A major research thrust in the pharmaceutical and chemical industry is the development of controlled release systems for drugs and bioactive agents. Many of these delivery systems in use and under development consist of a drug dispersed within a polymeric carrier. These carriers are designed to release the drugs in a controlled fashion for times ranging from minutes to years.

The emphasis on the development of novel controlled release devices is in response to the discovery and production of new drugs in today’s expanding biotechnology fields. However, due to the cost of production, it is imperative to develop new methods to deliver these drugs in the most effective manner. A major limitation in the pharmaceutical industry is that the current methods for drug delivery, such as injections, tablets and sprays, are very inefficient for certain drugs and as a result, multiple administrations may be required to keep the concentration of the drug in the blood at a therapeutically effective level for reasonable periods of time. Typically with these types of administration, the drug levels rise to a maximum and fall off to a minimum value, at which time another dosing of the drug is required. This is problematic for drugs with a narrow range of therapeutic concentration as the drug levels will continually rise above the effective range, into the toxic region during which time increased adverse side effects are likely, and fall below the minimum effective concentration, during which time the drug is not effective (Figure 1).

The objective of developing controlled release systems is to successfully engineer systems that could deliver the drug at a specified rate and time period. For the case shown in Figure 1, the release pattern from the device, with respect to rate and duration, would be such that the drug concentration in the body would be kept within the therapeutically effective range for a prolonged period. The obvious advantages of the controlled release system would be that the drug could be administered in a single dosage form with increased efficacy with the same amount drug and reduced side effects.
Figure 1. Plasma drug levels following administration of a drug from a conventional dosage form (a) as compared to an ideal controlled release system (b). The maximum and minimum therapeutic levels are represented by - - - - - (From Peppas and Langer, 1983).

A majority of controlled release devices consist of drugs dispersed within polymer matrices. One major class of polymers that has been identified for use in controlled release applications is hydrogels. Hydrogels are three-dimensional, water-swollen structures composed of mainly hydrophilic homopolymers or copolymers. These materials are for the most part insoluble due to the presence of chemical or physical crosslinks. The physical crosslinks can be entanglements, crystallites or weak associations such as van der Waals forces or hydrogen bonds. The crosslinks provide the network structure and physical integrity.

Hydrogels are classified in a number of ways. They can be neutral or ionic based on the nature of the side groups. They can also be classified based on the network morphology as amorphous, semicrystalline, hydrogen-bonded structures, supermolecular structures and hydrocolloidal aggregates. Additionally, in terms of their network structures, hydrogels can be classified as macroporous, microporous, or nonporous.

Because of their wide range of properties, hydrogels have been considered in drug delivery applications for over 30 years. Two of the most important characteristics in evaluating the ability of a polymeric gel to function in a particular controlled release application are the network
permeability and the swelling behavior. The permeability and swelling behavior of hydrogels are strongly dependent on the chemical nature of the polymer(s) composing the gel as well as the structure and morphology of the network. As a result, there are different mechanisms that control the release of drugs from hydrogel-based delivery devices and these characteristics allow these systems to provide many different release profiles to match desirable release profiles. These systems are commonly as smart or intelligent controlled release systems and classified by their drug release mechanism/profile as diffusion-controlled release systems, swelling-controlled release systems, chemically-controlled release systems and environmentally responsive systems. In this chapter, we review the structure and properties of these new smart pharmaceuticals.

STRUCTURE AND PROPERTIES OF HYDROGELS

In order to evaluate the feasibility of using a particular hydrogel as a drug delivery device, it is important know the structure and properties of the polymer network. The structure of an idealized hydrogel is shown in Figure 2. The most important parameters that define the structure and properties of swollen hydrogels are the polymer volume fraction in the swollen state, \( \nu_{2,s} \), effective molecular weight of the polymer chain between crosslinking points, \( \overline{M}_c \), and network mesh or pore size, \( \xi \).

The polymer fraction of the polymer in the swollen gel is a measure of the amount of fluid that a hydrogel can incorporate into its structure.

\[
\nu_{2,s} = \frac{\text{volume of polymer}}{\text{volume of swollen gel}} = \frac{V_p}{V_{gel}} = \frac{1}{Q}
\]

This parameter can be determined using equilibrium swelling experiments. The molecular weight between crosslinks is the average molecular weight of the polymer chains between junction points, both chemical and physical. This parameter provides a measure of the degree of crosslinking in the gel. This value is related to the degree of crosslinking in the gel (\( X \)) as:

\[
X = \frac{M_o}{2\overline{M}_c}
\]

Here, \( M_o \) is the molecular weight of the repeating units making up the polymer chains.
The network mesh size represents the distance between consecutive crosslinking points and provides a measure of the porosity of the network. These parameters, which are not independent, can be determined theoretically or through a variety of experimental techniques.

