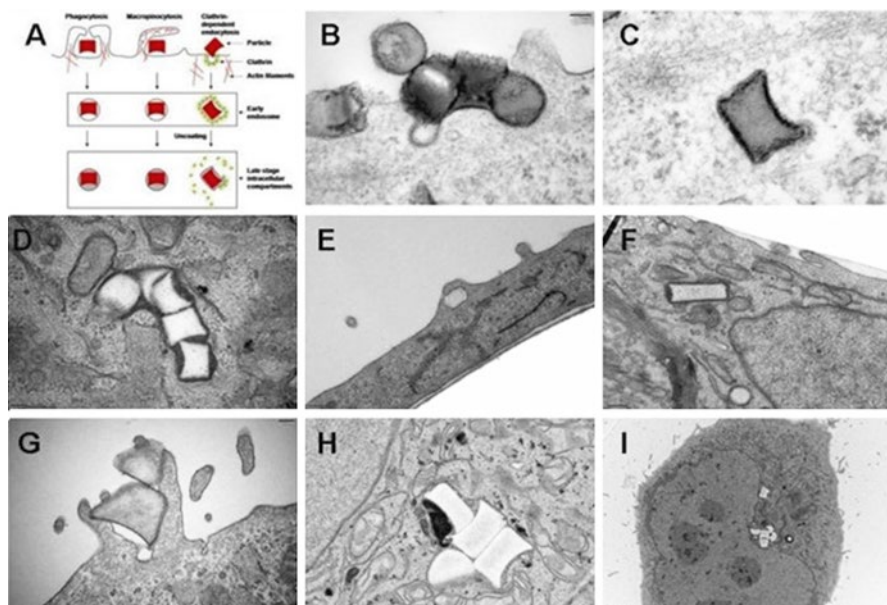


Fig. 2.21 Transmission electron microscopy images of HeLa cells at 37 °C (incubation times in parentheses). (a) Illustration depicting the major pathways of cellular internalization used by PRINT particles. (b–d) With 200-nm (AR-1) cylindrical particles (AR-1) (b and c, 15 min; d, 4 h). (e and f) With 150-nm (AR-3) cylindrical particles (e and f, 1 h). (g–i) With 1-μm (AR-1) cylindrical particles (g, 1 h; h and i, 4 h) [68]

the hydrogel as a mode of releasing drug as opposed to a true bulk erosion system where once the system erodes, the behavior is exhausted. Perhaps the more accurate indicator of the drug delivery within the hydrogel system described here is the zero-order release kinetics. The zero-order or *burst release* kinetics is dependent on the swelling of the hydrogel system and not the concentration of drug or environment (i.e., first-order) to induce the release of drug molecules. This allows for release upon hydration, the rate of which is dependent on crosslinking. The crosslinking within these hydrogels depends primarily on the crosslink density and the molecular weight of the PEG molecules. As an aside, to refer back to our discussion earlier in this section, the type of bonding in this case is covalent to form the crosslinks, the rigidity is considerably low due to the high number of bond rotations possible for PEG polymers, and the T_g is low since PEG is a highly flexible polymer with no functional side groups. The crosslink density dictates the pore size or void space within the hydrogel matrix. As the number of introduced crosslink points increases, the size of the voids decreases. This is, of course, only if the molecular weight is held constant. The molecular weight adds to what we will refer to as the *threshold void space*. This is the maximum void space permitted in the system and is achieved upon full hydration of the PEG polymer chains in water. Therefore, one has the ability to tune the hydrogel system by adjusting the molecular weight and crosslink density to dictate the size of polymer release possible. We discuss hydrogels in more

detail in Chap. 6. The crosslinks in the hydrogel system are covalent in nature, leaving few chemical reaction possibilities in physiological systems. This is somewhat of a relief since, for the most part, these systems are meant to be stable in physiological environments. Finally, these hydrogels are PEG-based, so they are bioinert but not biodegradable. This poses a challenge from the application standpoint since the goal of use is the internalization of the system within a cell, which exposes it to an unknown physiological circulation time. We discuss the advantages of using a biodegradable polymeric material later in this section.

2.3.1.2 Drug–Polymer Conjugates

Earlier in this chapter, we outlined the major criteria for the design of a drug–polymer conjugate system for drug delivery as it relates to its chemical functionality, physical properties, and physical behavior. We can now begin to look at examples of conjugate systems in contact with living cells and tissue.

In cancer therapies, there is often treatment that involves the delivery of two drug components that need to interact in order to become functional [69]. Two such drugs are all-trans-retanoic acid (RA), a metabolite of vitamin A, and cisplatin(IV)-pro-drug [Cis(IV)], a less toxic form of cisplatin that is an extremely effective solid tumor treatment. In combination, RA acts as a sensitizer to Cis(IV), acting to enhance its sensitivity concomitantly. Currently, the variability in the release kinetics, physiological sequestering, and transport inhibition across membranes has led to unpredictable efficaciousness of both drugs. Higher-potency combinations have led to serious side effects. One strategy adopted by Wang et al. [70] has been the use of a block copolymer [MPEG-b-p(LA-co-DHP)] composed of methylated-polyethylene glycol (MPEG) with a biodegradable copolymer of lactic acid (LA-co-DHP) as grafting agents for RA and Cis(IV). The design involves forming a reversible covalent linkage between the RA and the MPEG-b-p(LA-co-DHP) in one pot and forming a reversible covalent linkage between the Cis(IV) and the MPEG-b-p(LA-co-DHP) in a separate pot. The MPEG-b-p(LA-co-DHP) is what is known as an amphiphilic copolymer—which is discussed in more detail in Chap. 4—which self-assembles into large micelles (<200 nm) in water (Fig. 2.22).

The mixture of respective RA and Cis(IV) MPEG-b-p(LA-co-DHP) copolymers in water leads to the formation of a composite micelle of both drug forms within the same *micellar particle*. The premise of this approach is to introduce these micellar particles into the proximity of cancer cells, which will internalize these particles due to the *EPR effect* since their size is 100–200 nm. It should be noted that materials falling within the nanoscale size regime require a series of analytical methods to verify the size and size distribution. This is addressed in more detail in Chaps. 4 and 5. The endocytosis of the micellar particles compartmentalizes them into intracellular lysosomes, which have a lower pH(5) than in the extracellular environment (pH 7.4). The lower pH leads to hydrolysis of the biodegradable lactic acid segments of the MPEG-b-p(LA-co-DHP) copolymers. We know that both the molecular weight and composition of that lactic acid copolymer segment influence the rate

