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Review article

Hydrogels in pharmaceutical formulations

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Abstract

The availability of large molecular weight protein- and peptide-based drugs due to the recent advances in the field of molecular biology has given us new ways to treat a number of diseases. Synthetic hydrogels offer a possibly effective and convenient way to administer these compounds. Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fluids, and thus resemble, to a large extent, a biological tissue. They are insoluble due to the presence of chemical (tie-points, junctions) and/or physical crosslinks such as entanglements and crystallites. These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as pH, ionic strength and temperature. The aim of this article is to present a concise review on the applications of hydrogels in the pharmaceutical field, hydrogel characterization and analysis of drug release from such devices.

Keywords: pH-sensitive hydrogels; Temperature-sensitive hydrogels; Applications in drug delivery; Drug release; Polymer network structure

1. Introduction

On the occasion of the publication of the 50th volume of our illustrious journal, it is important to recall the major changes of the pharmaceutical field in the last 50 years. In this changing scientific and educational world, the contributions of the pharmaceutical industry are leading to major new solutions of significant medical problems. No longer is the treatment of diabetes, osteoporosis, asthma, cardiac problems, cancer and other diseases based only on conventional pharmaceutical formulations. In fact, Professor Kenneth Dill of the University of California in San Francisco pointed out in a recent article in 'Nature' [1] that 'a key problem of biology and medicine this century has been to reduce the problems of disease to problems of molecular science. Many of the associated methodological advances in biomedical sciences are the result of earlier investments in the basic sciences'. Dill eloquently closes by stating that 'breakthroughs in molecular science have opened a floodgate of new opportunities for curing disease'.

A significant such opportunity has appeared in the pharmaceutical sciences over the past 20 years with the examination of advanced drug delivery formulations. These formulations do not simply release the drug, peptide or protein at some characteristic rate, but do so in a way that the pharmaceutical scientist and molecular designer wants. For example, insulin maybe delivered only when needed, calcitonin may be directed to bypass the stomach and be delivered only in the upper small intestine, and large molecular weight, genetically-engineered molecules are delivered across tissues at acceptable rates.

These recent developments are the subject of this review, which addresses the use of water-swollen, crosslinked biomedical materials as carriers for the development of novel pharmaceutical formulations and for the delivery of drugs, peptides and proteins, as targeting agents for site-specific delivery, or as components for the preparation of protein or enzyme conjugates. The network structure and the thermodynamic nature of the components of these networks play a key role in their diffusional behavior, molecular mesh size changes (especially in environmentally-responsive hydrogels), and the associated molecular stability of the incorporated bioactive agents. We wish to present new and promising techniques for the production of drug and protein delivery formulations that have been developed in our or other laboratories.

1.1. Overview

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or

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biological fluids [2,3]. The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites [4–9]. The latter provide the network structure and physical integrity. These hydrogels exhibit a thermodynamic compatibility with water which allows them to swell in aqueous media [2,3,10–12].

There are numerous applications of these hydrogels, in particular in the medical and pharmaceutical sectors [13–15]. Hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue [13]. Furthermore, the high water content of the materials contributes to their biocompatibility. Thus, hydrogels can be used as contact lenses, membranes for biosensors, linings for artificial hearts, materials for artificial skin, and drug delivery devices [13–17].

1.2. Classification

Hydrogels can be classified as neutral or ionic, based on the nature of the side groups. According to their mechanical and structural characteristics, they can be classified as affine or phantom networks. Additionally, they can be homopolymer or copolymer networks, based on the method of preparation. Finally, they can be classified based on the physical structure of the networks as amorphous, semicrystalline, hydrogen-bonded structures, supermolecular structures and hydrocolloidal aggregates [2–9,18–22].

Hydrogels may also show a swelling behavior dependent on the external environment. These polymers are physiologically-responsive hydrogels [23], where polymer complexes can be broken or the network can be swollen as a result of the changing external environment. These systems tend to show drastic changes in their swelling ratio as a result. Some of the factors affecting the swelling of physiologically-responsive hydrogels include pH, ionic strength, temperature and electromagnetic radiation [23].

2. Monomers and hydrogel structure

2.1. Monomers

A convenient way to classify hydrogels is based on the nature of the side groups; they can be either neutral or ionic. The chemical nature and number of these pendent groups can be precisely controlled by the choice of the chemical entities used in the polymer synthesis. A summary of monomers most commonly used in the preparation of polymeric materials in the pharmaceutical field is given in Table 1.

The literature on the synthesis of new polymer materials has exploded since the first biomedical application of poly (hydroxyethyl methacrylate), known also as PHEMA, by Wichterle and Lim [24] in 1961. Instead of utilizing 'off-the-shelf' polymeric materials designed for use in consumer applications and adapting them for medical purposes, researchers are trying to intentionally design materials that would solve specific drug delivery problems [25]. Therefore, while novel materials based on polymers such as PHEMA, poly(*N*-isopropylacrylamide) (PNIPAAm), and poly(vinyl alcohol) (PVA), are synthesized primarily by new and innovative preparation techniques, a number of new monomers have been prepared for production of polymers with desired properties as well.

Hydrogels are also used as carriers that can interact with the mucosa lining in the gastrointestinal (GI) tract, colon, vagina, nose and other parts of the body due to their ability to prolong their residence time at the delivery location [26]. The interaction between such carriers and the glycoproteins in the mucosa is thought to occur primarily via hydrogen bonding. Therefore, materials containing a high density of carboxyl and hydroxy groups appear to be promising for this type of application. Monomers most often used for the synthesis of mucoadhesive polymers include acrylic and methacrylic acid (MAA). The idea of adhesion promoters diffusing across the polymer/mucin interface has also been introduced [27]. Chains of polymerized ethylene glycol, either freely loaded in the carrier or grafted to the polymer surface, have been utilized as adhesion promoters [27]. The 'stealth' properties of poly(ethylene glycol), known also as PEG, have also been used to reduce the uptake of particulate carriers by the reticuloendothelial system [28]. PEG has also been shown to both lengthen the biological half-life and reduce the immunogenicity of high molecular weight

Table 1
Monomers most often used in the synthesis of synthetic hydrogels for pharmaceutical applications

Monomer abbreviation	Monomer
HEMA	Hydroxyethyl methacrylate
HEEMA	Hydroxyethoxyethyl methacrylate
HDEEMA	Hydroxydiethoxyethyl methacrylate
MEMA	Methoxyethyl methacrylate
MEEMA	Methoxyethoxyethyl methacrylate
MDEEMA	Methoxydiethoxyethyl methacrylate
EGDMA	Ethylene glycol dimethacrylate
NVP	*N*-vinyl-2-pyrrolidone
NIPAAm	*N*-isopropyl AAm
VAc	Vinyl acetate
AA	Acrylic acid
MAA	MAA
HPMA	*N*-(2-hydroxypropyl) methacrylamide
EG	Ethylene glycol
PEGA	PEG acrylate
PEGMA	PEG methacrylate
PEGDA	PEG diacrylate
PEGDMA	PEG dimethacrylate

substances, such as adenosine deaminase (ADA) and asparaginase [29].

2.2. Network structure

The suitability of a hydrogel as a drug delivery device and its performance in a particular application depend to a large extent on its bulk structure. A number of excellent reviews discuss this topic in great detail [30–34]. The most important parameters used to characterize the network structure of hydrogels are the polymer volume fraction in the swollen state ($v_{2,s}$), molecular weight of the polymer chain between two neighboring crosslinking points (M_c), and the corresponding mesh size (ξ).

The polymer volume fraction in the swollen state is a measure of the amount of fluid imbibed and retained by the hydrogel. The molecular weight between two consecutive crosslinks, which can be either of a chemical or physical nature, is a measure of the degree of crosslinking of the polymer. It is important to note that due to the random nature of the polymerization process itself, only average values of M_c can be calculated. The correlation distance between two adjacent crosslinks, ξ, provides a measure of the space available between the macromolecular chains available for the drug diffusion; again, it can be reported only as an average value. These parameters, which are related to one another, can be determined theoretically or through the use of a variety of experimental techniques. Two methods that are prominent among the growing number of techniques utilized to elucidate the structure of hydrogels due to their frequent use, are the equilibrium swelling theory and the rubber elasticity theory.

2.2.1. Equilibrium swelling theory

The structure of hydrogels that do not contain ionic moieties can be analyzed by the Flory–Rehner theory [10]. This thermodynamic theory states that a crosslinked polymer gel, which is immersed in a fluid and allowed to reach equilibrium with its surroundings, is subject only to two opposing forces, the thermodynamic force of mixing and the retractive force of the polymer chains. At equilibrium, these two forces are equal. Eq. (1) describes the physical situation in terms of the Gibbs free energy.

$$\Delta G_{\text{total}} = \Delta G_{\text{elastic}} + \Delta G_{\text{mixing}} \tag{1}$$

Here, $\Delta G_{\text{elastic}}$ is the contribution due to the elastic retractive forces developed inside the gel, and ΔG_{mixing} is the result of the spontaneous mixing of the fluid molecules with the polymer chains. The term ΔG_{mixing} is a measure of the compatibility of the polymer with the molecules of the surrounding fluid. This compatibility is usually expressed by the polymer–solvent interaction parameter, χ_1 [12].

Differentiation of Eq. (1) with respect to the number of solvent molecules, while keeping the temperature and pressure constant, results in Eq. (2), where $\Delta\mu$ is the chemical potential of the penetrating solvent.

$$\mu_1 - \mu_{1,o} = \Delta\mu_{\text{elastic}} + \Delta\mu_{\text{mixing}} \tag{2}$$

In Eq. (2), μ_1 is the chemical potential of the solvent in the polymer gel. and $\mu_{1,o}$ is the chemical potential of the pure solvent. At equilibrium, the difference between the chemical potentials of the solvent outside and inside the gel must be zero. Therefore, the changes of the chemical potential due to mixing and elastic forces must balance each other. The change of chemical potential due to mixing can be expressed using heat and entropy of mixing.

The change of chemical potential due to the elastic retractive forces of the polymer chains can be determined from the theory of rubber elasticity [12,35]. Upon equating these two contributions, an expression can be written for the determination of the molecular weight between two adjacent crosslinks of a neutral hydrogel prepared in the absence of a solvent (Eq. (3))

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{(\bar{v}/V_1)\left[\ln(1 - v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}^2\right]}{v_{2,s}^{1/3} - \frac{v_{2,s}}{2}} \tag{3}$$

Here, $\bar{M}_n$, is the molecular weight of the polymer chains prepared under identical conditions, but in the absence of the crosslinking agent, $\bar{v}$ is the specific volume of the polymer, and V_1 is the molar volume of water.

Peppas and Merrill [36] modified the original Flory–Rehner theory for hydrogels prepared in the presence of water. The presence of water effectively modifies the change of chemical potential due to the elastic forces. This term must now account for the volume fraction density of the chains during crosslinking. Eq. (4) predicts the molecular weight between crosslinks in a neutral hydrogel prepared in the presence of water.

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{(\bar{v}/V_1)\left[\ln(1 - v_{2,s}) + v_{2,s} + \chi_1 v_{2,s}^2\right]}{v_{2,r}\left[\left(\frac{v_{2,s}}{v_{2,r}}\right)^{1/3} - \left(\frac{v_{2,s}}{2v_{2,r}}\right)\right]} \tag{4}$$

Here, $v_{2,r}$ is the polymer volume fraction in the relaxed state, which is defined as the state of the polymer immediately after crosslinking, but before swelling.