**FIGURE 2.** Schematic representation of the cross-linked structure of a hydrogels. $M_c$ is the molecular weight of the polymer chains between crosslinks and $\xi$ is the network mesh size.

**Network Pore Size Calculation**

As the network mesh or pore size is one of the most important parameters in controlling the rate release of a drug from a hydrogel, it is critical to be able to determine the value for a given material. The pore size can be determined theoretically or using a number of experimental techniques. Two direct techniques for measuring this parameter is quasi-elastic laser-light scattering or scanning electron microscopy. Some indirect experimental techniques for determination of the hydrogel pore size include mercury porosimetry, rubber elasticity measurements or equilibrium swelling experiments.

Rubber elasticity experiments represent a relatively easy way to determine the hydrogel mesh or pore size. In these experiments, we can take advantage of the fact that hydrogels are similar to natural rubbers in that they have the ability to respond to applied stresses in a nearly instantaneous manner. These polymer networks have the ability to deform readily under low stresses. Also, following small deformations (typically less than 20%) most gels can fully recover from the deformation in a rapid fashion. Under these conditions, the behavior of the gels can be approximated to be elastic. This property can be exploited to calculate the crosslinking density or molecular weight between crosslinks for a particular gel.
The elastic behavior of crosslinked polymers has been analyzed using classical thermodynamics, statistical thermodynamics and phenomenological models. Based on classical thermodynamics and assuming an isotropic system, the rubber elasticity equation for real, swollen polymer gels can be expressed as:

\[
\tau = \frac{\rho RT}{M_c}(1 - \frac{2M_c}{M_n})(\alpha - \frac{1}{\alpha^2})\left(\frac{\nu_{2,s}}{\nu_{2,r}}\right)^{1/3}
\]  

(3)

In this expression, \(\tau\) is the stress, defined as the force (either tensile or compressive) per cross-sectional area of the un-stretched sample, \(\rho\) is the density of the polymer, \(M_n\) is the molecular weight of linear polymer chains prepared using the same conditions in the absence of a crosslinking agent, \(\alpha\) is the elongation ratio defined as the elongated length over the initial length of the sample and \(\nu_{2,r}\) is the volume fraction of the polymer in the relaxed state, which is defined as the state in which the polymers were crosslinked.

For most any hydrogel, equation (3) can be applied to data obtained in a simple tensile test applied using a constant rate of strain. At short deformations, a plot of stress versus elongation factor \((\alpha - 1/\alpha^2)\) will yield a straight line where the slope is inversely proportional to the molecular weight between crosslinks in the polymer network (Figure 3).

\[\text{FIGURE 3. Tensile stress, } \tau, \text{ at short deformations of poly(methacrylic acid), plotted as a function of the extension factor, } (\alpha - 1/\alpha^2).\]
Based on values for the crosslinking density or molecular weight between crosslinks, the network pore size can be determined by calculating end-to-end distance of the swollen polymer chains between crosslinking points defined in the following equation.

\[ \xi = \alpha(r_o^2)^{1/2} \]  

(4)

In this expression, \( \alpha \) is the elongation of the polymer chains in any direction and \( (r_o^2)^{1/2} \) is the unperturbed end-to-end distance of the polymer chains between crosslinking points. Assuming isotropic swelling of the gels, and using the Flory characteristic ratio, \( C_n \), for calculation of the end-to-end distance, the pore size of a swollen polymeric network can be calculated using the following equation:

\[ \xi = \left( \frac{2C_n M_e}{M_o} \right)^{1/2} l \nu_2^{4/3} \]  

(5)

Where, \( l \) is the length of the bond along the backbone chain (1.54 Å for vinyl polymers).

**DIFFUSION IN HYDROGELS**

The release of drugs and other solutes from hydrogels results from combination of classical diffusion in the polymer network and mass transfer limitations. In order to optimize a hydrogel system for a particular application, the fundamental mechanism of solute transport in the membranes must be understood completely. In this section, we focus on the mechanism of drug diffusion in hydrogels as well as the importance of network morphology in controlling the transport of drugs in hydrogels.

**Macroscopic Analysis**

The transport or release of a drug through a polymeric controlled release device can be described by classical Fickian diffusion theory. This theory assumes that the governing factor for drug transport in the gels is ordinary diffusion. Drug delivery devices can be designed so that other mechanisms control the release rate such as gel swelling or polymer erosion.