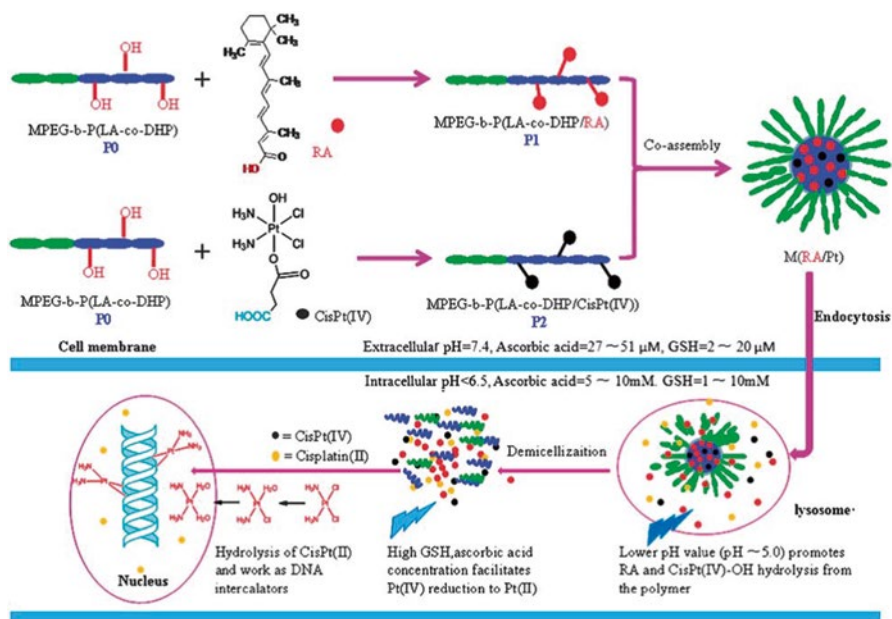


Fig. 2.22 Preparation of M(RA/Pt) micelles and possible mechanism of their action [70]

of hydrolysis within the cell. As an added degree of complexity, as the lactic acid segment degrades, the micelle begins to break down, or *demicellization* occurs. The demicellization exposes the Cis(IV) to the intracellular environment, which has a high concentration of reducing agents such as ascorbic acid to convert the Pt(IV) to Pt(II). The Pt(II) can then be further sensitized by RA. The hydrolyzed Pt(II) acts as a good DNA intercalator, which functions as an effective antitumor drug (Fig. 2.23).

One area of focus in relation to our discussion regarding design is associated with the release kinetics of the two drugs. In the case of Fig. 2.23b we can see that the rate of release of Pt appears to follow a burst release kinetics, whereas the RA follows a first-order release. In addition, the peak release of Pt is approximately five times greater than that of RA. In order to ensure effective hydrolysis of a two-component system within the cell, these components need to be closer in terms of both their peak release as well as their release kinetics. Despite the irregularity of the release kinetics, this drug-polymer conjugate approach does prove to be effective in terms of both the internalization of micellar particles and trafficking of Pt to the nuclei. Additionally, the cytotoxicity (i.e., cell toxicity) experiments using this approach show no significant cell death. This micellar particle drug-polymer conjugate approach highlights several important concepts related to the design of an effective controlled-release system. There is a definitive advantage in terms of cellular toxicity in the use of biodegradable materials for cellular internalization. The conjugation of drugs to a polymer system allows for the experimenter to expose it to a broad series of environmental conditions without the risk of drug decomposition or inactivity. There is an additional layer to this conjugation in that the system

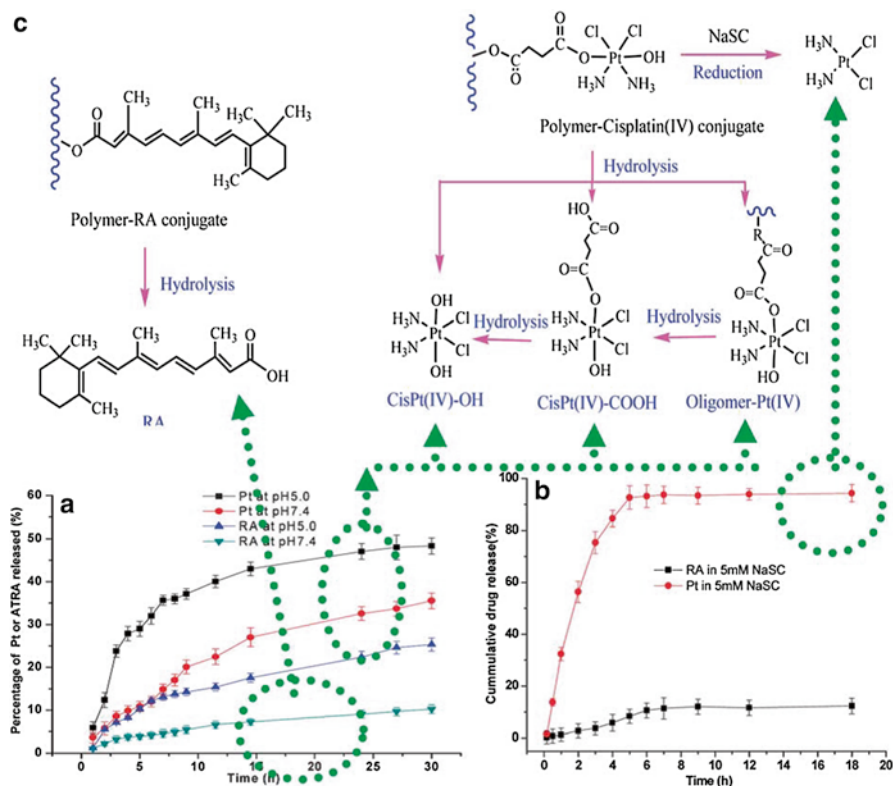


Fig. 2.23 Synthesis of MPEG-b-P(LA-co-DHP/RA) conjugate P1 and MPEG-b-P(LA-co-DHP/CisPt(IV)) conjugate P2 [70]

is also self-assembled into a higher-order micellar structure, further shielding the drug and allowing for multidrug delivery within the same system without significant risk of cross contamination or premature sensitization of the Cis(IV) by the RA. We look more closely at the advantages of using a biodegradable system in the remainder of this chapter (Fig. 2.24).