The presence of ionic moieties in hydrogels makes the theoretical treatment of swelling much more complex. In addition to the ΔG_{mixing} and $\Delta G_{\text{elastic}}$ in Eq. (1), there is an additional contribution to the total change in Gibbs free energy due to the ionic nature of the polymer network, ΔG_{ionic} (Eq. (5))

$$\Delta G_{\text{total}} = \Delta G_{\text{elastic}} + \Delta G_{\text{mixing}} + \Delta G_{\text{ionic}} \tag{5}$$

Upon differentiating Eq. (5) with respect to the number of moles of solvent keeping T and P constant, an expression similar to Eq. (2) for the chemical potential can be derived in Eq. (6)

$$\mu_1 - \mu_{1,o} = \Delta\mu_{\text{elastic}} + \Delta\mu_{\text{mixing}} + \Delta\mu_{\text{ionic}} \tag{6}$$

Here, the $\Delta\mu_{\text{ionic}}$ is the change of chemical potential due to

the ionic character of the hydrogel. Expressions for the ionic contribution to the chemical potential have been also developed [37–39]. They exhibit strong dependencies on the ionic strength of the surrounding media and on the nature of the ions present in the solvent. Eqs. (7) and (8) are expressions that have been derived for the swelling of anionic and cationic hydrogels prepared in the presence of a solvent, respectively.

$$\frac{V_1}{4I}\left(\frac{\upsilon_{2,s}^2}{\bar{\upsilon}}\right)\left(\frac{K_a}{10^{-pH}-K_a}\right)^2=\left[\ln(1-\upsilon_{2,s})+\upsilon_{2,s}+\chi_1\upsilon_{2,s}^2\right]$$

$$+\left(\frac{V_1}{\bar{\upsilon}\bar{M}_c}\right)\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)\upsilon_{2,r}\left[\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)^{1/3}-\left(\frac{\upsilon_{2,s}}{2\upsilon_{2,r}}\right)\right] \quad (7)$$

$$\frac{V_1}{4I}\left(\frac{\upsilon_{2,s}^2}{\bar{\upsilon}}\right)\left(\frac{K_b}{10^{pH-14}-K_a}\right)^2$$

$$=\left[\ln(1-\upsilon_{2,s})+\upsilon_{2,s}+\chi_1\upsilon_{2,s}^2\right]+\left(\frac{V_1}{\upsilon\bar{M}_c}\right)$$

$$\times\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)\upsilon_{2,r}\left[\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)^{1/3}-\left(\frac{\upsilon_{2,s}}{2\upsilon_{2,r}}\right)\right] \quad (8)$$

In these expressions, I is the ionic strength, and K_a and K_b are the dissociation constants for the acid and base, respectively.

2.2.2. Rubber elasticity theory

Hydrogels resemble natural rubbers in their remarkable property to elastically respond to applied stresses. A hydrogel subjected to a relatively small deformation, less than 20%, will fully recover to its original dimension in a rapid fashion. This elastic behavior of hydrogels can be used to elucidate their structure by utilizing the rubber elasticity theory originally developed by Treloar [35] and Flory [40,41] for vulcanized rubbers and modified to polymers by Flory [12]. However, the original theory or rubber elasticity does not apply to hydrogels prepared in the presence of a solvent. Such expressions were developed by Silliman [42] and later modified by Peppas and Merrill [43].

Here, we present only the form of rubber elasticity theory used to analyze the structure of hydrogels prepared in the presence of a solvent, and leave it up to the reader to consult the original reference for detailed derivations.

$$\tau=\frac{\rho RT}{\bar{M}_c}\left(1-\frac{2\bar{M}_c}{\bar{M}_n}\right)\left(\alpha-\frac{1}{\alpha^2}\right)\left(\frac{\upsilon_{2,s}}{\upsilon_{2,r}}\right)^{1/3} \quad (9)$$

In Eq. (9), τ is the stress applied to the polymer sample, ρ is the density of the polymer, R is the universal gas constant, T is the absolute experimental temperature, and $\bar{M}_c$ is the desired molecular weight between crosslinks.

In order to perform an analysis of the structure of hydrogels using the rubber elasticity theory, experiments need to be performed using a tensile testing system. Interestingly, the rubber elasticity theory has not only been used to analyze chemically, but also physically, crosslinked hydrogels [44–46], as well as hydrogels exhibiting temporary crosslinks due to hydrogen bonding [47].

2.3. Calculation of the mesh size

The primary mechanism of release of many drugs from hydrogels is diffusion, occurring through the space available between macromolecular chains. This space is often regarded as the 'pore'. Depending upon the size of these pores, hydrogels can be conveniently classified as (1), macro-porous; (2), micro-porous; and (3), non-porous. A structural parameter that is often used in describing the size of the pores is the correlation length, ξ, which is defined as the linear distance between two adjacent crosslinks, and can be calculated using the following Eq. (10)

$$\xi=\alpha\left(\bar{r}_o^2\right)^{1/2} \quad (10)$$

Here, α is the elongation ratio of the polymer chains in any direction and $(\bar{r}_o^2)^{1/2}$ is the root-mean-square, unperturbed, end-to-end distance of the polymer chains between two neighboring crosslinks [48]. For isotropically swollen hydrogels, the elongation ratio, α, can be related to the swollen polymer volume fraction, $\upsilon_{2,s}$, using Eq. (11).

$$\alpha=\upsilon_{2,s}^{-1/3} \quad (11)$$

The unperturbed end-to-end distance of the polymer chain between two adjacent crosslinks can be calculated using Eq. (12), where C_n is the Flory characteristic ratio, l is the length of the bond along the polymer backbone (for vinyl polymers 1.54 Å), and N is the number of links/chain that can be calculated by Eq. (13).

$$\left(\bar{r}_o^2\right)^{1/2}=l(C_nN)^{1/2} \quad (12)$$

$$N=\frac{2\bar{M}_c}{M_r} \quad (13)$$

In Eq. (13), M_r is the molecular weight of the repeating units from which the polymer chain is composed. Finally, when one combines Eqs. (10)–(13), the correlation distance between two adjacent crosslinks in a swollen hydrogel can be obtained (Eq. (14))

$$\xi=\upsilon_{2,s}^{-1/3}\left(\frac{2C_n\bar{M}_c}{M_r}\right)^{1/2}l \quad (14)$$

A detailed theoretical characterization of the network structure of the polymer carrier in terms of the correlation length, ξ, in combination with diffusion studies of model drugs and proteins, provides an invaluable insight into the very complex structure of polymer networks and aids in the design of drug delivery carriers [49].

3. Physical, chemical and toxicological properties of hydrogels

3.1. Factors affecting swelling of hydrogels

The crosslinking ratio is one of the most important factors that affects the swelling of hydrogels. It is defined as the ratio of moles of crosslinking agent to the moles of polymer repeating units. The higher the crosslinking ratio, the more crosslinking agent is incorporated in the hydrogel structure. Highly crosslinked hydrogels have a tighter structure, and will swell less compared to the same hydrogels with lower crosslinking ratios. Crosslinking hinders the mobility of the polymer chain, hence lowering the swelling ratio.

The chemical structure of the polymer may also affect the swelling ratio of the hydrogels. Hydrogels containing hydrophilic groups swell to a higher degree compared to those containing hydrophobic groups. Hydrophobic groups collapse in the presence of water, thus minimizing their exposure to the water molecule. As a result, the hydrogels will swell much less compared to hydrogels containing hydrophilic groups.

Swelling of environmentally-sensitive hydrogels can be affected by specific stimuli. Swelling of temperature-sensitive hydrogels can be affected by changes in the temperature of the swelling media. Ionic strength and pH affect the swelling of ionic strength- and pH-sensitive hydrogels, respectively. There are many other specific stimuli that can affect the swelling of other environmentally-responsive hydrogels.

3.2. Dynamics of swelling

The swelling kinetics of hydrogels can be classified as diffusion-controlled (Fickian) and relaxation-controlled (non-Fickian) swelling. When water diffusion into the hydrogel occurs much faster than the relaxation of the polymer chains, the swelling kinetics is diffusion-controlled. A nice mathematical analysis of the dynamics of swelling is presented by Peppas and Colombo [50].

3.3. Mechanical properties

Mechanical properties of hydrogels are very important for pharmaceutical applications. For example, the integrity of the drug delivery device during the lifetime of the application is very important to obtain FDA approval, unless the device is designed as a biodegradable system. A drug delivery system designed to protect a sensitive therapeutic agent, such as protein, must maintain its integrity to be able to protect the protein until it is released out of the system.

Changing the degree of crosslinking has been utilized to achieve the desired mechanical property of the hydrogel. Increasing the degree of crosslinking of the system will result in a stronger gel. However, a higher degree of crosslinking creates a more brittle structure. Hence, there is an optimum degree of crosslinking to achieve a relatively strong and yet elastic hydrogel. Copolymerization has also been utilized to achieve the desired mechanical properties of hydrogels. Incorporating a comonomer that will contribute to H-bonding can increase the strength of the hydrogel.

3.4. Cytotoxicity and in-vivo toxicity

Cell culture methods, also known as cytotoxicity tests, can be used to evaluate the toxicity of hydrogels. Three common assays to evaluate the toxicity of hydrogels include extract dilution, direct contact and agar diffusion. Most of the problems with toxicity associated with hydrogel carriers are the unreacted monomers, oligomers and initiators that leach out during application. Therefore, an understanding the toxicity of the various monomers used as the building blocks of the hydrogels is very important.

The relationship between chemical structures and the cytotoxicity of acrylate and methacrylate monomers has been studied extensively [51]. Several measures have been taken to solve this problem, including modifying the kinetics of polymerization in order to achieve a higher conversion, and extensive washing of the resulting hydrogel. The formation of hydrogels without any initiators has been explored to eliminate the problem of the residual initiator. The most commonly used technique has been gamma irradiation [52–56]. Hydrogels of PVA have been also made without the presence of initiators by using thermal cycle to induce crystallization [8]. The crystals formed act as physical crosslinks. These crystals will be able to absorb the load applied to the hydrogels.

4. Stimuli-sensitive swelling-controlled release systems

Environmentally-sensitive hydrogels have the ability to respond to changes in their external environment. They can exhibit dramatic changes in their swelling behavior, network structure, permeability or mechanical strength in response to changes in the pH or ionic strength of the surrounding fluid, or temperature [57]. Other hydrogels have the ability to respond to applied electrical or magnetic fields, or to changes in the concentration of glucose [57]. Because of their nature, these materials can be used in a wide variety of applications, such as separation membranes, biosensors, artificial muscles, chemical valves and drug delivery devices [57].

4.1. pH-sensitive hydrogels

Hydrogels exhibiting pH-dependent swelling behavior can be swollen from ionic networks. These ionic networks contain either acidic or basic pendant groups [37,38,58–67]. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize, developing fixed charges on the gel. As a result of the electrostatic repulsions, the uptake of solvent in the network is increased [37,38,58–67].

Ionic hydrogels are swollen polymer networks containing pendent groups, such as carboxylic or sulfonic acid, which

show sudden or gradual changes in their dynamic and equilibrium swelling behavior as a result of changing the external pH. In these gels, ionization occurs when the pH of the environment is above the pK_a of the ionizable group [37–39,58–69]. As the degree of ionization increases (increased system pH), the number of fixed charges increases, resulting in increased electrostatic repulsions between the chains. This, in turn, results in an increased hydrophilicity of the network, and greater swelling ratios. Conversely, cationic materials contain pendent groups such as amines [37,38,59–67,70–72]. These groups ionize in media which are at a pH below the pK_b of the ionizable species. Thus, in a low pH environment, ionization increases, causing increased electrostatic repulsions. The hydrogel becomes increasingly hydrophilic and will swell to an increased level.

There are many advantages to using ionic over neutral networks in drug delivery. Their characteristics can be exploited for applications in a wide variety of biomedical applications, such as dental adhesives and restorations, controlled release devices, prodrugs and adjuvants, and biocompatible materials. [62]. The swelling of polyelectrolyte gels is significantly affected by the ionic strength of the swelling agent [37–39,58–71]. As the ionic strength of the swelling agent increases, the concentration of ions within the gel must increase in order to satisfy the Donnan equilibrium. The swelling force is reduced due to increased gel-counter ion interaction and a decrease in the osmotic swelling forces.

Many researchers have studied the dynamic swelling of pH-sensitive networks. The early work of Katchalsky [37,58,59] established that the collapse and expansion of PMAA) gels occurred reversibly by simply adjusting the pH of the fluid. Ohmine and Tanaka [61] observed the sudden collapse of ionic networks in response to sudden changes in the ionic strength of the swelling medium. Studies by Khare and Peppas [69] examined the swelling kinetics of poly(MAA) or poly(acrylic acid) with poly(hydroxy ethyl methacrylate). They observed pH- and ionic strength-dependent swelling kinetics in these gels.