For the case of one-dimensional transport (i.e. slab geometry, see Figure 4), Fick’s law can be expressed as:

\[ J_i = -D_{ip} \frac{dC_i}{dX} \]  

(6)
Here, \( J_i \) is the molar flux of the drug (mol/cm\(^2\) s), \( C_i \) is the concentration of drug and \( D_{ip} \) is the diffusion coefficient of the drug in the polymer. For the case of a steady-state diffusion process, i.e. constant molar flux, and constant diffusion coefficient, equation (6) can be integrated to give the following expression:

\[
J_i = K \frac{D_{ip} \Delta C_i}{\delta}
\]  

Here, \( \delta \) is the thickness of the hydrogel and \( K \) is the partition coefficient, defined as

\[
K = \frac{\text{drug concentration in gel}}{\text{drug concentration in solution}}
\]

For many drug delivery devices, the release rate will be time dependent. For unsteady state diffusion problems, Fick’s 2\(^{nd}\) law is used to analyze the release behavior. Fick’s 2\(^{nd}\) law is written as:

\[
\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial x} \left( D_{ip} \frac{\partial C_i}{\partial x} \right)
\]

This form of the equation is for one-dimensional transport with non-moving boundaries and can be evaluated for the case of constant diffusion coefficients and concentration-dependent diffusion coefficients.

**FIGURE 4.** Depiction of the slab geometry used for one-dimensional analysis of Fick’s 2\(^{nd}\) law.
**Constant Diffusion Coefficients**

For the case of concentration independent diffusion coefficients, equation (9) can be analyzed by application of the appropriate boundary conditions. Most commonly, perfect-sink conditions are assumed. Under these conditions, the following boundary and initial conditions are applicable:

\[
t = 0, \quad X < \pm \frac{\delta}{2}, \quad C_i = C_o \tag{10a}
\]

\[
t > 0, \quad X = 0, \quad \frac{\partial C_i}{\partial t} = 0 \tag{10b}
\]

\[
t > 0, \quad X = \pm \frac{\delta}{2}, \quad C_i = C_s \tag{10c}
\]

Here, \(C_o\) is the initial drug concentration inside the gel and \(C_s\) is the equilibrium bulk concentration. Upon application of the boundary conditions, the solution to the diffusion equation can be written in terms of the amount of drug released at a given time, \(M_t\), normalized to the amount released at infinite times, \(M_\infty\).

\[
\frac{M_t}{M_\infty} = 4 \left( \frac{D_{ip} t}{\delta} \right)^{1/2} \left[ \frac{1}{\pi^{1/2}} + 2 \sum_{n=0}^{\infty} (-1)^n \text{erfc} \left( \frac{n\delta}{2(D_{ip} t)^{1/2}} \right) \right] \tag{11}
\]

At short times, this solution can be approximated as:

\[
\frac{M_t}{M_\infty} = 4 \left( \frac{D_{ip} t}{\pi \delta^2} \right)^{1/2} \tag{12}
\]

**Concentration-Dependent Diffusion Coefficients**

In most systems, the drug diffusion coefficient is dependent on the drug concentration as well as the concentration of the swelling agent. In order to analyze the diffusive behavior of drug delivery systems when this is the case, one must choose an appropriate relationship between the diffusion coefficient and the drug concentration. Based on theories that account for the void space in the gel structure, known as free-volume, researchers have proposed the following relationship between the diffusion coefficient and to the gel property. One of the most widely used equations, proposed by Fujita in 1961, relates the drug diffusion coefficient in the gel to the drug concentration in the following manner:

\[
D_{ip} = D_{iw} \exp \left[ -\beta (C_i - C_o) \right] \tag{13}
\]
Here, $D_{iw}$ is the diffusion coefficient in the pure solution, $\beta$ is a constant dependent on the system, and $C_o$ is the concentration of drug in solution. Additionally, a similar equation was written to relate the diffusion coefficient to the concentration of the swelling agent ($C_s$) and the drug in the gel.

$$D_{ip} = D_{iw} \exp[-\beta(C_s - C_i)]$$

(14)

Here, $C_i$ is the swelling agent concentration.

**Effects of Network Morphology**

The structure and morphology of a polymer network will significantly affect the ability of a drug to diffuse through a hydrogel. For all types of release systems, the diffusion coefficient (or effective diffusion coefficient) of solutes in the polymer is dependent on a number of factors such as the structure and pore size of the network, the polymer composition, the water content and the nature and size of the solute. Perhaps the most important parameter in evaluating a particular device for a specific application is the ratio of the hydrodynamic radius of the drug, $r_h$, to the network pore size, $\xi$ (Figure 5). Accordingly, hydrogels for controlled release applications are classified according to their pore size. The transport properties of drugs in each type of gel vary according to the structure and morphology of the network.