2.3.1.3 Biodegradable Particles

To finish our discussion of controlled-release systems, we will step back a bit from the biology and look more carefully at the implication of the biodegradation system on release kinetics. Throughout this chapter we have discussed a number of functional domains that have potential for use as biodegradable templates for the fabrication of controlled-release systems. One particular copolymer, poly(lactic-co-glycolic acid) (PLGA), has been the most widely studied in this area for use as matrix material for controlled-release systems [71]. Poly(lactic-co-glycolic acid) has the advantage of being highly tunable in terms of its degradation. The ratio of

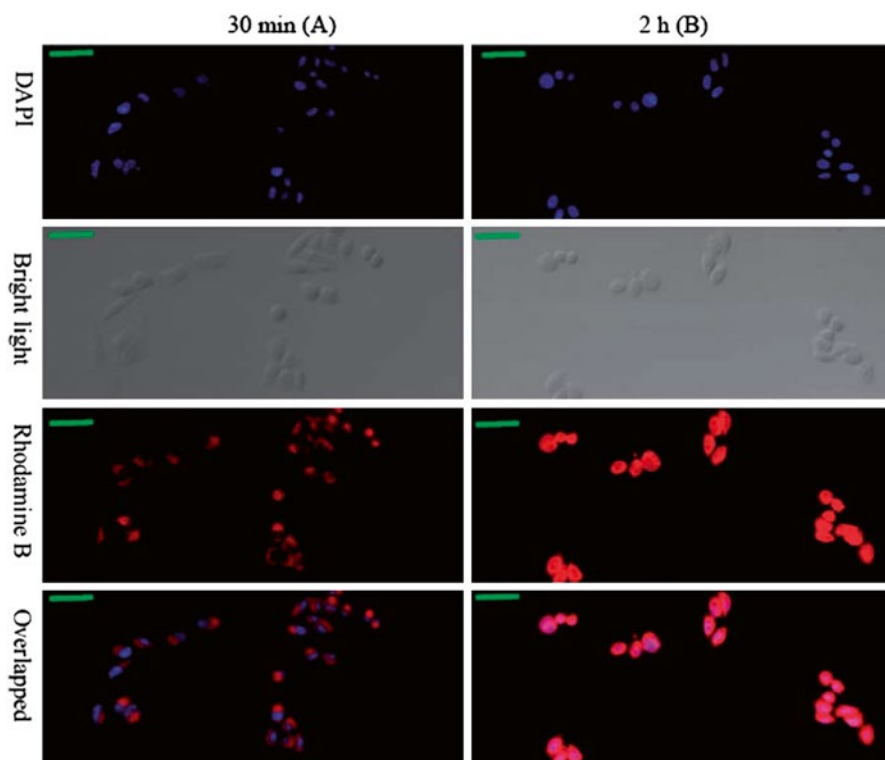


Fig. 2.24 Preparation of M(RA/Pt) micelles and possible mechanism of their action [70]

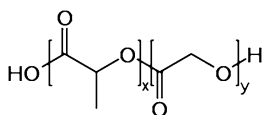


Fig. 2.25 Structure of poly(lactic-co-glycolic acid) (PLGA)

glycolic acid (GA)—the more rapidly degradable functionality—to lactic acid (LA)—the slower to degrade—in the copolymer composition as well as molecular weight allow the experimenter to adjust the biodegradation profile from a matter of days to a matter of months. The degradation of PLGA is a combination of surface diffusion, bulk diffusion, and erosion (Fig. 2.25).

Furthermore, the synthesis of this copolymer via *ring-opening polymerization* has several facile routes with chemistry allowing for amenable coupling reactions with other desired materials such as drug molecules, proteins, nanoparticles, and surfaces (Fig. 2.26).

In an early study into biodegradable nanospheres, Niwa et al. [71] explored the differences between compositions of PLGA fabricated into nanospheres using a spontaneous emulsification process. In the study, indomethacin and 5-fluorouracil

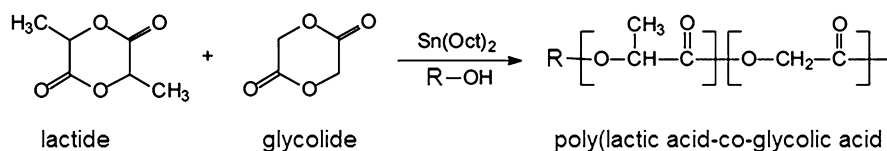


Fig. 2.26 Synthetic polymerization to form poly(lactic-co-glycolic acid) (PLGA) [71]

were used as the hydrophobic drugs in need of stabilization within biodegradable nanospheres for drug delivery. The fabrication of the nanosphere structure is a fairly representative method that we'll discuss in more detail in Chaps. 4 and 5. The process involves dissolving or dispersing the drug and PLGA in a common volatile (i.e., low-vapor-pressure) organic solvent such as acetone or methylene chloride, followed by homogenization. An emulsifying agent is then added to the solvent and the entire system is stirred and exposed to atmosphere for the volatile organic solvent to evaporate. During evaporation, the emulsifying agents stabilize PLGA particles that form around the drug molecule precipitate and allow for the stabilization of significantly smaller-sized species than possible without emulsifiers present.

If we now look more closely at these PLGA nanospheres, we can see the effect of the composition and molecular weight of LA and GA on the release kinetics of the system. Let's look first at the release of indomethacin. It is evident that the increase in the molecular weight of the biodegradable species contributes to the reduction of the indomethacin released. Upon a closer review, it is also evident that the mode of release appears to differ with changes to the molecular weight from 12,279 to 127,598 Da, which correlates with a change from burst release kinetics to first-order kinetics, respectively. This is not entirely surprising if we revisit our previous conversation regarding polymer molecular weight and degradation. The spaghetti analogy suggested that the degradation rate would occur more rapidly in the lower-molecular-weight system. The other point that has not been mentioned thus far is related to a high-molecular-weight polymer phenomenon known as physical entanglements. If we move back to spaghetti as an analogy, we know that often, unbroken spaghetti becomes entangled when you pick it up with a fork, prompting cutting. This entanglement occurs when long pieces of spaghetti form button hooks (i.e., entanglements) with one another or with groups of other pieces. Similarly with polymers, the button hooking of polymer chains occurs in all molecular weight systems. The probability of this effect increases dramatically with molecular weights >30,000, where systems begin to appear similar to a chemically networked or crosslinked matrix. In polymers, this phenomenon also manifests itself by exhibiting a rubberlike or networked behavior that is dependent on the flexibility of the polymer chains (Fig. 2.27).