Hydrogels composed of lightly crosslinked *N*-isopropylacrylamide (NIPAAm) and MAA were synthesized and characterized for their sensitivity to external conditions and their ability to control the release of two antithrombotic agents, heparin and streptokinase. PNIPAAm is noted for its sharp change in swelling behavior across the lower critical solubility temperatures of the polymer, while PMAA shows pH-sensitive swelling due to ionization of the pendant carboxylic groups in the polymer. Hydrogel copolymers of NIPAAm and MAA with appropriate compositions were designed to sense small changes in blood stream pH and temperature to deliver antithrombotic agents, such as streptokinase or heparin, to the site of a blood clot [73].

Experiments were performed to show that hydrogels with certain compositions could show both temperature- and pH-sensitivity, and that these changes could control the release of heparin or streptokinase. Equilibrium and pulsatile swelling studies were performed on all polymers to determine to what extent the hydrogels would respond to changes in environmental temperature and pH, and how fast that response would be.

Antithrombotic agents were loaded into the hydrogels by partitioning, and released into buffered solutions as a function of pulsatile changes in pH, temperature and a combination of temperature and pH. The results show that crosslinked polymers containing at least 75% NIPAAm, the rest being MAA, showed a sharp temperature-dependent swelling behavior, while gels even with minimal MAA content were sensitive to solution pH, swelling to a large extent in basic buffer solutions. The drug release studies indicated that pH- or temperature-control of the drug release was marginal, while the combined effects of temperature and pH over small ranges caused the drug release to be patterned after the swelling state of the hydrogel. Because the response time of the gels was long, drug release was often not immediate upon external stimulation, but lagged behind the pH or temperature profile.

We have also synthesized hydrogels based on polyacrylamide, pH-sensitive hydrogel (poly(acrylamide (AAm)-co-acrylic acid)), and temperature-sensitive hydrogels, e.g. poly(AAm-co-diethylAAm). The swelling behavior of these networks was characterized over a temperature range of 16–45°C, and a pH range from 2 to 9. Only the diethylAAm-containing hydrogel demonstrated temperature-sensitivity, with swelling ratios decreasing with increasing temperature over the temperature range studied. In pH buffer solutions, acrylic copolymers showed relatively small swelling ratios in low pH buffers, and extremely high degrees of swelling in high pH regions.

These systems were functionalized with an enzyme (trypsin) by binding the enzyme into a polymer network during a polymerization reaction. The activity of trypsin was then recorded under various temperature and pH conditions, using an assay of a substrate affected by trypsin. Trypsin activity was found to be largely a function of the swelling behavior of the hydrogel networks, with the largest difference being between the high and low temperature regions, which influence the swelling characteristics of the poly(-diethylAAm-co-AAm) hydrogel.

4.2. Temperature-sensitive hydrogels

Temperature-sensitive hydrogels have gained considerable attention in the pharmaceutical field due to the ability of the hydrogels to swell or deswell as a result of changing the temperature of the surrounding fluid. Numerous researchers studied various applications of these hydrogels, such as on–off drug release regulations, biosensors and intelligent cell culture dishes [74].

Thermosensitive hydrogels can be classified as positive or negative temperature-sensitive systems. A positive temperature-sensitive hydrogel has an upper critical solution temperature (UCST). Such hydrogels contract upon cooling

below the UCST. Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST). These hydrogels contract upon heating above the LCST.

Some of the earliest work with temperature-sensitive hydrogels was done by the group of Tanaka [75]. PNIPAAm is the best example of a negative temperature-sensitive hydrogel. Hitotsu et al. [76] worked with crosslinked PNIPAAm and determined that the LCST of the PNIPAAm gels was 34.3°C. They also found that the LCST could be increased by mixing small amounts of ionic copolymers in the gels. Beltran et al. [77] also worked with PNIPAAm gels containing ionic comonomers. They observed results similar to those achieved by Tanaka.

Hoffman [78] proposed the application of PNIPAAm and its copolymers for temperature-modulated drug release by bulk squeezing and surface regulation. In the bulk squeezing system, the drug that is distributed evenly inside the matrix is squeezed out of the system due to the deswelling of the hydrogel as a result of increasing the temperature of the environment above the volume phase transition temperature. In the surface regulation system, the swelling ratio of the skin layer is increased as the temperature of the system is lowered below the volume phase transition temperature, and hence, the drug molecules will be able to diffuse through the skin layer.

Chen and Hoffman [79] prepared P(NIPAAm-g-AA) gels which exhibited temperature- and pH-sensitive behavior. These gels were able to respond rapidly to both temperature and pH changes. The temperature- and pH-dependent swelling behavior were more pronounced in the graft copolymers than in random copolymers containing similar amounts of pH- and temperature-sensitive components.

The group of Okano [80–82] developed an ingenious method to prepare comb-type graft hydrogels of PNIPAAm. The main chain of the crosslinked PNIPAAm contained small molecular weight grafts of PNIPAAm. Under conditions of gel collapse (above the LCST), hydrophobic regions were developed in the pores of the gel, resulting in a rapid collapse. These materials had the ability to collapse from a fully swollen conformation in less than 20 min, while comparable gels that did not contain graft chains required up to a month to fully collapse.

The ability of PNIPAAm and its copolymers to exhibit a hydrophilic nature below the LCST and a hydrophobic nature above the LCST has attracted many researchers to create surfaces for cell culture systems [83–87]. Most cells attach and grow on hydrophobic surfaces, such as polystyrene. However, cells do not attach to a hydrophilic surface, and hence, will not grow. Currently, the method to detach the grown cell is by using enzyme or mechanical means. These methods have been proven to cause damages to the cells. By applying a coating of the temperature-sensitive polymer on top of the cell culture dishes, the cells can be detached easily by their own mechanism by simply changing the temperature. By changing the temperature from above the LCST to below it, the nature of the coating changes from hydrophobic to hydrophilic, and hence, the cells will detach from the hydrophilic surface.

Inoue et al. [88] synthesized hydrogels grafted with oligomers with two different LCSTs. The oligomers of choice were carboxy-terminated oligo NIPAAm, oligo(*N*-vinylcaprolactam) (VCL) and a random co-oligomer of NIPAAm and AAm. The resulting hydrogels showed two volume phase transition temperatures corresponding to the LCSTs of the grafted side chains of oligo NIPAAm and oligo VCL. They explored the possibility of applying this hydrogel to store and retrieve information as a function of temperature.

Conjugates of PNIPAAm with various enzymes have also been reported [89,90]. Hoffman and associates synthesized conjugates of oligomer of PNIPAAm and trypsin. These conjugates are soluble in solution and can catalyze enzymatic reactions. They can then be separated from the solution by thermal precipitation. The recovery of the conjugates by thermal precipitation was highly efficient (more than 95%) even after 14 cycles through the LCST. The enzyme conjugates were found to be more stable than the native trypsin both in solution and precipitated states.

Jeong et al. [91] synthesized a new biodegradable triblock copolymer of poly(ethylene glycol-b-(DL-lactic acid-co-glycolic acid)-b-ethylene glycol) (PEG–PLGA–PEG). This copolymer shows sol-to-gel or gel-to-sol transitions as temperature increases monotonically. This thermoreversible copolymer is very important for drug delivery applications because it can be injected as a free-flowing solution (sol) at room temperature. Upon injection into the body, the copolymer becomes a gel at body temperature.

Another promising application of temperature-sensitive gels is controlled drug delivery for highly sensitive therapeutic agents. Kim and associates [92] developed a hydrogel of PNIPAAm and PAA which was able to effectively release the protein drug, calcitonin, in response to temperature and pH changes. Similar work was done by the group of Peppas [93]. They prepared block copolymers of PNIPAAm and PMAA which had the ability to respond to both temperature and pH. Using these materials, they were effectively able to modulate the release kinetics of streptokinase.

Micro- or nano-particulate devices composed of hydrogels or containing hydrogel components may have a great advantage over disk- or film-shaped macrogels hitherto developed, because they may have an improved swelling kinetics of hydrogels involving thermosensitivity of drug release property and a wide variety of biomedical applications due to their small size. A typical example of such devices was reported very recently [94]. Fig. 1 illustrates microcapsules showing the thermosensitive, controlled release in question. A key structural feature of this microcapsules is their composite coat, consisting of nanoparticles with crosslinked poly(NIPAAm) shells dispersed in a thermo-insensitive ethylcellulose matrix. As shown in Fig. 1, at low temperatures, the permeability of the membranes is low because of absence of void formation by the swollen PNIPPAm shells in the microcapsule membrane, leading to

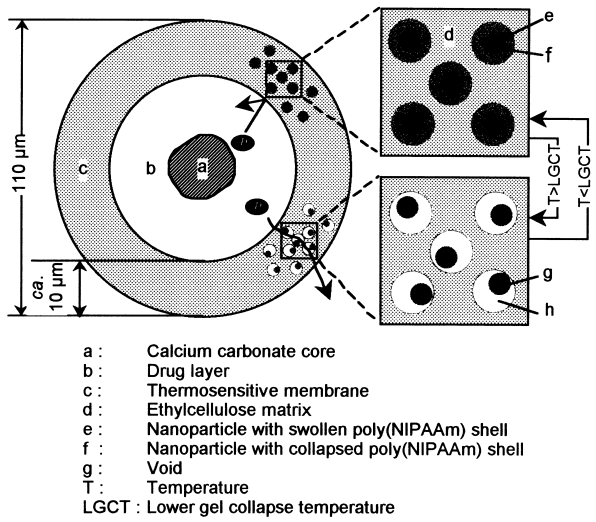

Fig. 1. Schematic diagram showing the ideal structure of microcapsules with thermally-modulated on–off pulsatile drug release.

a low release rate of drugs. At high temperatures, the PNIPAAm shells should collapse. Thus, numerous voids can be formed in the membranes providing high drug release rates. This microcapsule demonstrated thermally on–off switching release rate changes within a few min. As such, miniaturization of the hydrogel, as well as the device, make it possible to achieve an exceptionally rapid, sharp thermosensitive response.

4.3. Other stimuli-sensitive hydrogels

Several stimuli, other than pH and temperature, can trigger drug release from a depot. These include physical stimuli, such as light [95], magnetic field [96], electric current [97] and ultrasound [98], which can be applied to the systems externally, and chemical stimuli, like ionic species [99], certain chemical substances and biological compounds [100]. In some cases, their effective applications can be found in engineering, rather than pharmaceutical, fields.

Versatile stimuli-sensitive controlled release systems can be fabricated, provided that the hydrogels are well designed to alter their configuration in response to these stimuli based on almost infinitely available mechanisms. Meanwhile, the elucidation of the release mechanisms relying on more complicated mass transport phenomena over conventional diffusion-regulating systems is a practically important issue in the substantial application of stimuli-sensitive controlled release devices. In this context, Lavon and Kost [97] examined mass transport enhancement in non-erodible polymeric controlled release systems by ultrasound for a better understanding of the ultrasound-enhancing drug release phenomenon. They suggested that the enhancing effect of ultrasound on drug release from the systems is due to the contribution of a convective term, generated by cavitation, without any destructive effect of the morphology of the polymers. Hsu and Block [98] studied electrokinetic phenomena in three types of anionic gels (agarose, agarose–carbomer 934P, and agarose–xanthan gum) under an applied electric current for electrically-modulated drug delivery. It was shown that electrical current strength and gellant content could influence both syneresis and drug migration. These findings reported by the two research groups may give a practically useful insight into the application of hydrogels to transdermal delivery assisted by electroportion, iontophoresis, or sonophoresis.

Several classes of hydrogels that respond to specific molecules have been proposed to date. Calcium-responsive bioerodible drug delivery systems were devised by Goldbart and Kost [99]. The system composed of a starch–cellulose matrix containing α-amylase, the activity of which is regulated by calcium. The principle relying on calcium-responsiveness is based on the mechanism that α-amylase in its non-active form is incorporated into the matrix composed of starch, and the matrix thus responds to calcium which causes the non-active α-amylase to become active. As the unstabilized calcium shows the calcium concentration-dependent activity, the release of drugs incorporated in the matrix accompanying the degradation of the starch matrix is regulated in a calcium concentration-dependent manner.