**FIGURE 5.** The effects of molecular size ($r_h$) on the diffusion of a solute in a network of pore size $\xi$. 
**Macroporous Hydrogels**

Macroporous hydrogels have large pores, usually between 0.1 and 1 µm. Typically, the pores of these gels are much larger than the diffusing species. In the case of these membranes, the pores are sufficiently large so that the solute diffusion coefficient can be described as the diffusion coefficient of the drug in the water-filled pores. The process of solute transport is hindered by the presence of the macromolecular mesh. The solute diffusion coefficient can be characterized in terms of the diffusion coefficient of the solute in the pure solvent ($D_{iw}$) as well as the network porosity ($\varepsilon$) and tortuosity ($\tau$). Additionally, the manner in which the solute partitions itself within the pore structure of the network will affect the diffusion of the drug. This phenomenon is described in terms of the partition coefficient, $K_p$. These parameters can be incorporated to describe the transport of the drug in the membranes in terms of an effective diffusion coefficient ($D_{eff}$).

$$D_{eff} = D_{iw} \frac{K_p \varepsilon}{\tau}$$  \hspace{1cm} (15)

**Microporous Hydrogels**

These membranes have pore sizes between 100 and 1000 Å. In these gels, the pores are water filled and drug transport occurs due to a combination of molecular diffusion and convection in the water filled pores. In these gels, significant partitioning of the solute within the pore walls may occur for systems in which the drug and polymer are thermodynamically compatible. The effective diffusion coefficient can be expressed in a form similar to that for macroporous membranes.

Transport in microporous membranes is different from macroporous membranes because the pore size begins to approach the size of the diffusing solutes. Numerous researchers have attempted to describe transport for the case of the solute pore size being approximately equal to the network pore size. The rate of the diffusion coefficient in the membrane, $D_{ip}$, and pure solvent, $D_{iw}$, is related to $\lambda$, the ratio of the solute diameter ($d_h$) to the pore size ($\bar{\xi}$).

$$\frac{D_{ip}}{D_{iw}} = (1 - \lambda^2)(1 - 2.104\lambda + 2.09\lambda^3 - 0.95\lambda^5)$$  \hspace{1cm} (16)

$$\lambda = \frac{d_h}{\bar{\xi}}$$  \hspace{1cm} (17)
Nonporous Hydrogels

Non-porous gels have molecular sized pores equal to the macromolecular correlation length, $\xi$ (between 10 and 100 Å). Gels of this type are typically formed by the chemical or physical crosslinking of the polymer chains. In these gels, the polymer chains are densely packed and serve to severely limit solute transport. Additionally, the crosslinks serve as barriers to diffusion. This distance between the physical obstructions is known as the mesh size. Transport of solutes in these membranes occurs only by diffusion.

The macromolecular mesh of nonporous membranes is not comparable to the pore structure microporous gels. Therefore, the theories developed for the microporous membranes are non-applicable to nonporous gels. The diffusional theories developed for nonporous membranes are based on the concept of free-volume. The free-volume is the area within the gel not occupied by the polymer chains. Diffusion of solutes in nonporous membranes will occur within this free volume.

Yasuda presented the first theory describing transport in nonporous gels in the early 1970’s. This theory relates the normalized diffusion coefficient, the ratio of the diffusion coefficient of the solute in the membrane ($D_{2,13}$) to the diffusion coefficient of the solute in the pure solvent ($D_{2,1}$), to degree of hydration of the membrane, $H$ (g water/g swollen gel). The subscripts 1, 2 and 3 represent the solvent or water, solute and the polymer. The normalized diffusion coefficient can be written as

$$\frac{D_{2,13}}{D_{2,1}} = \varphi(q_s) \exp \left[ -B \left( \frac{q_s}{V_{f,1}} \right) \left( \frac{1}{H} - 1 \right) \right] \quad (18)$$

Where $V_{f,1}$ is the free volume occupied by the water, $\varphi$ is a sieving factor which provides a limiting mesh size below which solutes of cross-sectional area $q_s$ cannot pass and $B$ is a parameter characteristic of the polymer. Based on this theory, a permeability coefficient for the drug in the swollen membrane, $P$ is given by

$$P = \frac{D_{2,13}K}{\delta} \quad (19)$$

Peppas later developed a theoretical model to describe solute transport in highly swollen, nonporous hydrogels. In this description, the diffusional jump lengths of the solute were assumed the same in the gel and the pure solvent. Additionally, the free volume of the hydrogel was taken to be the same as the free volume of the pure solvent. Using this approach, the
normalized diffusion coefficient can be described in terms of the degree of swelling and the molecular weight of the polymer chains as

$$\frac{D_{2,13}}{D_{2,1}} = k_1 \left( \frac{\overline{M}_c - \overline{M}_c^*}{\overline{M}_n - \overline{M}_c} \right) \exp \left( - \frac{k_2 r^2_s}{Q - 1} \right)$$

(20)

Where \(k_1\) and \(k_2\) are parameters based on the polymer structure, \(Q\) is the degree of swelling (g swollen polymer/g dry polymer), \(r_s\) is the solute radius, \(\overline{M}_c\) is the molecular weight of the polymer chains between crosslinks, \(\overline{M}_n\) is the molecular weight of linear polymer chains prepared using the same conditions in the absence of a crosslinking agent and \(\overline{M}_c^*\) is the critical molecular weight between crosslinks below which a solute of size \(r_s\) could not diffuse. In this depiction, the term \(\frac{\overline{M}_c - \overline{M}_c^*}{\overline{M}_n - \overline{M}_c}\) is comparable to the sieving factor (\(\varphi\)) presented by Yasuda.