It should be noted that the PDI of these PLGA polymers fell in the somewhat anomalous 1.5–1.9 range, which we know from our previous discussion in this chapter is somewhere between a statistically uniform and statistically broad distribution of molecular weights. The composition of PLGA in terms of its ratio of LA to GA functional components contributes to the degradation profile as well. Zhou et al. identified

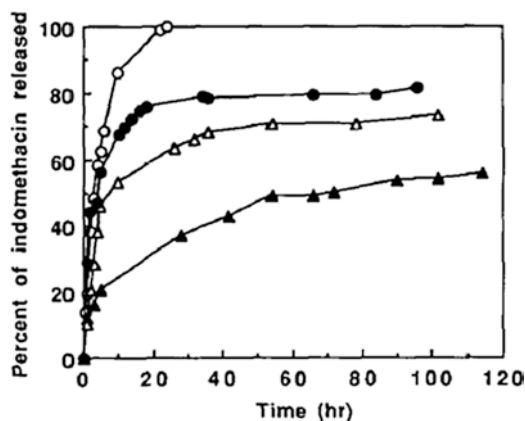


Fig. 2.27 Release profiles of indomethacin from PLGA nanospheres in phosphate buffer (0.1 M, pH 7.4). Key: (open circle) solution; nanospheres with (filled circle) PLGA (85-15)-12 279; (open triangle) PLGA (85-15)-66 671; (filled triangle) PLGA (85-15)-127 598 [71]

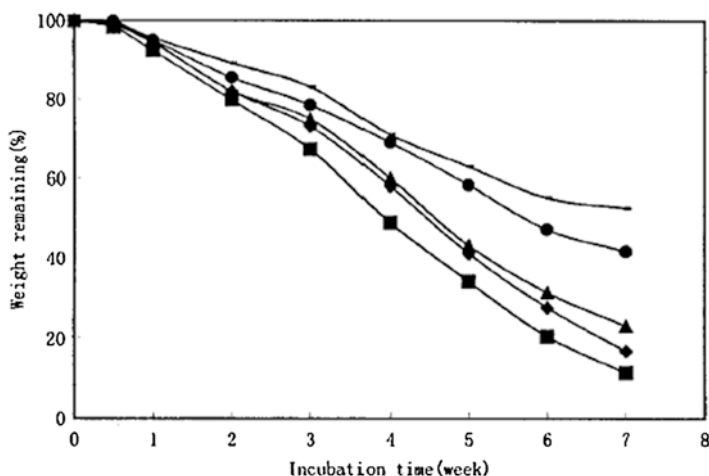


Fig. 2.28 Weight remaining percentage of (hyphen) PLA, (filled circle) PLGA (85/15), (filled triangle) PLGA (75/25), (filled diamond) PLGA (65/35), and (filled square) PLGA (50/50) containing microspheres has incubated in PBS at 37 °C. Each point represents the mean of three individual samples of microspheres [71]

the effects of changes to the LA/GA ratio on low-molecular-weight PLGA species. The lower-molecular-weight species of PLGA have been identified for their utility in applications such as biodegradable linkers and surface treatments as well as in matrix-based controlled-release systems. If we observe the effects of an increased GA composition on the percentage of polymer weight reduction, it is evident that they are indirectly proportional. The decrease in polymer weight with incubation time appears to show a differently shaped curve with each incremental increase in [GA] (Fig. 2.28).

If we look at the degradation profile more closely, there appears to be a sharper dropoff in remaining polymer weight as the GA content >15 %. If we think of this from a chemical perspective, there are critical compositions, depending on respective molecular weights, that allow for more rapid degradation of PLGA. These compositions are dependent on [GA] within the PLGA polymer, which introduces a higher degree of chain flexibility due to decreased sterics in the molecule. Therefore, it is highly predictable to know the degradation kinetics of PLGA provided we know the molecular weight, composition [LA], and composition [GA].

2.3.2 *Summary*

The release of drug species within a physiological environment is critical to its therapeutic function. In Sect. 2.1, we discussed the fundamentals and building blocks for the design of basic controlled-release drug delivery systems. The concepts of diffusion and degradation have provided a grounding in the governing physics and chemistry behind delivering drug molecule systems. In Sect. 2.2, we focused on networked and porous systems ranging from biodegradable matrices, hydrogel particles, conjugated materials, and solid microparticles/nanoparticles and discussed their pharmacokinetic behavior with material modification. Finally, in Sect. 2.3, we discussed nearly commercial systems capable of fine control over the shape and composition of their controlled-release materials. The remaining chapters of this book will expand a number of these fundamentals into other systems designed to exploit physiological behavior to deliver a desired drug molecule(s) to an intended target cell or tissue (Table 2.3).

2.4 Clinical Applications

2.4.1 *Translational Pathways for Novel Drug Delivery Systems*

As shown in the first three sections of this chapter, drug delivery systems present a novel opportunity for the controlled and targeted release of essential therapeutics. Drug delivery systems are increasingly being recognized as a beneficial means for lessening the global disease burden. For instance, a controlled-release system for antibiotics can dramatically simplify the treatment of infectious diseases such as tuberculosis while also lessening the risk of drug-resistant bacterial infections. A controlled-release system for insulin can raise the efficacy of diabetes treatment while also lowering the rate of complications from the disease. The emerging generation of drug delivery systems can enable healthcare that is both more effective and more affordable.

Table 2.3 Common scientific disciplines tied to critical fundamentals in controlled-release drug delivery systems

Fundamental	Disciplines
Degradation (i.e., chemical hydrolysis)	• Chemistry • Materials engineering • Chemical engineering
Biodegradation (i.e., enzymatic degradation)	• Biochemistry • Protein chemistry • Enzymatics • Chemistry
Material fabrication	• Chemistry • Electrical and computer engineering • Materials engineering
Diffusion	• Chemistry • Chemical engineering • Materials engineering • Physics
Erosion (i.e., abrasion, fatigue, cavitation, fatigue)	• Physics • Chemistry • Materials engineering
Pharmacokinetics	• Medicine • Pharmaceutical engineering • Biology
Polymer composition	• Chemistry • Materials engineering
Crosslinking	• Materials engineering • Chemistry

2.4.1.1 Product Development Considerations

Because drug delivery systems incorporate new biomaterials that can modify the pharmacokinetics of therapeutics, the safety and efficacy of such systems must be proven and not assumed. Modern polymeric biomaterials must meet stringent performance requirements and overcome difficult practical challenges. A number of technical factors must be considered in the selection and development of new biomaterials. First, biomaterials must demonstrate sufficient physical and mechanical properties to survive the physiological environment. Second, novel biomaterials must meet biocompatibility specifications. The biomaterial must be biocompatible to the target site, performing in its desired application without causing adverse effect. Both the biomaterial construct and any residuals or degradation products must be noncytotoxic, nonhemolytic, and noninflammatory; undesirable responses such as irritation and sensitization must be avoided. The biomaterial must not interfere with wound healing or induce fibrosis or a foreign body response; it is also necessary that the material does not act as a hospitable environment for bacteria, so that it does not propagate an infection.

If the drug delivery vehicle is degradable, the degradation products must be easily excreted by the kidneys. The molecular weight cutoff for kidney elimination of native globular proteins is considered to be 70,000, which is close to the molecular weight of serum albumin [72]. Hydrophilic polymers utilized in biomaterials may have a higher molecular volume than compact globular proteins; because of the larger effective size of polymers, the molecular weight cutoff for kidney excretion of polymers may be even more stringent. An additional consideration is that polymers with higher molecular weights exhibit longer retention times in the blood.