Very recently, two fascinating stimuli-sensitive hydrogel-based drug delivery systems were proposed in quick succession. Miyazaki et al. [100,101] designed a novel reversibly antigen-responsive hydrogel based on a unique idea. This hydrogel was an AAm-based semi-interpenetrating polymer network (IPN), consisting of an antibody-grafted linear PAAm and the crosslinked PAAm grafted with the corresponding antigen. In the absence of a free antigen, the hydrogel can shrink due to the intra-chain antigen–antibody binding in the polymer network, while it swells in the presence of the free antigen because of dissociation of the intra-chain binding by exchange of the grafted antigen for free antigen. This swelling/shrinking process was shown to be reversible. Due to this property, the hydrogel membrane allowed the antigen-responsive change of hemoglobin permeation through the membrane in response to stepwise changes in the antigen concentration. A striking feature of the antigen-sensitive hydrogel would be the specificity of molecular recognition. Using this hydrogel, a sensing device with a broad application for immunoassay and antigen sensing is expected to be fabricated. A series of studies on the fabrication of a novel microbial infection-responsive drug release system was accomplished by Suzuki and associates [102–105]. They prepared a PVA-based hydrogel with specially designed thrombin-sensitive peptide linkers. In this system, a remarkably increased thrombin-like activity in microbial-infected wound exudates is utilized as a biological signal for microbial infection. Antibiotics covalently attached to the PVA-based hydrogel via the thrombin-sensitive peptide linkers can be released from the hydrogel only in the presence of infection, because of thrombin-sensi-

tive cleavage of the peptide linkers. The hydrogel can be used for a wound dressing with microbial infection-responsive controlled release of antibiotics.

The ultimate goal of stimuli-sensitive controlled release is the ability to integrate the systems to respond to more than two stimuli. Such a multi-stimuli-sensitive device has been fabricated by Kaetsu et al. [106]. It was realized by the idea based on the simultaneous installation of discrete hydrogels showing different stimuli-response into the device.

5. Applications of hydrogels in drug delivery

A number of strategies have been proposed to achieve drug delivery systems for efficient therapy. Among them, hydrogels have attracted considerable attention as excellent candidates for controlled release devices, bioadhesive devices, or targetable devices of therapeutic agents.

Hydrogel-based delivery devices can be used for oral, rectal, ocular, epidermal and subcutaneous application. Fig. 2 illustrates various sites that are available for the application of hydrogels for drug delivery. Excellent reviews in relation to this topic are readily available [107–111]. Historical research trends on hydrogel formulations for pharmaceutical applications, as well as the anatomy and physiology of each administration site, can be found in these reviews. Therefore, the present paper will mainly survey recent reports published in the last few years.

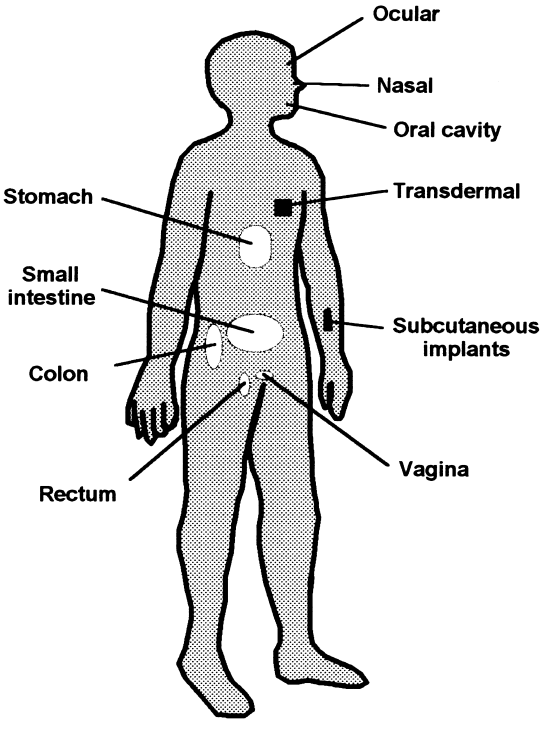

Fig. 2. Tissue locations applicable for hydrogel-based drug delivery systems.

5.1. Peroral drug delivery

Drug delivery through the oral route has been the most common method in the pharmaceutical applications of hydrogels. In peroral administration, hydrogels can deliver drugs to four major specific sites; mouth, stomach, small intestine and colon. By controlling their swelling properties or bioadhesive characteristics in the presence of a biological fluid, hydrogels can be a useful device for releasing drugs in a controlled manner at these desired sites. Additionally, they can also adhere to certain specific regions in the oral pathway, leading to a locally increased drug concentration, and thus, enhancing the drug absorption at the release site.

5.1.1. Drug delivery in the oral cavity

Drug delivery to the oral cavity can have versatile applications in local treatment of diseases of the mouth, such as periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers. Long-term adhesion of the drug-containing hydrogel against copious salivary flow, which bathes the oral cavity mucosa, is required to achieve this local drug delivery. For this purpose, many types of bioadhesive hydrogel systems have been devised since the early 1980s. Some of these are already on the market. For example, a bioadhesive tablet developed by Nagai et al. [112] is commercially available under the brand name Aftach®. This product is composed of a double layer, with a bioadhesive layer made of hydroxypropyl cellulose and poly(acrylic acid) and a lactose non-adhesive backing layer. It is a local delivery system of triamcinolone acetonide for the treatment of aphthous ulcers.

A hydrogel-based ointment can also be utilized for the topical treatment of certain diseases in the oral cavity. It can be used not only as a drug delivery device, but also as a liposome delivery vehicle. The possible advantage of liposome delivery with this ointment is that the use of liposomal formulations with encapsulated drug can lead to an increase of local, and a decrease of systemic, drug concentration, because of the encapsulation of drugs with phospholipids. This may provide more desirable properties for topical use, such as reduction of uncontrolled release of drugs into the blood circulation and certain undesirable side effects, compared with the conventional ointment-drug formulations.

Petelin et al. [113] investigated the pharmaceutical performance of three different hydrogel-based ointments as possible vehicles for liposome delivery into the oral cavity tissues by electron paramagnetic resonance (EPR). The vehicles employed were Orabase® (a sodium carboxymethylcellulose, pectin and gelatin combination in a polyethylene–paraffin base), Carbopol 934P® and neutralized poly(MAA-co-methyl methacrylate (MMA)). Liposome-containing mucoadhesive ointments were prepared by simply mixing multilamellar liposomes with each ointment prediluted with phosphate-buffered saline of pH 7.4 in the volume ratio of 1:4. An EPR study showed that P(MAA-co-

MMA) was the most appropriate ointment in terms of liposomal stability in the ointment, transport of liposome-entrapped molecules from the ointment into the oral soft tissues, and washing-out time from oral mucosa or gingvia.

The oral cavity can also provide a useful location as a transport route for heavily metabolized drugs, since the drugs absorbed from this route bypass first-pass hepatic metabolism. Kitano et al. [114] proposed a hydrogel ointment containing absorption enhancers for the buccal delivery of 17 β-estradiol (E_2) to treat osteoporosis. It is well known that the oral administration of E_2 results in very low availability due to its high first-pass effect. Ethanol solution containing E_2, and glyceryl monolaurate as an absorption enhancer, and an aqueous solution of a commercial carboxyvinyl polymer (Hiviswako 103) and triethanolamine were mixed together to produce the hydrogel ointment. In-vivo studies using hamsters demonstrated that the buccal administration of E_2 with this formulation allowed the maintenance of the E_2 plasma level at over 300 ng/ml per cm^3 for 7 h, while no primary morphological change of buccal membrane was observed 7 h after application.

Remunán-López et al. [115] reported new buccal bilayered tablets containing nifedipine and propranolol hydrochloride intended for systemic drug administration. The tablets, comprising two layers, a drug-containing mucoadhesive layer of chitosan with polycarbophil and a backing layer of ethylcellulose, were obtained by direct compression. The double-layered structure design provided a unidirectional drug delivery towards the mucosa, and avoided a loss of drug resulting from wash-out with saliva flow. The striking feature of this device would be the utilization of an in-situ crosslinking reaction between cationic chitosan and anionic polycarbophil, which progressed upon penetration of the aqueous medium into the tablet. As a result of the crosslinking effect, the tablets showed controlled swelling and prolonged drug release, and an adequate adhesiveness could be obtained.

5.1.2. Drug delivery in the GI tract

The GI tract is unquestionably the most popular route of drug delivery because of the facility of administration of drugs for compliant therapy, and its large surface area for systemic absorption. It is, however, the most complex route, so that versatile approaches are needed to deliver drugs for effective therapy.

Like buccal delivery, hydrogel-based devices can be designed to deliver drugs locally to the specific sites in the GI tract. For example, Patel and Amiji [116] proposed stomach-specific antibiotic drug delivery systems for the treatment of *Helicobacter pylori* infection in peptic ulcer disease. For localized antibiotic delivery in the acidic environment of the stomach, they developed cationic hydrogels with pH-sensitive swelling and drug release properties. The hydrogels were composed of freeze-dried chitosan–poly (ethylene oxide) (PEO) IPN. pH-dependent swelling properties and the release of two common antibiotics, amoxicillin and metronidazole, entrapped in the chitosan–PEO semi-IPN were evaluated in enzyme-free simulated gastric fluid (SGF; pH 1.2) and simulated intestinal fluid (SIF; pH 7.2). The swelling ratio of the hydrogels after 1 h in SGF was found to be 16.1, while that in SIF was only 8.60. Additionally, the freeze-dried chitosan–PEO semi-IPN demonstrated fast release of the entrapped antibiotics in SGF because of its highly porous matrix structure resulting from freeze-drying. More than 65 and 59% of the entrapped amoxicillin and metronidazole, respectively were released from the hydrogels after 2 h in SGF. The rapid swelling and drug release demonstrated by these hydrogel formulations may be beneficial for site-specific antibiotic delivery in the stomach, because of the limitations of the gastric emptying time. Amiji et al. [117] also reported enzymatically degradable gelatin–PEO semi-IPN with pH-sensitive swelling properties for oral drug delivery. In this case, the incorporation of gelatin in the IPN made it possible to swell in the acidic pH of the gastric fluid, due to the ionization of the basic amino acid residues of gelatin. The IPN was found to be degraded by proteolytic enzymes, such as pepsin and pancreatin.

Undoubtedly, peroral delivery of peptides and proteins to the GI tract is one of the most challenging issues, and thus, under much investigation. However, there are many hurdles, including protein inactivation by digestive enzymes in the GI tract, and poor epithelial permeability of these drugs. However, certain hydrogels may overcome some of these problems by appropriate molecular design or formulation approaches. For example, Akiyama et al. [118] reported novel peroral dosage forms of hydrogel formulations with protease inhibitory activities using Carbopol® (C934P), a poly(acrylic acid) product, which has been shown to have an inhibitory effect on the hydrolytic activity of trypsin, and its neutralized freeze-dried modification (FNaC934P). They demonstrated that two-phase formulations, consisting of the rapid gel-forming FNaC934P and the efficient enzyme-inhibiting, but more slowly swelling, C934P, had the most profound effect on trypsin activity inhibition.

Recently, oral insulin delivery using pH-responsive complexation hydrogels was reported by Lowman et al. [119]. The hydrogels used to protect the insulin in the harsh, acidic environment of the stomach before releasing the drug in the small intestine were crosslinked copolymers of PMAA with graft chains of polyethylene glycol (P(MAA-g-EG)). The insulin-containing P(MAA-g-EG) microparticles demonstrated strong dose-dependent hypoglycemic effects in in-vivo oral administration studies using both healthy and diabetic rats. The blood glucose levels in these animals were decreased significantly for at least 8 h due to the absorption of insulin in the GI tract. It is worth noting that these effects were observed without the addition of additives, such as absorption enhancers or protease inhibitors.

Due to a lower proteolytic activity in comparison to that

in the small intestine, the colonic region has also been considered as a possible absorption site for orally administered peptides and proteins. Several hydrogels are currently being investigated as potential devices for colon-specific drug delivery. These include chemically or physically cross-linked polysaccharides, such as dextran [120], amidated pectin [121], guar gum [122] and inulin [123–126], and azocross-linked poly(acrylic acid) [127,128]. They are designed to be highly swollen or degraded in the presence of colonic enzymes or microflora, providing colon-specificity in drug delivery.