Peppas developed another theory for the case of moderately or poorly swollen, nonporous networks. In this case, the diffusional jump length of the solute in the membrane (\(\lambda_{2,13}\)) does not equal the diffusional jump length of the solute in the pure solvent (\(\lambda_{2,13}\)) and the free volume of the gel does not equal the free volume of the pure solvent. In this model, the normalized diffusion coefficient is written as

$$\frac{D_{2,13}}{D_{2,1}} = f(\nu_2^{-3/4}) \exp \left[ k_3 (\overline{M}_c - \overline{M}_n) - \pi r^2_s l_s \Phi(V) \right]$$

(21)

where \(f(\nu_2^{-3/4})\) is a parameter representing the characteristic size of the diffusional area, \(k_3\) is a structural parameter and \(l_s\) is the length of the solute. The free volume contributions, \(\Phi(V)\), are expressed as

$$\Phi(V) = \frac{V_f - V_3}{(Q - 1)V_f^2 + V_f V_3}$$

(22)

Where \(V_f\) and \(V_3\) are the free volumes of the polymer and the pure solvent.

One special case of nonporous hydrogel that has been modeled extensively is semi-crystalline hydrogels. In this type of gel, the material is physically crosslinked by crystallites in the gel. The diffusion is significantly hindered by the presence of the bulky, crystalline regions. The diffusion coefficient of the solute in the crystalline phase (\(D_c\)) can be expressed in terms of the diffusion coefficient in the amorphous phase (\(D_a\)) as
\[ D_c = \frac{D_a(1 - \nu_c)}{\tau} \]  

(23)

Where \( \tau \) is the tortuosity and \( \nu_c \) is the volume fraction of the crystalline region.

For the case of semi-crystalline hydrogels, the crystallites present the greatest obstacle to diffusion. Therefore, the diffusion coefficient for the gel in the swollen membrane is assumed to be equal to the diffusion coefficient of the solute in the crystalline regions. For the case of moderately or poorly swollen networks, the normalized diffusion coefficient can be written as

\[ \frac{D_{2,13}}{D_{2,1}} = \left( \frac{1 - \nu_c}{\tau} \right) f(\nu_{2,s}^{-3/4}) \exp\left[k_3\left(\bar{M}_c - \bar{M}_n\right) - \pi r_s^2 l_s \Phi(V)\right] \]

(24)

For highly swollen networks, the normalized diffusion coefficient can be expressed as

\[ \frac{D_{2,13}}{D_{2,1}} = \left( \frac{1 - \nu_c}{\tau} \right) \left( \frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*} \right) \exp\left( -\frac{\pi r_s^2 \nu_a}{V_w \nu_s} \right) \]

(25)

Where \( \nu_a \) is the volume fraction of the amorphous region, \( \nu_s \) is the volume fraction of the solvent and \( V_w \) is the volume fraction of the water.

**Experimental Determination of Diffusion Coefficients**

**Membrane Permeability Experiments**

The membrane permeation method is used to study the diffusion coefficients of solutes through thin membranes. The drug permeates through an equilibrium-swollen membrane from a reservoir containing a high concentration of drug (donor cell) to a reservoir containing a lower concentration (receptor).

In these experiments, the drug concentration should be monitored over time in the receptor cell. The solute permeability, \( P \), can be determined from the following expression.

\[ \ln\left(\frac{2C_o}{C_t} - 1\right) = \frac{2A}{Vl} Pt \]

(26)

In this expression, \( C_o \) is the donor cell concentration (initially), \( C_t \) is the time-dependent receptor cell concentration, \( A \) is the cross-sectional area of the membrane, \( V \) is the volume of the cells and \( l \) is the membrane thickness. A plot of \((Vl / 2A) \ln\left(\frac{2C_o}{C_t} - 1\right)\) versus time will yield a straight line of slope \( P \) for a gel swollen at equilibrium. An example of this type of behavior is shown in Figure 6 for the diffusion of vitamin B\(_{12}\) through a poly(ethylene glycol) (PEG) hydrogel.
The diffusion coefficient is related to the partition coefficient by equation (19). The partition coefficient can be determined experimentally through equilibrium partitioning studies. In this type of experiment, hydrogels are swollen to equilibrium in drug solutions of concentration $C_0$. Once equilibrium has been reached, the partition coefficient is calculated using equation (8).