Finally, drug delivery systems must satisfy commercial requirements and clinical needs. The ideal biomaterial for medical usage should be readily delivered through a user-friendly device. The system should demonstrate adequate shelf stability, and an optimal system should be storable at room temperature, requiring minimal advance preparation time. Production of the biomaterial must be scalable to allow cost-effective manufacture; this quality is particularly critical for global health, as low- and middle-income countries carry 80 % of the worldwide disease burden. The reality is that biomaterials will be most needed in low-resource settings, where staffing and facilities are severely limited. Drug delivery systems that are low-cost and easy to use will have the largest impact on public health.

Throughout the development process, new polymeric biomaterials must be assessed to ensure their suitability for medical applications; the characterization should include mechanical properties, physical/chemical properties, biological properties, shelf stability, and usability. A listing of recommended tests for biomaterials is presented in Table 2.4. The precise properties required of each biomaterial are determined to a large extent by the clinical target. Clinician input is an essential component of the design process, so that surgeon needs and patient needs can be translated into technical specifications. The clinical target should continually guide and inspire the creation of a drug delivery system. Both developing and developed nations are battling poverty and ill health; the situation demands innovative drug delivery solutions.

2.4.1.2 Regulatory Considerations

Regulatory approval is absolutely essential to the translation of novel systems from bench to bedside. Since drug delivery systems are often combinations of drugs with polymeric biomaterials, it is important for drug delivery scientists to understand U.S. Food and Drug Administration (FDA) Standards and Regulations for testing, manufacturing, approval, and marketing of medical devices containing biopolymers.

The first issue that the drug delivery scientist must appreciate is that the FDA does not actually grant blanket approval for individual biopolymers. Rather, the FDA grants approval for complete medical devices for specific clinical indications. In order to correctly specify the approval status of a device containing a biopolymer, the clinical indications of the device must be stated. So, for instance, it would be inaccurate to state, “Alginate is an FDA-approved biopolymer.” It would also be

Table 2.4 Methods for characterization of polymeric biomaterials

Mechanical characterization	Biological characterization
Mechanical strength	Sterility properties
• Tensile strength	• Bioburden
• Shear strength	• Bacterial endotoxin assay
• Impact strength	Tissue compatibility
• Cohesive and adhesive strength	• Cytotoxicity
Physical/chemical characterization	• Cellular inflammation
Curing and reaction properties	• Cell and protein attachment
• Extent of reaction	• Tissue irritation
• Residual starting materials	• Tissue implantation response
• Heat of reaction	• Wound healing
Degradation properties	Hemolysis testing
• Degradation rate	Systemic effects
• Degradation products	• Pyrogenicity
Swelling determination	• Sensitization
Drug release properties	Toxicokinetic evaluation
• Drug delivery rate	• Metabolic fate
• Drug bioactivity	Antimicrobial effects
Device characterization	Encapsulated live cell viability
Accelerated shelf stability test	Clinical characterization
Physical integrity	Ease of use
Device functionality	Patient and clinician acceptance
Device preparation time	Clinical efficacy
	Cost-effectiveness

inaccurate to state, “Calcium alginate wound dressings are FDA-approved.” It would be most accurate to state

Silverlon[®] calcium alginate wound dressings, which consist of a sterile, non-woven pad composed of a High M (mannuronic acid) alginate and a silver nylon contact layer, are FDA-approved for the following clinical indications: management of moderately to heavily exudating partial and full thickness wounds, including first- and second-degree burns, skin graft and donor sites, chronic wounds such as pressure ulcers, dermal ulcers, vascular ulcers, diabetic ulcers, traumatic and surgical wounds.

The FDA explicitly forbids manufacturers from marketing medical devices for any uses other than approved indications. Therefore, biopolymer scientists must be conscientious about endorsing approved clinical uses of medical devices containing biopolymers, and may not promote off-label uses.

2.4.1.3 FDA Definition of a Medical Device

The U.S. Food and Drug Administration defines a medical device as “an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is

- Recognized in the official National Formulary, or the United States Pharmacopoeia, or any supplement to them,
- Intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- Intended to affect the structure or any function of the body of man or other animals, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.” [73]

Medical devices are regulated through the FDA’s Center for Devices and Radiological Health (CDRH). The FDA regulates a broad range of medical devices, including complicated, high-risk medical devices, such as artificial hearts, and relatively simple, low-risk devices, including tongue depressors, as well as devices that fall somewhere in between, for instance, sutures. The FDA has the authority to regulate medical devices before and after they reach the marketplace [74].

2.4.1.4 Medical Device Classifications

Medical devices are classified into Class I, II, and III depending on the intended use and indications of the device as well as the amount of control that the device requires to ensure safety and effectiveness. The classification procedures are described in the Code of Federal Regulations, Title 21, part 860 (usually known as 21 CFR 860) [75]. Regulatory control increases from Class I to Class III. The device classification regulation defines the regulatory requirements for a general device type.

Class I devices are deemed to be low-risk and are therefore subject to the fewest regulatory controls. Class I devices typically have limited, external contact with the human body and are not life-sustaining devices. Class I devices will have almost no role in preventing impairment to human health. For example, dental floss is classified as a Class I device. Other devices that are simple in design such as tongue depressors, elastic bandages, handheld dental instruments, and examination gloves would be classified as Class I devices. Medical devices classified as Class I are subject to “general controls.” This means that Class I devices must follow general FDA policy, which includes registering the medical device, proper branding and labeling, and proper manufacturing techniques. In addition, the FDA must be notified prior to marketing the device.

Class II devices are higher-risk devices than Class I devices and require greater regulatory controls to provide reasonable assurance of the device’s safety and effectiveness. Class II devices have more contact with the human body than Class I devices, yet Class II devices are still not life-sustaining devices. Most medical devices fall into the Class II medical devices category; this category includes X-ray machines, powered wheelchairs, infusion pumps, and surgical and acupuncture needles. Medical devices classified as Class II are subject to “general controls” plus “special controls.” This means that Class II devices must satisfy all requirements for

Class I devices as well as special labeling, mandatory performance standards, and postmarketing surveillance.

Class III devices are generally the highest-risk devices and are therefore subject to the highest level of regulatory control. Class III devices must usually be approved by the FDA before they are marketed. Class III medical devices are typically life-sustaining devices that maintain intimate contact with the human body; a malfunction of such a device would be life-threatening. Class III medical devices include implanted pacemakers, HIV diagnostic tests, heart valves, and implanted cerebral simulators. Medical devices classified as Class III are subject to “general controls” plus “premarket approval.” This means that Class III devices must satisfy all requirements for Class I and Class II devices and, in addition, Class III devices must be premarket-approved by the FDA. Premarket approval necessitates a scientific review of the medical device prior to marketing.