5.2. Rectal delivery

The rectal route has been used to deliver many types of drugs, although patient acceptability is variable due to the discomfort arising from administered dosage forms. Its primary applications have been for local treatment of diseases associated with the rectum, such as hemorrhoids. Additionally, it is well known that drugs absorbed from the lower part of the rectum drain into the systemic circulation directly. Thus, the rectal route is a useful administration route for drugs suffering heavy first-pass metabolism. Conventional suppositories hitherto adapted as dosage forms for rectal administration are solids at room temperature, and melt or soften at body temperature. A problem associated with rectal administration using conventional suppositories is that drugs diffusing out of the suppositories in an uncontrolled manner are unable to be sufficiently retained at a specific position in the rectum, and sometimes migrate upwards to the colon. This often leads to a variation of the bioavailability of certain drugs, in particular, for drugs that undergo extensive first-pass elimination.

In this context, hydrogels may offer a valuable way to overcome the problem in conventional suppositories, provided that they are designed to exhibit a sufficient bioadhesive property following their rectal administration. For example, Ryu et al. [129] reported that increased bioavailability of propranolol subject to extensive first-pass metabolism was observed by adding certain mucoadhesive polymeric compounds to poloxamer-based thermally gelling suppositories. Among the mucoadhesive polymeric compounds tested, polycarbophil and sodium alginate provided the largest mucoadhesive force and the smallest intrarectal migration to the suppositories, resulting in the largest bioavailability of propranolol (82.3 and 84.7%, respectively). Miyazaki et al. [130] investigated the potential application of xyloglucan gels with a thermal gelling property as vehicles for rectal drug delivery. Xyloglucan processed by the researchers has the sol–gel transition temperature of around 22–27°C, and thus, it can be a gel at body temperature; on the other hand, it can be easily administered since it can behave as a liquid at room temperature. In-vivo rectal administration of xyloglucan gels containing indomethacin using rabbits showed a well-controlled drug plasma concentration-time profile without reduced bioavailability, when compared to commercial indomethacin suppositories.

Avoiding rectal irritation caused by vehicles is another important issue in rectal drug delivery. Both Ryu's [129] and Miyazaki's [130] products, described above, revealed no evidence of mucosal irritation after rectal administration. A significantly reduced irritation by rectal hydrogels prepared with water-soluble dietary fibers, xanthan gum and locust bean gum, was also reported by Watanabe et al. [131].

5.3. Ocular delivery

In ocular drug delivery, many physiological constraints prevent a successful drug delivery to the eye due to its protective mechanisms, such as effective tear drainage, blinking and low permeability of the cornea. Thus, conventional eye drops containing a drug solution tend to be eliminated rapidly from the eye, and the drugs administered exhibit limited absorption, leading to poor ophthalmic bioavailability. Additionally, their short-term retention often results in a frequent dosing regimen to achieve the therapeutic efficacy for a sufficiently long duration. These challenges have motivated researchers to develop drug delivery systems that provide a prolonged ocular residence time of drugs.

Certain dosage forms, such as suspensions and ointments, can be retained in the eye, although these sometimes give patients an unpleasant feeling because of the characteristics of solids and semi-solids. Due to their elastic properties, hydrogels can also represent an ocular drainage-resistant device. In addition, they may offer better feeling, with less of a gritty sensation to patients. In particular, in-situ-forming hydrogels are attractive as an ocular drug delivery system because of their facility in dosing as a liquid, and their long-term retention property as a gel after dosing.

Cohen et al. [132] developed an in-situ-gelling system of alginate with high guluronic acid contents for the ophthalmic delivery of pilocarpine. This system significantly extended the duration of the pressure-reducing effect of pilocarpine to 10 h, compared to 3 h when pilocarpine nitrate was dosed as a solution. Rheological evaluation of Gelrite®, deacetylated gellan gum which gels upon instillation in the eye due to the presence of cations, was carried out by Carlfors et al. [133]. Their study indicated that a high rate of the sol/gel transition of Gelrite® in-situ gels results in long precorneal contact times.

Chetoni et al. [134] reported silicone rubber/hydrogel composite ophthalmic inserts. Poly(acrylic acid) or poly (MAA) IPN was grafted on the surface of the inserts to achieve a mucoadhesive property. The ocular retention of IPN-grafted inserts was significantly higher with respect to ungrafted ones. An in-vivo study using rabbits showed a prolonged release of oxytetracycline from the inserts for several days.

5.4. Transdermal delivery

Drug delivery to the skin has been traditionally conducted for topical use of dermatological drugs to treat skin diseases, or for disinfection of the skin itself. In recent years, a transdermal route has been considered as a possible site for the systemic delivery of drugs. The possible benefits of transdermal drug delivery include that drugs can be delivered for a long duration at a constant rate, that drug delivery can be easily interrupted on demand by simply removing the devices, and that drugs can bypass hepatic first-pass metabolism. Furthermore, because of their high water content, swollen hydrogels can provide a better feeling for the skin in comparison to conventional ointments and patches. Versatile hydrogel-based devices for transdermal delivery have been proposed so far. Sun et al. [135] devised composite membranes comprising of crosslinked PHEMA with a nonwoven polyester support. Depending on the preparation conditions, the composite membranes can be tailored to give a permeation flux ranging from 4 to 68 $\mu g/cm^2$ per h for nitroglycerin. A Carbopol 934®-based formulation containing phosphatidylcholine liposomes (liposome-gel) was prepared by Kim et al. [136]. In their study, the skin absorption behavior of hydrocortisone-containing liposome-gel was assessed. Gayet and Fortier [137] reported hydrogels obtained from the copolymerization of bovine serum albumin (BSA) and PEG. Due to their high water content over 96%, allowing the release of hydrophilic and hydrophobic drugs, their use as controlled release devices in the field of wound dressing was proposed as the potential application of the BSA–PEG hydrogels. Comprehensive studies on in-situ photopolymerizable hydrogels made from terminally diacrylated ABA block copolymers of lactic acid oligomers (A) and PEG (B) for barriers and local drug delivery in the control of wound healing have been carried out by Hubbell [138].

Recent research trends in transdermal applications are focusing on electrically-assisted delivery, using iontophoresis and electroporation [139]. Several hydrogel-based formulations are being investigated as vehicles for transdermal iontophoresis to obtain the enhanced permeation of luteinizing hormone releasing hormone [140], sodium nonivamide acetate [141], nicotine [142] and enoxacin [143]. On the other hand, a methyl cellulose-based hydrogel was used as a viscous ultrasonic coupling medium for transdermal sonophoresis assisted with an AC current, resulting in an enhanced permeation of insulin and vasopressin across human skin in vitro [144].

5.5. Subcutaneous delivery

As described through Sections 1–4, hydrogels posses a wide variety of possible pharmaceutical applications. Among them, their substantial application may be found in implantable therapeutics. Subcutaneously inserted exogenous materials may more or less evoke potentially undesirable body responses, such as inflammation, carcinogenecity and immunogenecity. Therefore, biocompatibility is a prerequisite that makes materials implantable. Due to their high water content, hydrogels are generally considered as biocompatible materials. They also provide several promising properties: (1), minimal mechanical irritation upon in-vivo implantation, due to their soft, elastic properties; (2), prevention of protein adsorption and cell adhesion arising from the low interfacial tension between water and hydrogels; (3), broad acceptability for individual drugs with different hydrophilicities and molecular sizes; and (4), unique possibilities (crosslinking density and swelling) to manipulate the release of incorporated drugs [116,145]. Some of these may offer an advantage for the delivery of certain delicate drugs, such as peptides and proteins.

Giammona et al. [146] developed new hydrogels originating from the chemical reticulation of α,β-polyasparthydrazide (PAHy) by glutaraldehyde. PAHy is a new water-soluble macromolecule, synthesized from a polysuccinimide by reaction with hydrazine. Histological analysis revealed that this hydrogel was inert when implanted subcutaneously into rats.

Several hydrogel formulations for the subcutaneous delivery of anticancer drugs have been also proposed. For example, crosslinked PHEMA with good biocompatibility was applied to cystabine (Ara-C) [147] and methotrexate [148]. Poly(AAm-co-monomethyl or monopropyl itaconate) developed by Blanco's group was employed for the controlled release of Ara-C [149] and 5-fluorouracil [150,151].

Current studies on implantable hydrogels have been directed towards the development of biodegradable systems requiring no follow-up surgical removal once the drug supply is depleted. A bioerodible hydrogel based on a semi-IPN structure composed of a poly(ε-caprolactone) and PEG macromer terminated with acrylate groups was devised by Cho et al. [152]. Long-term constant release over 45 days of clonazepam entrapped in the semi-IPN was achieved in vivo. Recently, two types of novel degradable PEG hydrogels for the controlled release of proteins were developed by Zhao and Harris [153]. One type is prepared by a polycondensation reaction between difunctional PEG acids and branched PEG polyols. Upon hydrolysis of the resulting ester linkages, these gels degrade into only PEG and PEG derivatives. The other is PEG-based hydrogels having functional groups in which protein drugs can be covalently attached to the gel network via ester linkage. Thus, the release of the protein drugs immobilized would be controlled by the hydrolysis of the ester linkage between the gel and the protein, followed by the diffusion of the protein out of the gel, and by the degradation of the gel. Extensive research efforts on degradable dextran hydrogels have been carried out by Hennink and his coworkers [154–158]. These hydrogels are based on acrylate derivatives of dextran. In their studies, the application of the hydrogels to the controlled release of protein was thoroughly investi-

gated. Biodegradable crosslinked dextran hydrogels containing PEG (PEG-Dex) were reported by Moriyama and Yui [159]. Insulin release from these hydrogels was regulated by the surface degradation of PEG-Dex microdomain-structured.

6. Mathematical treatment of release kinetics

One of the most important and challenging areas in the drug delivery field is to predict the release of the active agent as a function of time, using both simple and sophisticated mathematical models. The importance of such models lies in their utility during both the design stage of a pharmaceutical formulation and the experimental verification of a release mechanism [160].

In order to design a particular release mechanism, experimental data of statistical significance are compared to a solution of the theoretical model. It is therefore clear that only a combination of accurate and precise data, with models accurately depicting the physical situation, will provide an insight into the actual mechanism of release.

The vast majority of theoretical models are based on diffusion equations. The phenomenon of diffusion is intimately connected with the structure of the material through which the diffusion takes place; thus, the morphology of the polymeric materials should be accounted for in a successful model. There have been a limited number of reviews that have addressed these aspects of controlled release formulations [160–162]. The mechanisms of drug release offer a convenient way to categorize controlled release systems into (1), diffusion-controlled; (2), chemically-controlled; and (3), swelling-controlled [156]. We will devote a separate section to each of these mechanisms. Due to the fact that ordinary diffusion takes place in each of these mechanisms to a certain degree, and since most of the models used are based on diffusion equations, a separate section describing the fundamentals of diffusion will precede them.

6.1. Fundamentals of ordinary diffusion

The release of an active agent from a polymeric carrier consists of the movement of the drug through the bulk of the polymer. This phenomenon, known as diffusion, is to a large degree controlled by the mass transfer limitations at the boundary between the polymer carrier and its surroundings. On a macroscopic level, the diffusion of drug molecules through the polymer carrier can be described by Fick's law of diffusion, which is mathematically stated by Eqs. (15) and (16) for transport in one dimension [163]:

$$j_i = -D_{ip}\frac{dc_i}{dx} \tag{15}$$

$$\frac{\partial c_i}{\partial t} = D_{ip}\frac{\partial^2 c_i}{\partial x^2} \tag{16}$$

Here, the concentration and mass flux of species, i, are designated as c_i and j_i, respectively; D_{ip} is the diffusion coefficient of species, i, in the polymer matrix, and x and t stand for the independent variables of position and time, respectively.

Several important assumptions have been implicitly incorporated in Eqs. (15) and (16). Firstly, these equations describe the release of a drug from a carrier of a thin planar geometry, equivalent equations for the release from thick slabs, cylinders and spheres have been derived [163]. It should also be emphasized that in the above written form of Fick's law, the diffusion coefficient is assumed to be independent of concentration. This assumption, while not conceptually correct, has been largely accepted due to the computational simplicity. Finally, j_i is a flux with respect to the mass average velocity, v, of the system.

Initial and boundary conditions, which are necessary for solving Eqs. (15) and (16), allow for the appropriate description of the experimental conditions imposed upon the drug release device. The solutions of Eqs. (15) and (16), subject to a number of boundary conditions that can be applied to various in-vitro and ex-vivo experiments, have been obtained [163].