**FIGURE 6.** Permeability of vitamin B$_{12}$ through PEG hydrogels.

**Controlled Release Experiments**

Another relatively easy technique for determination of diffusion coefficients is to measure the release of drug release from thin hydrogels (see Figure 4 for the appropriate geometric dimensions). In release experiments, the membranes containing the dispersed drug are placed in drug-free solutions and the concentration of the drug in the solutions is monitored over time. It is recommended that nearly perfect sink conditions, i.e. low drug concentration in the release medium, be maintained throughout the experiment.
For the initial 60% of the drug release, the data can be fit to the short time approximation to the solution of Fick’s 2nd law to determine the diffusion coefficient.

\[ \frac{M_t}{M_\infty} = 4 \left( \frac{D_0 t}{\pi \delta^2} \right)^{1/2} \]  

This technique is most accurate for systems in which diffusion is the dominant mechanism for drug release.

However, in many systems, the release rate is controlled by diffusion and some other physically phenomenon such as swelling or degradation. In order to determine whether a particular device is diffusion-controlled, the early-time release data can be fit to the following empirical relationship.

\[ \frac{M_t}{M_\infty} = kt^n \]  

The constants, \( k \) and \( n \), are characteristics of the drug-polymer system. The diffusional exponent, \( n \), is dependent on the geometry of the device as well as the physical mechanism for release. For classical Fickian diffusion, the diffusional exponent is 0.5 for slab geometries, 0.45 for cylindrical devices and 0.43 for spherical devices.

By determining the diffusional exponent, \( n \), one can gain information about the physical mechanism controlling drug release from a particular device. Based on the diffusional exponent, the drug transport in slab geometry is classified as Fickian diffusion, Case II transport, Non-Fickian or anomalous transport and Super Case II transport (Table I). Representative release curves for each case are shown in Figure 7. For systems exhibiting Case II transport, the dominant mechanism for drug transport is due to polymer relaxation as the gels swells. These types of devices, known as swelling-controlled release systems, will be described in more detail later. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation.

For the case of anomalous transport, the following model could also be used to describe the release behavior of dynamically swelling hydrogels.

\[ \frac{M_t}{M_\infty} = k_1t + k_2t^{1/2} \]  

This expression describes the release rates in terms of relaxation-controlled transport process, \( k_1t \), and the diffusion-controlled process, \( k_2t^{1/2} \).
Other Techniques

There are several other methods for more precise experimental determination of diffusion coefficients in polymeric systems. These techniques involve more complex instrumentation techniques that cannot be described in depth in this work. These techniques include NMR spectroscopy, scanning electron microscopy, Fourier transform infrared spectroscopy and quasi-elastic laser-light scattering.

Table I. Drug transport mechanisms and diffusional exponents for hydrogel slabs.

<table>
<thead>
<tr>
<th>Diffusional Exponent, $n$</th>
<th>Type of Transport</th>
<th>Time Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Fickian diffusion</td>
<td>$t^{1/2}$</td>
</tr>
<tr>
<td>$0.5 &lt; n &lt; 1$</td>
<td>Anomalous transport</td>
<td>$t^{n-1}$</td>
</tr>
<tr>
<td>1</td>
<td>Case II transport</td>
<td>time independent</td>
</tr>
<tr>
<td>$n &gt; 1$</td>
<td>Super case II transport</td>
<td>$t^{n-1}$</td>
</tr>
</tbody>
</table>

**FIGURE 7.** Comparison of the release profiles of systems exhibiting (- - -) classical Fickian diffusion behavior, (— —) anomalous release behavior and (——) zero-order release or Case II transport.
CLASSIFICATIONS

Because of their nature, hydrogels can be used in many different types of controlled release systems. These systems are classified according to the mechanism controlling the release of the drug from the device. Hydrogel-based drug delivery systems are classified as diffusion-controlled systems, swelling-controlled systems, chemically-controlled systems and environmentally responsive systems. In this section, the mechanism of drug release in each type of system is described.

Diffusion-controlled Release Systems

Diffusion is the most common mechanism controlling release in hydrogel-based drug delivery system. There are two major types of diffusion-controlled systems; reservoir devices (Figure 8) and matrix devices (Figure 9). Drug release from each type of system occurs by diffusion through the macromolecular mesh or through the water filled pores.

Reservoir Systems

Reservoir systems consist of a polymeric membrane surrounding a core containing the drug (Figure 8). Typically, reservoir devices are capsules, cylinders, slabs or spheres. The rate-limiting step for drug release is diffusion through the outer membrane of the device. For a device with a membrane thickness of $\delta$, the molar flux of drug leaving the device is described by equation (7).

$$J_i = K \frac{D_{ip} \Delta C_i}{\delta}$$

(7)

To maintain a constant release rate or flux of drug from the reservoir, the concentration difference must remain constant. This can be achieved by designing a device with excess solid drug in the core. Under these conditions, the internal solution in the core will remain saturated. This type of device is an extremely useful device as it allows for time-independent or zero-order release.