The FDA maintains an online searchable database of classifications for all currently approved medical devices at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm>.

2.4.1.5 FDA Regulatory Approval Process for Medical Devices

The approval pathway for a medical device depends on the device classification. The approval pathways for various device classifications are summarized in the following table.

Device class	Description	Approval path	Example
Class I	Safest devices	Preapproved	Walking cane, toothbrush
Class II	Some risk if misused	Premarket notification (510K)	Blood glucose tester
Class III	Misuse could result in severe injury or death	Premarket approval (PMA)	Heart valve

Class I devices are preapproved; the applicant must provide a notification to the FDA prior to marketing, but there is typically no requirement for a regulatory application.

Class II devices typically require the applicant to file a 510 K premarket notification to the FDA. A 510 K is a premarket submission made to the FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, “substantially equivalent,” to a legally marketed device [76]. The advantage of a 510 K application is that it does not require a clinical trial of the new medical device. For example, suppose you have manufactured a new surgical suture made of a novel silk biopolymer; you could file a 510 K application for the surgical suture and argue that your new suture is “substantially equivalent” to existing silk sutures. The FDA maintains an online searchable database of all submitted 510 K applications at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm>.

A device is substantially equivalent if, in comparison to a predicate, it

- has the same intended use as the predicate, **and**
- has the same technological characteristics as the predicate, **or**
- has the same intended use as the predicate, **and**
- has different technological characteristics and the information submitted to FDA,
 - does not raise new questions of safety and effectiveness, **and**
 - demonstrates that the device is at least as safe and effective as the legally marketed device.

A claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable. A device may not be marketed in the United States until the submitter receives a letter declaring the device substantially equivalent [77].

Class III devices will always require the applicant to file a premarket approval (PMA) application to the FDA. A PMA is the most stringent type of device marketing application required by the FDA. The applicant must receive FDA approval of its PMA application prior to marketing the device. Premarket approval is based on a determination by the FDA that the PMA contains sufficient valid scientific evidence to assure that the device is safe and effective for its intended use(s). An approved PMA is, in effect, a private license granting the applicant (or owner) permission to market the device [78]. The PMA application will always require the applicant to conduct a clinical trial. The FDA maintains an online searchable database of all submitted PMA applications at <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm>.

2.4.1.6 Good Manufacturing Practices

Regardless of classification, all medical devices must be manufactured according to good manufacturing practices (GMPs). Good manufacturing practice ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. Good marketing practice is primarily concerned with pharmaceuticals, biotech products, medical devices, and some foods. Good manufacturing practice regulations address issues including recordkeeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling.

Good manufacturing practice regulations are issued by the FDA and are laid out in Section 21 of the Code of Federal Regulations, Part 820, for medical devices. These regulations are enforced via inspections of manufacturing facilities; failure to comply with GMP requirements can result in regulatory actions against manufacturers and can even jeopardize FDA approval of a new device. Chemical professionals

must recognize that GMP regulations are continually evolving to meet the demands of new technologies; for this reason, GMP is often denoted as cGMP, meaning current good manufacturing practice. Also, keep in mind that GMP regulations represent the minimum requirements for a compliant process; many companies choose to exceed these standards.

To allow manufacturers the maximum flexibility in equipment selection and process design, the FDA does not maintain a list of approved cGMP manufacturing equipment. Instead, the cGMP standards require that equipment be appropriately designed for its intended use and that equipment be designed for thorough cleaning and maintenance. The equipment surfaces in contact with the starting materials, in-process materials, or products must be nonreactive, nonadditive, and nonabsorptive.

Good manufacturing practice also requires documentation of any changes to the fermentation process or equipment; this is known as change control. Change-control procedures apply to changes in operating conditions, standard operating procedures, manufacturing facilities, raw materials, production equipment, technical specifications, software, and quality assurance protocols [79]. A rule of thumb is that change control applies to any change that affects one of the five inputs of a process (also known as the five Ms): man, material, method, machine, and Mother Nature. The goal of change-control procedures is to limit risk by assessing the impacts of any process changes. Whenever engineers introduce a process alteration, the change must be documented and reported, and the adverse impacts on the safety, quality, efficacy, potency, and purity of the product must be evaluated and appropriately mitigated.

2.4.1.7 Good Clinical Practices

For Class III devices requiring clinical trials, these clinical trials must be conducted according to good clinical practices (GCPs). Good clinical practice is a standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials. The objective of GCP is “to provide a unified standard for the European Union (EU), Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions” [80]. Good clinical practice provides assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial subjects are protected.

A quality clinical trial research site must

- protect the welfare and rights of all trial participants,
- assure that the research data generated are valid and can be used to draw reliable conclusions about study outcomes, ensuring benefits to current and future patients,
- comply with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines (<http://ichgcp.net>).

The main elements of GCP are

- the subject's rights, welfare, and confidentiality,
- data validity, integrity, and credibility.

Patient safety and data credibility are important not only for GCP, but also for regulatory authorities as their requirements for clinical investigations on human therapeutic products.

Compliance with GCP also provides public assurance that patients' rights are respected and that the clinical trial data are credible.

The foundation of GCP is the Declaration of Helsinki. The World Medical Association developed the Declaration of Helsinki as a statement of principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data. Good clinical practice should be considered applicable to any investigation where human subjects are participants.

In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. The design of all studies should be publicly available. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

The subjects must be volunteers and informed participants in the research project. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.

To summarize, clinical trials conducted according to GCP must satisfy 13 core principles:

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favorable opinion.
7. The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
12. Investigational products should be manufactured, handled, and stored in accordance with applicable GMP. They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Good clinical practice is an international scientific and ethical standard; it is absolutely crucial for clinical trials of all medical devices containing biopolymers.

2.4.1.8 FDA Advisory Panels

The FDA's advisory committees provide independent, expert advice to the agency on a range of complex scientific, technical, and policy issues. This includes questions related to the development and evaluation of products regulated by the FDA. The agency currently has 48 technical and scientific advisory committees and panels. Although advisory committees provide recommendations to the agency, the FDA makes the final decisions.

An FDA advisory committee is utilized to conduct public hearings on matters of importance that come before the FDA, to review the issues involved, and to provide advice and recommendations to the commissioner. The commissioner has sole discretion concerning action to be taken and policy to be expressed on any matter considered by an advisory committee. An advisory committee may be a standing advisory committee or an ad hoc advisory committee. An advisory committee may

be a policy advisory committee or a technical advisory committee. A policy advisory committee advises on broad and general matters. A technical advisory committee advises on specific technical or scientific issues, which may relate to regulatory decisions before the FDA.