In order to improve the predictive power of the Fickian diffusion theory, a concentration-dependent diffusion coefficient is used in Eqs. (15) and (16). Eq. (16) is then rewritten and solved with the appropriate boundary conditions (see Eq. (17))

$$\frac{\partial c_i}{\partial t} = \frac{\partial}{\partial z}\left(D_{ip}(c_i)\frac{\partial c_i}{\partial x}\right) \tag{17}$$

In Eq. (17), $D_{ip}(c_i)$ is the concentration-dependent diffusion coefficient; its form of concentration dependence is affected by the structural characteristics of the polymer carrier. A selective summary of the various forms of the diffusion coefficient is provided in Table 2.

One of earliest approaches of estimating the diffusion coefficient through a polymer carrier is that of Eyring [164]. In this theory, the diffusion of a solute through a medium is presented as a series of jumps instead of a continuous process. Therefore, in Eq. (21) in Table 2, which comes from the Eyring analysis, λ is the diffusional jump of the drug in the polymer and v is the frequency of jumping.

Fujita [165] utilized the idea of free volume in polymers to estimate the drug diffusion coefficient, and arrived at an exponential dependence of the drug diffusion coefficient on the free volume, v_f, which is given by Eq. (24) in Table 2. Yasuda and Lamaze [166] refined the Fujita's theory and presented a molecularly-based theory, which predicts the diffusion coefficients of drugs through a polymer matrix rather accurately (Eq. (25)). In their treatment, the normalized diffusion coefficient, the ratio of the diffusion coefficient of the solute in the polymer, $D_{2,13}$, to the diffusion coefficient of the solute in the pure solvent, $D_{2,1}$, is related to the degree of hydration, H, and free volume occupied by the swelling medium, $V_{f,1}$. In addition, ϑ is a sieving factor

Table 2
Selective summary of drug diffusion coefficient equations

Type of carrier	Equation	Form of D_{ip}		Reference
Porous	Eq. (21)	$D_{ip} = \frac{\lambda^2 v}{6}$	(21)	[4]
Porous	Eq. (22)	$D_{eff} = D_{iw} K_p K_r \frac{\varepsilon}{\tau}$	(22)	[6]
Micro-porous	Eq. (23)	$\frac{D_{ip}}{D_b} = (1-\lambda)^2\left(1 + \alpha\lambda + \beta\lambda^3 + \gamma\lambda^5\right)$	(23)	[7]
Non-porous	Eq. (24)	$D_{ip} = D_o \exp\left\{-\frac{k}{v_f}\right\}$	(24)	[7]
Non-porous	Eq. (25)	$\frac{D_{2,13}}{D_{2,1}} = \varphi(q_s)\exp\left[-B\left(\frac{q_s}{V_f, 1}\right)\left(\frac{1}{H} - 1\right)\right]$	(25)	[8]
Non-porous (highly swollen)	Eq. (26)	$\frac{D_{2,13}}{D_{2,1}} = k_1\left(\frac{\bar{M}_c - \bar{M}_c^*}{\bar{M}_n - \bar{M}_c^*}\right)\exp\left(-\frac{k_2 r_s^2}{Q-1}\right)$	(26)	[9]

which provides a limiting mesh size impermeable to drugs with cross-sectional area, q_s, and B is a parameter characteristic of the polymer. In Eq. (25), the subscripts 1, 2, and 3 refer to the swelling medium, drug and polymer, respectively.

Peppas and Reinhart [167] also developed a theoretical model based on a free volume of the polymer matrix. In their effort, they assumed the free volume of the polymer to be the same as the free volume of the solvent and they arrived at Eq. (26) in Table 2. They related the normalized diffusion coefficient to the degree of swelling, Q, the solute radius, r_s, and the molecular weight of the polymer chains. More specifically, $\bar{M}_c$ is the average molecular weight of the polymer chains between adjacent crosslinks, $\bar{M}_n$ is the average molecular weight of the linear polymer chains prepared under identical conditions in the absence of the crosslinking agent, and $\bar{M}_c^*$ is the critical molecular weight between crosslinks, below which a drug of size r_s could not diffuse through the polymer network. In addition, k_1 and k_2 are constants related to the polymer structure. This theory is applicable to drug transport in highly swollen, non-porous hydrogels. Equations for moderately or poorly swollen [168], and semicrystalline [169] hydrogels were also developed.

Yet another approach for the prediction of the diffusion coefficient of a drug in a controlled release device has been adopted from the chemical engineering field [170]. More specifically, the transport phenomena in porous rocks, ion-exchange resins, and catalysis are of a very similar nature to a drug diffusing through a macro- or micro-porous polymer. In these types of polymers, the diffusion is assumed to be taking place predominantly through the water, or bodily fluids, filled pores. The diffusion coefficient of a drug in a polymer, D_{ip}, in Eqs. (15) and (16) is replaced by an effective diffusive coefficient, D_{eff}, which is defined by Eq. (22) in Table 2. In Eq. (22), ε is the porosity, or void fraction, of the polymer, which is a measure of the volume of the pores available for diffusion, and τ is the tortuosity, which describes the geometric characteristics of the pores. The term K_p is the equilibrium-partitioning coefficient, which is a parameter needed when the drug is soluble in the polymer matrix; it is the ratio of the concentration inside of the pore to the concentration outside of the pore. The term K_r describes the fractional reduction in diffusivity within the pore when the solute diameter, d_s, is comparable in size to the pore diameter, d_r. Eq. (23) in Table 2 is a semiempirical relation proposed by Faxen [171] for the diffusion of spheres through porous media. In this equation, λ is the ratio of the drug radius, r_s, to the pore average radius, r_p, D and D_b are the diffusion coefficients of the sphere through the pore and in bulk, respectively; and α, β and γ are constants. It is clear that as the size of the drug gets smaller with respect to the size of the pore, the ratio of D/D_b approaches the limit of one.

6.2. Diffusion-controlled systems

Reservoir diffusion-controlled systems consist of a bioactive agent containing a core that is separated from the external environment by a polymer membrane. Analysis of drug release from such systems using Eq. (15) shows that the release rate is independent of time, i.e. zero-order, for both planar, cylindrical and spherical geometry. For example, Eqs. (18) and (19) give the rate of drug release and the total amount of drug released for systems of spherical geometry.

$$\frac{dM_t}{dt} = \frac{4\pi D_{ip} K}{(r_e - r_i)/(r_e r_i)}(c_{i2} - c_{i1}) \tag{18}$$

$$M_t = \frac{4\pi D_{ip} K(c_{i2} - c_{i1})}{(r_e - r_i)/(r_e r_i)} \quad (19)$$

In Eqs. (18) and (19), D_{ip} is the concentration independent diffusion coefficient, M_t is the amount of drug released at time t, K is the drug partition coefficient, and r_e and r_i are the external and internal radius of the sphere, respectively. Finally, c_{i1} and c_{i2} are the drug concentrations inside and outside of the matrix, respectively.

A comparison of analogous equations for the planar and cylindrical geometries reveals that the drug release can be controlled by the geometry of the system. In addition, it is also clear that the amount of drug release can be controlled by the thickness of the membrane, concentration difference of the drug across the membrane, the thermodynamic characteristics of the system via the partition coefficient, and the structure of the polymer through the solute diffusion coefficient.

In matrix systems, which are also diffusion-controlled, the drug can be either dissolved or dispersed throughout the network of the hydrogels. The drug release from these systems is modeled using Eq. (17) with the concentration-dependent coefficient given by either of Eqs. (24)–(26). It is clear from solutions to Eq. (17) that the fractional drug release obtained form these systems is proportional to $t^{1/2}$.

6.3. Chemically-controlled systems

Chemically-controlled systems consist of two major subclasses of controlled release systems, based on the mechanisms that control the drug release. In erodible systems, the drug release rate is controlled by degradation or dissolution of the polymer. In pendent chain systems, the drug is attached to the polymer via a hydrolytically or enzymatically labile bond, and the drug release is controlled by the rate of degradation of the bond.

Unlike in pendent chain systems, ordinary diffusion takes place in erodible systems, and the actual mechanism of drug release depends on whether diffusion or erosion is the rate-controlling step. If erosion of the matrix is much slower than the diffusion of the drug through the polymer, the drug release can be analyzed using the equations described in Section 6.2. In the other scenario, the drug remains incorporated in the matrix due to the low rate of diffusion, and therefore, the drug release is erosion-controlled. The two possible mechanisms of erosion, heterogeneous and homogeneous, can be predicted from polymer hydrophobicity and morphology. Hydrophilic polymers absorb water, therefore, erosion throughout the polymer matrix (i.e. homogeneous erosion) will take place. On the other hand, hydrophobic polymers will erode only at the surface, or heterogeneously, because water is excluded from the bulk of the matrix. In the pharmaceutical field, surface eroding polymer matrices have received much more attention due to the fact that they exhibit near zero-order release kinetics.

6.4. Swelling-controlled systems

Formulations consisting of hydrophilic matrixes, and from which the drug release is controlled by the inward flux of solvent molecules and consequent swelling of the polymer matrix, are referred to as swelling-controlled systems. In these systems, the drugs are initially dissolved or dispersed in the glassy polymers. Upon contact with biological fluids, the polymer matrix begins to swell and two distinct phases can be observed in the polymer; the inner glassy phase and the swollen rubbery phase. The drug molecules are able to diffuse out of the rubbery phase of the polymer. Clearly, the drug release is controlled by the velocity and position of the glass–rubbery interface, since no drug diffuses out of the glassy region of the polymer. A very important phenomenon of macromolecular relaxation takes place at the glass–rubbery interface, and significantly affects the drug release. The relative importance of macromolecular relaxation on the mechanism of drug release can be easily assessed by fitting experimental release data to Eq. (20) and determining the exponent, n.

$$\frac{M_t}{M_\infty} = kt^n \quad (20)$$

It is of paramount importance that Eq. (20) be applied only to the first 60% of the total amount of drug released. Here, M_t and M_∞ are the amounts of drug released at time, t, and at equilibrium, respectively; k is a proportionality constant, and n is the diffusional exponent. Ritger and Peppas [172] performed analysis of the Fickian and non-Fickian diffusional behavior in terms of the value of the coefficient, n.

Rigorous mathematical analysis of the release behavior from this type of formulations falls into the category of moving-boundary problems. A detailed review of solutions of this type of problem is discussed by Crank [173]. Our laboratories have provided several theoretical models of drug release from swelling-controlled release devices. The first detailed model of drug transport with concentration-dependent diffusion coefficients was developed by Korsmeyer at al. [174]. Lustig et al. [175] proposed a different model for drug release based on rational thermodynamics, which also included a complete viscoelastic description of the polymer matrix and concentration-dependent diffusion coefficient of the drug.

7. The future

Recent advances in the development of neutral and ionic hydrogels for drug delivery applications have concentrated on several aspects of their synthesis, characterization and behavior. Major questions that have been addressed or are presently researched in our work include:

- synthetic methods of preparation of hydrophilic polymers with desirable functional groups.
- synthetic methods of preparation of multifunctional or

multiarm structures including branched or grafted copolymers and star polymers.
- understanding of the criticality and the swelling/syneresis behavior of novel anionic or cationic polymers.
- development of ultrapure polymers, such as crosslinked-free PVA gels produced by freezing–thawing of aqueous solutions.
- synthesis and characterization of biomimetic hydrogels.
- understanding of the relaxational behavior during dynamic swelling.
- modeling of any associated dissolution or biodegradation.

New promising methods of delivery of chemotherapeutic agents using hydrogels have been recently reported. For example, biorecognition of various sugar-containing copolymers can be used for the release of chemotherapeutic agents. Kopecek and associates have used poly(*N*-2-hydroxypropyl methacrylamide) carriers for the release of a wide range of such agents.

In the last few years, there have been new creative methods of preparation of hydrophilic polymers and hydrogels that may be used in the future in drug delivery applications. For example, we have synthesized self-organized nanostructures based on triblock copolymers that may have applications in controlled drug delivery. Novel biodegradable polymers include polyrotaxanes, which are considered to be particularly exciting molecular assemblies for drug delivery.