The major drawback of this type of drug delivery system is the potential for catastrophic failure of the device. In the event that the outer membrane ruptures, the entire content of the device will be delivered nearly instantaneously. When preparing these devices, care must be taken to ensure that the device does not contain pinholes or other defects that may lead to rupture.
**FIGURE 8.** Schematic depiction of drug-release from a hydrogel-based reservoir delivery system.

**Matrix Systems**

In matrix devices, the drug is dispersed throughout the three-dimensional structure of the hydrogel (Figure 9). Release occurs due to diffusion of the drug throughout the macromolecular mesh or water filled pores. The fractional release from a one-dimensional device can be modeled using the Fick's 2\textsuperscript{nd} law. In these systems, the release rate is proportional to time to the one-half power. This is significant in that it is impossible to obtain time independent or zero-order release in this type of system with simple geometries.

Drug can be incorporated into the gels by equilibrium partitioning, where the gel is swollen to equilibrium in concentrated drug solution, or during the polymerization reaction. Equilibrium partitioning is the favorable loading method for drug/polymer systems with large partition coefficients or for sensitive macromolecular drugs such as peptides or proteins that could be degraded during the polymerization.

**FIGURE 9.** Schematic depiction of drug-release from a hydrogel-based matrix delivery system.
Swelling-controlled Release Systems

In swelling-controlled release systems, the drug is dispersed within a glassy polymer. Upon contact with biological fluid, the polymer begins to swell. No drug diffusion occurs through the polymer phase. As the penetrant enters the glassy polymer, the glass transition of the polymer is lowered allowing for relaxations of the macromolecular chains. The drug is able to diffuse out of the swollen, rubbery area of the polymers. This type of system is characterized by two moving fronts; the front separating the swollen (rubbery) portion and the glassy regions which moves with velocity, $\upsilon$, and the polymer/fluid interface (Figure 10). The rate of drug release is controlled by the velocity and position of the front dividing the glassy and rubbery portions of the polymer.

For true swelling-controlled release systems, the diffusional exponent, $n$, is 1. This type of transport is known as Case II transport and results in zero-order release kinetics. However, in some cases, drug release occurs due to a combination of macromolecular relaxations and Fickian diffusion. In this case, the diffusional exponent is between 0.5 and 1. This type of transport is known as anomalous or non-Fickian transport.

![FIGURE 10](image-url) **FIGURE 10.** Schematic representation of the behavior of a one-dimensional swelling controlled release system. The water (W) penetrates the glassy polymer (P) to form a gel (G). The drug (D) is released through the swollen layer.
Chemically-controlled Release Systems

There are two major types of chemically-controlled release systems; erodible drug delivery systems and pendant chain systems. In erodible systems, drug release occurs due to degradation or dissolution of the hydrogel. In pendant chain systems, the drug is affixed to the polymer backbone through degradable linkages. As these linkages degrade, the drug is released.

**Erodible Drug Delivery Systems**

Erodible drug delivery systems, also known as degradable or absorbable release systems, can be either matrix or reservoir delivery systems. In reservoir devices, an erodible membrane surrounds the drug core. If the membrane erodes significantly after the drug release is complete, the dominant mechanism for release would be diffusion. Predictable, zero-order release could be obtained with these systems. In some cases, the erosion of the membrane occurs simultaneously with drug release. As the membrane thickness decreased due to erosion, the drug delivery rate would also change. Finally, in some erodible reservoir devices, drug diffusion in the outer membrane will occur. Under these conditions, drug release will not occur until the outer membrane erodes completely. In this type of device, the entire contents will be released in a single, rapid burst. These types of systems have been investigated for use as enteric coatings.

For erodible matrix devices, the drug is dispersed within the three-dimensional structure of the hydrogel. Drug release is controlled by drug diffusion through the gel or erosion of the polymer. In true erosion controlled devices, the rate of drug diffusion will be significantly slower than the rate of polymer erosion and the drug is released as the polymer erodes (Figure 11).

In erodible system, there are three major mechanisms for erosion of the polymer. The first mechanism for erosion is the degradation of the crosslinks. This degradation can occur by hydrolysis of water labile linkages, enzymatic degradation of the junctions, or dissolution of physical crosslinks such as entanglements or crystallites in semi-crystalline polymers. The second mechanism for erosion is solubilization of insoluble or hydrophobic polymers. This could occur as a result of hydrolysis, ionization or protonation of pendant groups along the polymer chains. The final mechanism of erosion is the degradation of backbone bonds to produce small molecular weight molecules. Typically, the degradation products are water-soluble. This type of erosion can occur by hydrolysis of water-labile backbone linkages or by enzymatic degradation of backbone linkages. The most commonly studied erodible polymer
systems are poly(lactic acid) (PLA), poly(glycolic acid) (PGA) and copolymers of PLA and PGA.