For specific products, advisory committees consider the available evidence and provide scientific and medical advice on safety, effectiveness, and appropriate use. Committees might also advise the agency on broader regulatory and scientific issues. An advisory committee lends credibility to the product review process and provides a forum for public discussion of certain controversial issues. The process helps air issues that do not have simple answers.

An advisory committee must meet the following standards:

1. Its purpose is clearly defined.
2. Its membership is balanced fairly in terms of the points of view represented in light of the functions to be performed. Although proportional representation is not required, advisory committee members are selected without regard to race, color, national origin, religion, age, or sex.
3. It is constituted and utilizes procedures designed to ensure that its advice and recommendations are the result of the advisory committee's independent judgment.
4. Its staff is adequate. The commissioner designates an executive secretary and alternate for every advisory committee, who are employees of the FDA. The executive secretary is responsible for all staff support unless other agency employees are designated for this function.
5. Whenever feasible, or required by statute, it includes representatives of the public interest.

The FDA will consider the following questions in deciding whether to convene an advisory committee:

1. Is the matter of such significant public interest that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?
2. Is the matter at issue so controversial that it would be highly beneficial to obtain the advice of an advisory committee as part of the agency's regulatory decision-making process?
3. Is there a special type of expertise that an advisory committee could provide that is needed for the agency to fully consider a matter?

If one or more of these factors is met, the matter is referred to an advisory committee.

The FDA will convene an advisory committee in the following scenarios [81]:

- The FDA is evaluating a first-of-a-kind, first-in-class medical product for human use.
- The FDA is evaluating a first-in-class antimicrobial for use in food-producing animals.

- The FDA is evaluating a medical product for a significant new indication.
- The FDA is evaluating a novel product or use of new technology.
- The FDA is evaluating a medical product that involves a significant diagnostic, therapeutic, or preventative advance.
- The FDA's assessment of the risk–benefit ratio of a product or class of products is likely to be controversial or it appears that the risks and benefits are of similar magnitude, especially where the products may have a narrow therapeutic effect.
- The FDA has significant safety concerns about a class of products. This scenario includes such concerns in pre- or postmarket situations (e.g., significant safety concerns relating to the premarket review of a medical product regulated by the FDA, or significant safety concerns relating to the postmarket review of such a medical product, including significant concerns about adverse event reports or other data that signal a potential safety issue).
- The FDA has significant questions or concerns about the use of a product in certain subpopulations (e.g., pediatric dosing or a newly discovered contraindication).
- The FDA has significant questions or concerns about a study, including a clinical trial, postmarket assessment, or product development protocol (PDP). The questions or concerns may relate to any aspect of such a study, including human subject protection, novel endpoints or surrogates, the study's design, or its results.
- FDA personnel have a significant difference of scientific opinion on a complex matter, for example, on the interpretation of data or judgments about the risk–benefit ratio of a regulated product.
- The FDA has questions or concerns involving the intersection of several scientific disciplines.
- The FDA is seeking outside expertise on scientific techniques or research.
- The FDA is evaluating whether to switch a product class from one regulatory status to another (e.g., switching a class of drug products from prescription to over-the-counter status.)
- The FDA has significant questions or concerns regarding the development or implementation of a regulatory policy or guidance document.
- The FDA wants independent, outside evaluation of the quality, relevance, or productivity of an agency communication program or research program.

Committee membership typically includes ethnic, gender, and geographic diversity. Members have recognized expertise and judgment in a specific field. Typical members include

- physician-scientists,
- statisticians,
- epidemiologists,
- pharmacologists,
- nutritionists,
- nurses,
- experts in animal (preclinical) studies.

Every meeting of an FDA advisory panel is comprised of an open public hearing followed by closed deliberations, with the committee ultimately delivering a recommendation to the FDA. Such panels can play a crucial role in determining the fate of a novel medical device.

2.4.1.9 FDA GRAS List

Biopolymers may be used not only in medical devices, but also as food additives. It is therefore worthwhile for biopolymer scientists to understand the FDA's Generally Recognized as Safe (GRAS) list. Under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act, any substance that is intentionally added to food is a food additive and is subject to premarket review and approval by the FDA, unless the substance is designated GRAS. A GRAS designation means that the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use [82]. A substance with a GRAS designation can be added to foods without premarket review and approval by the FDA. Moreover, a substance with a GRAS designation is likely to be viewed favorably when incorporated into a medical device.

Under sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act, and the FDA's implementing regulations in 21 CFR 170.3 and 21 CFR 170.30, the use of a food substance may be GRAS either through scientific procedures or, for a substance used in food before 1958, through experience based on common use in food.

- Under 21 CFR 170.30(b), general recognition of safety through scientific procedures requires the same quantity and quality of scientific evidence as is required to obtain approval of the substance as a food additive and ordinarily is based upon published studies, which may be corroborated by unpublished studies and other data and information.
- Under 21 CFR 170.30(c) and 170.3(f), general recognition of safety through experience based on common use in foods requires a substantial history of consumption for food use by a significant number of consumers.

Biopolymers currently listed on the FDA GRAS list include alginate, starch, agar, carrageenan, cellulose, cornsilk, carob bean gum, dextran, dextrans, guar gum, methylcellulose, and pectin.

2.4.2 Summary

Regulatory approval of drug delivery systems is essential for translation into clinical applications. This section has described FDA regulations and standards for medical device classification and approval, as well as the requirements of GMPs and GCPs for the production and evaluation of novel medical devices. This section has also described the important roles of FDA Advisory Panels and the FDA GRAS listings.

With these considerations in mind, the drug delivery scientist can clearly understand the high bar that must be met by medical devices incorporating polymeric biomaterials.

2.5 Problems

2.1 An oncologist has decided to use SIR-Spheres as a targeted release anticancer treatment for a patient with liver tumors. SIR-Spheres are microspheres, typically 10 μm in diameter, which are delivered through a catheter tube in the hepatic artery. The oncologist wants to test the microspheres ahead of time in vitro to verify the pharmacokinetic profile prior to use as a therapy. If the doctor recorded the following data, answer the subsequent questions:

(i) Do the SIR-Spheres follow a first-order or zero-order release profile?

$$\text{Surface area of sphere} = S = 4\pi r^2$$

t	C	C_s	C_t	k	S	dm/dt
Time (h)	Total concentration (ng/ml)	Surface concentration (ng/ml)	Solution concentration (ng/ml)	Diffusion rate constant (/h)	Surface area (μm^2)	Release rate
1	10	10	0	120	314.2	377,040
2	6	6	4	120	314.2	75,408
3	4	4	6	120	314.2	-75,408
4	3	3	7	120	314.2	-150,816
5	2	2	8	120	314.2	-226,224
6	1	1	9	120	314.2	-301,632
7	0.4	0.4	9.6	120	314.2	-346,877

(ii) Are these spheres good candidates as cancer therapies? Why?