Dendrimers and star polymers are exciting new materials because of the large number of functional groups available in a very small volume. Merrill [176] has offered an exceptional review of PEO star polymers and their applications in the biomedical and pharmaceutical fields, whereas Keys and Peppas [177] have prepared gels of controlled structure and large biological functionality by irradiation of PEO star polymers. Such gels may be promising materials as carriers for drug delivery if combined with the techniques of molecular imprinting. Indeed, there have been several reports of the use of crosslinked polymers as templates for drug imprinting and subsequent release. Still, this field is relatively new and its applications may not be immediately available.

Thus, new synthetic methods have been used to prepare homo- and co-polymeric hydrogels for a wide range of drug, peptide, and protein delivery applications. Random copolymers with balanced hydrophobicity/hydrophilicity can offer desirable release rates and dissolution profiles, but graft, block and comb-like copolymers offer additional advantages, especially when they contain temperature- or pH-sensitive pendent groups. Several interesting applications of such systems in the treatment of diabetes, osteoporosis, cancer or thrombosis have been discussed. Other hydrogels with great promise as drug delivery vehicles include neutral gels of PEO or PVA, and gels of star molecules and other complex structures.

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References

[1] K.A. Dill, Strengthening biomedicine's roots, Nature 400 (1999) 309–310.
[2] N.A. Peppas, A.G. Mikos, Preparation methods and structure of hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, Vol. 1, CRC Press, Boca Raton, FL, 1986, pp. 1–27.
[3] L. Brannon-Peppas, Preparation and characterization of crosslinked hydrophilic networks, in: L. Brannon-Peppas, R.S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, 1990, pp. 45–66.
[4] N.A. Peppas, E.W. Merrill, PVA hydrogels: reinforcement of radiation-crosslinked networks by crystallization, J. Polym. Sci. Polym. Chem. Ed. 14 (1976) 441–457.
[5] N.A. Peppas, E.W. Merrill, Differential scanning calorimetry of crystallized PVA hydrogels, J. Appl. Polym. Sci. 20 (1976) 1457–1465.
[6] N.A. Peppas, Hydrogels of poly(vinyl alcohol) and its copolymers, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, Vol. 2, CRC Press, Boca Raton, FL, 1986, pp. 1–48.
[7] S.R. Stauffer, N.A. Peppas, Poly(vinyl alcohol) hydrogels prepared by freezing–thawing cyclic processing, Polymer 33 (1992) 3932–3936.
[8] A.S. Hickey, N.A. Peppas, Mesh size and diffusive characteristics of semicrystalline poly(vinyl alcohol) membranes prepared by freezing/thawing techniques, J. Membr. Sci. 107 (1995) 229–237.
[9] N.A. Peppas, N.K. Mongia, Ultrapure poly(vinyl alcohol) hydrogels with mucoadhesive drug delivery characteristics, Eur. J. Pharm. Biopharm. 43 (1997) 51–58.
[10] P.J. Flory, J. Rehner, Statistical mechanics of cross-linked polymer networks. II. Swelling, J. Chem. Phys. 11 (1943) 521–526.
[11] P.J. Flory, Statistical mechanics of swelling of network structures, J. Chem. Phys. 18 (1950) 108–111.
[12] P.J. Flory, Principles of Polymer Chemistry, Cornell University Press, Ithaca, NY, 1953.
[13] B.D. Ratner, A.S. Hoffman, Synthetic hydrogels for biomedical applications, in: J.D. Andrade (Ed.), Hydrogels for Medical and Related Applications, ACS Symposium Series, No. 31, American Chemical Society, Washington, DC, 1976, pp. 1–36.
[14] N.A. Peppas, Hydrogels in Medicine, CRS Press, Boca Raton, FL, 1986.
[15] N.A. Peppas, R. Langer, New challenges in biomaterials, Science 263 (1994) 1715–1720.
[16] K. Park, Controlled Release: Challenges and Strategies, American Chemical Society, Washington, DC, 1997.
[17] N.A. Peppas, Hydrogels and drug delivery, Curr. Opin. Coll. Int. Sci. 2 (1997) 531–537.
[18] V.A. Kabanov, I.M. Papisov, Formation of complexes between complementary synthetic polymers and oligomers in dilute solution, Vysokolmol. Soedin. A21 (1979) 243–281.
[19] E.A. Bekturov, L.A. Bimendina, Interpolymer complexes, Adv. Polym. Sci. 43 (1981) 100–147.
[20] E. Tsuchida, K. Abe, Interactions between macromolecules in solution and intermacromolecular complexes, Adv. Polym. Sci. 45 (1982) 1–119.
[21] J. Klier, N.A. Peppas, Structure and swelling behavior of poly(ethylene glycol)/poly(methacrylic acid) complexes, in: L. Brannon-

Peppas, R.S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, 1990, pp. 147–169.
[22] C.L. Bell, N.A. Peppas, Biomedical membranes from hydrogels and interpolymer complexes, Adv. Polym. Sci. 122 (1995) 125–175.
[23] N.A. Peppas, Physiologically responsive gels, J. Bioact. Compat. Polym. 6 (1991) 241–246.
[24] O. Wichterle, D. Lim, Hydrophilic gels for biological use, Nature 185 (1960) 117–118.
[25] R. Langer, Drug delivery and targeting, Nature 392 (1998) 5–10.
[26] Y. Huang, W. Leobandung, A. Foss, N.A. Peppas, Molecular aspects of muco- and bio-adhesion: tethered structures and site-specific surfaces, J. Control. Release (2000) in press.
[27] N.A. Peppas, J.J. Sahlin, Hydrogels as mucoadhesive and bioadhesive materials: a review, Biomaterials 17 (1996) 1553–1561.
[28] S. Stolnik, L. Illum, S.S. Davis, Long circulating microparticulate drug carriers, Adv. Drug Deliv. Rev. 16 (1995) 195–214.
[29] N.L. Burnham, Polymers for delivering peptides and proteins, Am. J. Hosp. Pharm. 51 (1994) 210–218.
[30] A.M. Lowman, N.A. Peppas, Hydrogels, in: E. Mathiowitz (Ed.), Encyclopedia of Controlled Drug Delivery, Wiley, New York, 1999, pp. 397–418.
[31] B.D. Ratner, A.S. Hoffman, Synthetic hydrogels for biomedical applications, in: J.D. Andrade (Ed.), Hydrogels for Medical and Related Applications, ACS Symposium Series, Vol. 3, American Chemical Society, Washington, DC, 1976, pp. 1–33.
[32] N.A. Peppas, A.G. Mikos, Preparation methods and structure of hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, Vol. I, CRC Press, Boca Raton, FL, 1986, pp. 1–26.
[33] M.T. am Ende, A.G. Mikos, Diffusion-controlled delivery of proteins from hydrogels and other hydrophilic systems, in: L.M. Sanders, R.W. Hendren (Eds.), Protein Delivery: Physical Systems, Plenum Press, Tokyo, 1997, pp. 139–165.
[34] N.A. Peppas, B.D. Barr-Howell, Characterization of the cross-linked structure of hydrogels, in: N.A. Peppas (Ed.), Hydrogels in Medicine and Pharmacy, Vol. I, CRC Press, Boca Raton, FL, 1986, pp. 27–56.
[35] R.G. Treloar, The Physics of Rubber Elasticity, 2nd Edition, Oxford University Press, Oxford, 1958.
[36] N.A. Peppas, E.W. Merrill, Crosslinked poly(vinyl alcohol) hydrogels as swollen elastic networks, J. Appl. Polym. Sci. 21 (1977) 1763–1770.
[37] A. Katchalsky, I. Michaeli, Polyelectrolyte gels in salt solution, J. Polym. Sci. 15 (1955) 69–86.
[38] L. Brannon-Peppas, N.A. Peppas, Equilibrium swelling behavior of pH-sensitive hydrogels, Chem. Eng. Sci. 46 (1991) 715–722.
[39] J. Ricka, T. Tanaka, Swelling of ionic gels: quantitative performance of the Donnan theory, Macromolecules 17 (1984) 2916–2921.
[40] P.J. Flory, N. Rabjohn, M.C. Shaffer, Dependence of elastic properties of vulcanized rubber on the degree of cross linking, J. Polym. Sci. 4 (1949) 225–245.
[41] P.J. Flory, N. Rabjohn, M.C. Shaffer, Dependence of elastic properties of vulcanized rubber on the degree of cross linking, J. Polym. Sci. 4 (1949) 435–455.
[42] J.E. Silliman, Network hydrogel polymers-application in hemodialysis, Sc.D. Thesis, Massachusetts Institute of Technology, Cambridge, MA, 1972.
[43] N.A. Peppas, E.W. Merrill, Crosslinked poly(vinyl alcohol) hydrogels as swollen elastic networks, J. Appl. Polym. Sci. 21 (1977) 1763–1770.
[44] J.E. Mark, The use of model polymer networks to elucidate molecular aspects of rubberlike elasticity, Adv. Polym. Sci. 44 (1982) 1–26.
[45] K.S. Anseth, C.N. Bowman, L. Brannon-Peppas, Mechanical properties of hydrogels and their experimental determination, Biomaterials 17 (1996) 1647–1657.
[46] K.G. Patterson, S.J. Padgett, N.A. Peppas, Microcrystallinity and three-dimensional network structure in plasticized PVC, Colloid Polym. Sci. 260 (1982) 851–858.
[47] A.M. Lowman, N.A. Peppas, Analysis of the complexation/decomplexation phenomena in graft copolymer networks, Macromolecules 30 (1989) 4959–4965.
[48] T. Canal, N.A. Peppas, Correlation between mesh size and equilibrium degree of swelling of polymeric network, J. Biomed. Mater. Res. 23 (1989) 1183–1193.
[49] B. Narasimhan, N.A. Peppas, Molecular analysis of drug delivery systems controlled by dissolution of the polymer carrier, J. Pharm. Sci. 86 (1997) 297–304.
[50] N.A. Peppas, P. Colombo, Analysis of drug release behavior from swellable polymer carriers using the dimensionality index, J. Control. Release 45 (1997) 35–40.
[51] E. Yoshi, Cytotoxic effects of acrylates and methacrylates: relationships of monomer structures and cytotoxicity, J. Biomed. Mater. Res. 37 (1997) 517–524.
[52] E. Nedkov, S. Tsvetkova, Structure of poly(ethylene glycol) hydrogels obtained by gamma irradiation, Radiat. Phys. Chem. 44 (1994) 81–87.
[53] N.A. Peppas, K.B. Keys, M. Torres-Lugo, A.M. Lowman, Poly (ethylene glycol)-containing hydrogels in drug delivery, J. Control. Release 62 (1999) 81–87.
[54] H.A. Allcock, A.M.A. Ambrosio, Synthesis and characterization of pH-sensitive poly(organophosphazene) hydrogels, Biomaterials 17 (1996) 2295–2302.
[55] J.L. Stringer, N.A. Peppas, Diffusion of small molecular weight drugs in radiation-crosslinked poly(ethylene oxide) hydrogels, J. Control. Release 42 (1996) 195–202.
[56] P. Akkas, M. Sari, M. Sen, O. Guven, The effect of external stimuli on bovine serum albumin adsorption capacity of poly(acrylamide/maleic acid) hydrogels prepared by gamma rays, Radiat. Phys. Chem. 55 (1999) 717–721.
[57] N.A. Peppas, Physiological responsive gels, J. Bioact. Compat. Polym. 6 (1991) 241–246.
[58] A. Katchalsky, Rapid swelling and deswelling of reversible gels of polymeric acids by ionization, Experimentia 5 (1949) 319–320.
[59] A. Katchalsky, S. Lifson, H. Eisenberg, Equation of swelling for polyelectrolyte gels, J. Polym. Sci. 7 (1951) 571–574.
[60] T. Tanaka, Phase transition in gels and a single polymer, Polymer 20 (1979) 1404–1412.
[61] L. Brannon-Peppas, N.A. Peppas, The equilibrium swelling behavior of porous and non-porous hydrogels, in: L. Brannon-Peppas, R.S. Harland (Eds.), Absorbent Polymer Technology, Elsevier, Amsterdam, 1990, pp. 67–75.
[62] W. Oppermann, Swelling behavior and elastic properties of ionic hydrogels, in: R.S. Harland, R.K. Prud'homme (Eds.), Polyelectrolyte Gels: Properties, Preparation, and Applications, ACS Symposium Series, No. 480, American Chemical Society, Washington, DC, 1992, pp. 159–170.
[63] A.B. Scranton, B. Rangarajan, J. Klier, Biomedical applications of polyelectrolytes, Adv. Polym. Sci 120 (1995) 1–54.
[64] R. Skouri, F. Schoesseler, J.P. Munch, S.J. Candau, Swelling and elastic properties of polyelectrolyte gels, Macromolecules 28 (1995) 197–210.
[65] M. Rubinstein, R.H. Colby, A.V. Dobrynin, J.F. Joanny, Elastic modulus and equilibrium swelling of polyelectrolyte gels, Macromolecules 29 (1996) 398–426.
[66] U.P. Schroder, W. Opperman, Properties of polyelectrolyte gels, in: J.P. Cohen Addad (Ed.), The Physical Properties of Polymeric Gels, Wiley, New York, 1996, pp. 19–38.
[67] E. Yu, A. Kramarenko, A.R. Khoklov, Collapse of polyelectrolyte macromolecules revisited, Macromolecules 30 (1997) 3383–3388.
[68] I. Ohmine, T. Tanaka, Salt effects on the phase transition of ionic gels, J. Chem. Phys. 77 (1992) 5725–5729.
[69] A.R. Khare, N.A. Peppas, Swelling/deswelling of anionic copolymer gels, Biomaterials 16 (1995) 559–567.
[70] B.A. Firestone, R.A. Siegel, Dynamic pH-dependent swelling of a