**Pendant Chain Systems**

Pendant chain systems consist of linear homo- or copolymers with the drug attached to the backbone chains. The drug is released from the polymer by hydrolysis or enzymatic degradation of the linkages (Figure 12). Zero-order release can be obtained with these systems, provided that the cleavage of the drug is the rate-controlling mechanism.

![Figure 11](image1.png)

**FIGURE 11.** Schematic diagram of drug release from a hydrogel-based erodible delivery system.

![Figure 12](image2.png)

**FIGURE 12.** Schematic diagram of the release of drug from a pendant chain system due to scission of the bonds connecting the drug to the polymer backbone.

**Environmentally Responsive Systems**

Hydrogels may exhibit swelling behavior dependent on the external environment. Over the last thirty years there has been a significant interest in the development and analysis of environmentally or physiologically responsive hydrogels. Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature,
ionic strength, nature and composition of the swelling agent, enzymatic or chemical reaction and electrical or magnetic stimulus. In most responsive networks, a critical point exists at which this transition occurs.

Responsive hydrogels are unique in that they are many different mechanisms for drug release and many different types of release systems based on these materials. For instance, in most cases drug release occurs when the gel is highly swollen or swelling and is typically controlled by gel swelling, drug diffusion, or a coupling of swelling and diffusion. However, in a few instances, drug release occurs during gel syneresis by a squeezing mechanism. Also, drug release can occur due to erosion of the polymer caused by environmentally responsive swelling.

Another interesting characteristic about many responsive gels is that the mechanism causing the network structural changes can be entirely reversible in nature. This behavior is depicted in Figure 13 for a pH- or temperature-responsive gel. The ability of these materials to exhibit rapid changes in their swelling behavior and pore structure in response to changes in environmental conditions lend these materials favorable characteristics as carriers for bioactive agents, including peptides and proteins. This type of behavior may allow these materials to serve as self-regulated, pulsatile drug delivery systems. This type of behavior is shown in Figure 14 for pH- or temperature-responsive gels. Initially, the gel is in an environment in which no swelling occurs. As a result, very little drug release occurs. However, when the environment changes and the gel swells, rapid drug release occurs (either by Fickian diffusion, anomalous transport or case II transport). When the gel collapses as the environment changes, the release can be turned off again. This can be repeated over numerous cycles. Such systems could be of extreme importance in the treatment of chronic diseases such as diabetes.

**FIGURE 13.** Swollen temperature- and pH-sensitive hydrogels may exhibit an abrupt change from the expanded (left) to the collapsed state (center) and then back to the expanded state (right) as temperature and pH change.
FIGURE 14. Cyclic change of pH, T or ionic strength (I) leads to abrupt changes in the drug release rates at certain time intervals in some environmentally responsive polymers.

**Magnetically Responsive Systems**

Magnetically responsive systems consist of polymers or copolymers containing magnetic micro-beads. These systems can be prepared from most polymers, however, the most commonly used copolymer for these systems is the hydrophobic polymer, poly(ethylene-co-vinyl acetate). It is important to note that systems are not typically classified as hydrogels because they do not swell to any appreciable degree. However, this system represents the potential of polymers as smart pharmaceuticals.

The drug release mechanism from a typical magnetic system is shown in Figure 15. The three-dimensional structure of these systems is such that no drug release can occur when no magnetic field is applied. However, when a magnetic field is applied, the microbeads pulsate
allowing for the formation of micropores. Additionally, the pulsation of the beads “squeezes” the drug out of the gel through these pores. When the field is removed, drug release is halted rapidly. Such systems have been targeted for use as pulsatile drug delivery vehicles and have shown to exhibit extremely reproducible behavior.

**FIGURE 15.** Schematic representation of drug release from a magnetically controlled system. Initially, when the field is off (a.), no drug release occurs. When the field is turned on (b.), the oscillations of the beads creates macropores (●) through which drug release occurs (c.). Drug release is halted when the field is switched off.
SUMMARY

Polymeric systems, particularly hydrogels, can be engineered with a wide range of properties that makes them ideal as carriers for pharmaceutically active agents. These new systems can be combined with different drugs and provide for release of drugs at different rates for varying time periods. Furthermore, these systems could provide for modulated drug release in response to physiological changes. This generation of materials represents the beginning of new “smart pharmaceuticals” that will lead to improvements in biological efficacy of administered drugs as well as reduced treatment costs.

RECOMMENDED READING