(iii) What if the particle shape for SIR-Spheres were actually cylindrical? How would that affect the pharmacokinetic profile?

2.2 Draw *one example* for the chemical reaction for each of the following:

(i) Chemical degradation of a polypeptide

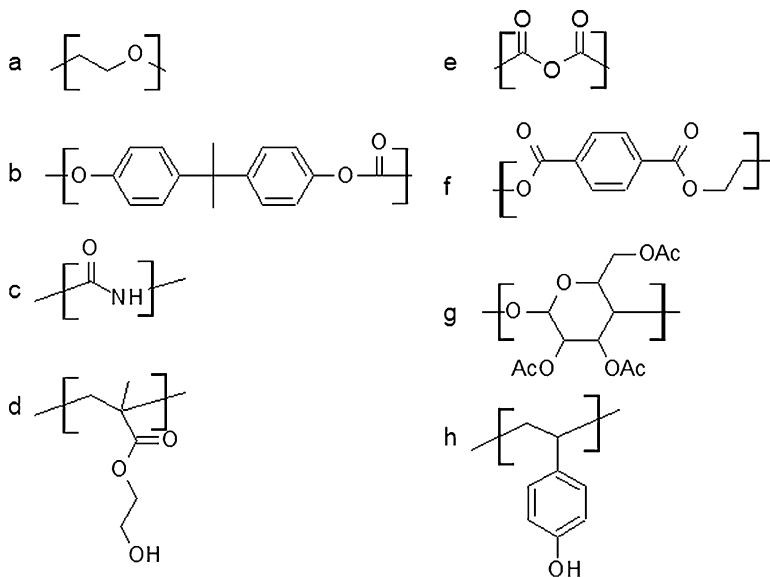
(ii) Enzymatic degradation of a polypeptide

2.3 A pharmaceutical company has developed a drug that requires delivery via the circulatory system. In order to improve the effective dosage range, the R&D department requires the development of a biodegradable polymer with a viscosity similar to that of human blood (i.e., 3–4 cP), which for this polymer corresponds to an $M_n < 1,000$ Da ($\text{PDI} < 2$) at a concentration of 0.1 % (w/v) in water. The research chemist has decided to mix the following different molecular weights in order to reach the desired target. From the following data, please answer the following questions:

- (i) What are the M_n , M_w , and PDI of the resulting mixed-polymer system?
- (ii) Is this mixture going to achieve the effective target?
- (iii) How could the research chemist adjust the polymer mixture to achieve the desired target viscosity?

n	M_w
Polymers	Molecular weight (Da)
2	20,000
4	1,000
1	5,000
1	2,000
4	6,000

2.4 A biomaterials scientist is trying to design a system that has a high-amplitude burst release pharmacokinetic drug release profile. In order to fabricate a relevant system, several factors are necessary. Look at the following polymer structures and answer the following questions:



- (i) What do the structural characteristics of a crosslinked material typically contribute to high burst release behavior?
- (ii) Which of the polymers above exhibit these characteristics from (i)? Why?
- (iii) From the components above, how might a biomaterials scientist change the pharmacokinetic release profile for a crosslinked system from a burst release to Fickian release kinetics?

2.5 The drug molecule *rosuvastatin calcium* is marketed by Astra Zeneca as Crestor® as a lipid-lowering agent for patients with high cholesterol. Oral

cardiovascular treatments typically require a specific residence time in order to increase the efficacy of the drug. One method we have discussed involves the formation of a prodrug system. From your knowledge of prodrug drug delivery systems, answer the following questions:

- (i) We will learn in later chapters that polymers with a high persistence length have been shown to have desirable circulation lifetimes due to their behavior in flowable environments, such as tubes or blood vessels. Using this logic, what polymer structure from Problem 2.4 could be used to enhance the flow of a prodrug system? Why?
- (ii) How would increasing the molecular weight affect the circulation lifetime of the prodrug system from (i)?
- (iii) Which of the following design strategies would offer the most effective degradation (i.e., drug release) profile: End-Group Linkage or Side-Chain Linkage? Why?

2.6 A group has invented a novel drug release technology (listed below as Composition 1) and is comparing it to a currently marketed product. The group compared release of the drug metoprolol from the new composition with that from the existing marketed product (these data are from U.S. Patent Application US20090053310 A1). From your knowledge of controlled-release drug delivery systems, answer the following questions:

Time (hours)	Composition 1 % Cumulative Drug Release	A Marketed product % Cumulative Drug Release
0	0	0
1	15.5	11.87
2	21.2	14.34
4	33.2	25.43
6	42.3	35.50
8	53.7	45.75
12	65.4	64.46
16	76.6	77.44
20	84.9	91.5

- (i) Prepare a plot of drug release versus time for each of these technologies (the new composition and the existing marketed product).
- (ii) Then conduct an analysis to determine the mechanism of drug release from each of these technologies.
- (iii) Calculate rate constants where necessary, and be sure to use correct units.

2.7 Alginic acid, also called algin or alginate, is a viscous gum that is abundant in the cell walls of brown algae. Alginate is biocompatible and forms gels when exposed to calcium ions, so it is under intense investigation as a drug delivery vehicle. Surita Bhatia's research group at the University of Massachusetts–Amherst has studied the release of glucose from various alginate formulations. The ability to tune glucose release could have applications for diabetes management.

- (i) The following glucose release data were obtained for two different alginate formulations:

1% alginate, 0.1 M Ca

Time (min)	% glucose released
1	36.70
2	47.00
3	58.40
4	62.30
5	64.00
6	69.20
8	74.40
10	82.50
15	90.00
20	95.40
25	95.50
30	99.10

3% alginate, 0.1 M Ca

Time (min)	% glucose released
2	46.60
3	53.24
4	57.46
5	60.58
6	67.29
7	69.63
8	71.90
10	79.39
15	82.36
20	91.41
25	95.00
30	94.77
35	98.13

- (ii) Based on your analysis, what is the effect of increasing the alginate concentration on the Higuchi rate constant? How does the alginate concentration affect the diffusivity of glucose out of alginate in this system?

- (iii) The group also studied the effect of calcium ion concentration on glucose release. For example, the following data were obtained for a 1 % alginate, 1.0 M Ca system:

1% alginate, 1.0 M Ca	
Time (min)	% glucose released
1	41.01
2	60.85
3	75.41
4	77.40
5	88.93
6	87.74
7	87.74
8	90.53
9	97.29

Conduct a Higuchi analysis for this formulation, and derive the Higuchi rate constant k_H .

- (iv) Based on your analysis, what is the effect of increasing the Ca concentration on the Higuchi rate constant? How does the Ca concentration affect the diffusivity of glucose out of alginate in this system?

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