hydrophobic polyelectrolyte gel, Polym. Commun. 29 (1988) 204–208.
[71] R.A. Siegel, B.A. Firestone, pH-dependent equilibrium swelling properties of hydrophobic polyelectrolyte copolymer gels, Macromolecules 21 (1988) 3254–3259.
[72] J.M. Cornejo-Bravo, R.A. Siegel, Water vapor sorption behavior of copolymers of *N,N*-diethlyaminoethyl methacrylate and methyl methacrylate, Biomaterials 17 (1996) 1187–1193.
[73] S.K. Vakkalanka, C.S. Brazel, N.A. Peppas, Temperature and pH-sensitive terpolymers for modulated delivery of streptokinase, J. Biomed. Mater. Sci. Polym. Ed. 8 (1996) 119–129.
[74] A. Kikuchi, T. Okano, Temperature-responsive polymers as on–off switches for intelligent biointerfaces, in: T. Okano (Ed.), Biorelated Polymers and Gels, Academic Press, Boston, MA, 1998, pp. 1–28.
[75] T. Tanaka, Collapse of gels and the critical endpoint, Phys. Rev. Lett. 40 (1978) 820–823.
[76] S. Hirotsu, Y. Hirokawa, T. Tanaka, Volume-phase transitions of ionized *N*-isopropyl acrylamide, J. Chem. Phys. 87 (1987) 1392–1395.
[77] S. Beltran, J.P. Baker, H.H. Hooper, H.W. Blanch, J.M. Prausnitz, Swelling equilibria for weakly ionizable, temperature sensitive hydrogels, Macromolecules 24 (1991) 549–551.
[78] A.S. Hoffman, Applications of thermally reversible polymers and hydrogels in therapeutics and diagnostics, J. Control. Release 6 (1987) 297–305.
[79] G.H. Chen, A.S. Hoffman, Graft copolymers that exhibit temperature induced phase transitions over a wide range of pH, Nature 373 (1995) 49–52.
[80] Y. Kaneko, S. Nakamura, K. Sakai, A. Kikuchi, T. Aoyagi, Y. Sakurai, T. Okano, Deswelling mechanism for comb-type grafted poly(*N*-isopropylacrylamide) hydrogels with rapid temperature responses, Polym. Gels Network 6 (1998) 333–345.
[81] R. Yoshida, K. Uchida, Y. Kaneko, K. Sakai, A. Kikcuhi, Y. Sakurai, T. Okano, Comb-type grafted hydrogels with rapid de-swelling response to temperature changes, Nature 374 (1995) 240–242.
[82] Y. Kaneko, K. Saki, A. Kikuchi, Y. Sakurai, T. Okano, Fast swelling/deswelling kinetics of comb-type grafted poly(*N*-isopropyl acrylamide) hydrogels, Macromol. Symp. 109 (1996) 41–53.
[83] H.A. von Recum, S.W. Kim, A. Kikuchi, M. Okuhara, Y. Sakurai, T. Okano, Novel thermally reversible hydrogel as detachable cell culture substrate, J. Biomed. Mater. Res. 40 (1998) 631–639.
[84] H. Sakai, Y. Doi, T. Okano, N. Yamada, Y. Sakurai, Thermo-responsive polymer surfaces for cell culture: analysis of the surfaces and control of the cell attachment/detachment, in: N. Ogata, S.W. Kim, J. Feijen, T. Okano (Eds.), Advanced Biomaterials in Biomedical Engineering and Drug Delivery Systems, Springer, Tokyo, 1996, pp. 229–230.
[85] T. Okano, N. Yamada, H. Sakai, Y. Sakurai, A novel recovery system for cultured cells using plasma treated polystyrene dishes grafted with poly(*N*-isopropylacrylamide), J. Biomed. Mater. Res. 27 (1993) 1243–1251.
[86] T. Okano, N. Yamada, M. Okuhara, H. Sakai, Y. Sakurai, Mechanism or cell detachment from temperature-modulated, hydrophilic–hydrophobic polymer surfaces, Biomaterials 16 (1995) 297–303.
[87] A. Kikuchi, M. Okuhara, F. Karikusa, H. Sakai, Y. Sakurai, T. Okano, Two-dimensional manipulation of confluent cultured cells, Transaction of 5th World Biomaterials Congress, Transactions, Toronto, Canada, Vol. I, 1996, p. 907.
[88] T. Inoue, G. Chen, K. Nakamae, A.S. Hoffman, Temperature sensitivity of a hydrogel network containing different LCST oligomers grafted to the hydrogel backbone, Polym. Gels Network 5 (1997) 561–575.
[89] Z. Ding, G. Chen, A.S. Hoffman, Unusual properties of thermally sensitive oligomers–enzyme conjugates of poly(*N*-isopropylacrylamide)–trypsin, J. Biomed. Mater. Res. 39 (1998) 498–505.
[90] M. Matsukata, T. Aoki, K. Sanui, N. Ogata, A. Kikuchi, Y. Sakurai, T. Okano, Effect of molecular architecture of poly(*N*-isopropylacrylamide)-trypsin conjugates on their solution and enzymatic properties, Bioconjug. Chem. 7 (1996) 96–101.
[91] B. Jeong, Y.H. Bae, S.W. Kim, Thermoreversible gelation of PEG–PLGA–PEG triblock copolymers aqueous solutions, Macromolecules 32 (1999) 7064–7069.
[92] A. Serres, M. Baudys, S.W. Kim, Temperature and pH-sensitive polymers for human calcitonin delivery, Pharm. Res. 13 (1996) 196–201.
[93] S.K. Vakkalanka, C.S. Brazel, N.A. Peppas, Temperature and pH-sensitive terpolymers for modulated delivery of streptokinase, J. Biomater. Sci. Polym. Ed. 8 (1996) 119–129.
[94] H. Ichikawa, Y. Fukumori, A novel positively thermosensitive controlled-release microcapsule with membrane of nano-sized poly(*N*-isopropylacrylamide) gel dispersed in ethylcellulose matrix, J. Control. Release 63 (1999) 107–119.
[95] M.G. Kodzwa, M.E. Staben, D.G. Rethwisch, Photoresponsive control of ion-exchange in leucohydroxide containing hydrogel membranes, J. Membr. Sci. 158 (1999) 85–92.
[96] M. Zrínyi, D. Szabó, H.-G. Kilian, Kinetics of the shape change of magnetic field sensitive polymer gels, Polym. Gels Networks 6 (1998) 441–454.
[97] I. Lavon, J. Kost, Mass transport enhancement by ultrasound in non-degradable polymeric controlled release systems, J. Control. Release 54 (1998) 1–7.
[98] C.-S. Hsu, L.H. Block, Anionic gels as vehicles for electrically-modulated drug delivery. I. Solvent and drug transport phenomena, Pharm. Res. 13 (1996) 1865–1870.
[99] R. Goldbart, J. Kost, Calcium responsive bioerodible drug delivery system, Pharm. Res. 16 (1999) 1483–1486.
[100] T. Miyazaki, N. Asami, T. Urgami, A reversibly antigen-responsive hydrogel, Nature 399 (1999) 765–769.
[101] T. Miyazaki, N. Asami, T. Urgami, Preparation of an antigen-sensitive hydrogel using antigen–antibody bindings, Macromolecules 32 (1999) 2082–2084.
[102] Y. Suzuki, M. Tanihara, Y. Nishimura, K. Suzuki, Y. Kakimaru, Y. Shimizu, A novel wound dressing with an antibiotic delivery system stimulated by microbial infection, ASAIO J. 43 (1997) M854–M857.
[103] M. Tanihara, Y. Suzuki, Y. Nishimura, K. Suzuki, Y. Kakimaru, Thrombin-sensitive peptide linkers for biological signal-responsive drug release systems, Peptides 19 (1998) 421–425.
[104] Y. Suzuki, M. Tanihara, Y. Nishimura, K. Suzuki, Y. Kakimaru, Y. Shimizu, A new drug delivery system with controlled release of antibiotic only in the presence of infection, J. Biomed. Mater. Res. 42 (1998) 112–116.
[105] M. Tanihara, Y. Suzuki, Y. Nishimura, K. Suzuki, Y. Kakimaru, Y. Fukunishi, A novel microbial infection-responsive drug delivery system, J. Pharm. Sci. 88 (1999) 510–514.
[106] I. Kaetsu, K. Uchida, H. Shindo, S. Gomi, K. Sutani, Intelligent type controlled release systems by radiation techniques, Radiat. Phys. Chem. 55 (1999) 193–201.
[107] H.E. Junginger, Mucoadhesive hydrogels, Pharm. Ind. 53 (1991) 1056–1065.
[108] K. Knuth, M. Amiji, J.R. Robinson, Hydrogel delivery systems for vaginal and oral applications, Adv. Drug Deliv. Rev. 11 (1993) 137–167.
[109] T. Nagai, Y. Machida, Buccal delivery systems using hydrogels, Adv. Drug Deliv. Rev. 11 (1993) 179–191.
[110] H. Park, K. Park, Biocompatibility issues of implantable drug delivery systems, Pharm. Res. 13 (1996) 1770–1776.
[111] X. Yang, J.R. Robinson, Bioadhesion in mucosal drug delivery, in: T. Okano (Ed.), Biorelated Polymers and Gels, Academic Press, San Diego, CA, 1998, pp. 135–192.
[112] T. Nagai, Y. Machida, Y. Suzuki, H. Ikura, U.S. Patent No. 4226848, 1980.
[113] M. Petelin, M. Sentjurc, Z. Stolic, U. Skaleric, EPR study of

mucoadhesive ointments for delivery of liposomes into the oral mucosa, Int. J. Pharm. 173 (1998) 193–202.
[114] M. Kitano, Y. Mitani, K. Takayama, T. Nagai, Buccal absorption of golden hamster cheek in vitro and in vivo of 17β-estradiol from hydrogels containing three types of absorption enhancers, Int. J. Pharm. 174 (1998) 19–28.
[115] C. Remuñán-López, A. Portero, J.L. Vila-Jato, M.J. Alonso, Design and evaluation of chitosan/ethylcellulose mucoadhesive bilayered devices for buccal drug delivery, J. Control. Release 55 (1998) 143–152.
[116] V.R. Patel, M.M. Amiji, Preparation and characterization of freeze-dried chitosan–poly(ethylene oxide) hydrogels for site-specific antibiotic delivery in the stomach, Pharm. Res. 13 (1996) 588–593.
[117] M. Amiji, R. Tailor, M.-K. Ly, J. Goreham, Gelatin–poly(ethylene oxide) semi-interpenetrating polymer network with pH-sensitive swelling and enzyme-degradable properties for oral drug delivery, Drug Dev. Ind. Pharm. 23 (1997) 575–582.
[118] Y. Akiyama, H.L. Lueßen, A.G. de Boer, J.C. Verhoef, H.E. Junginger, Novel peroral dosage forms with protease inhibitory activities. II. Design of fast dissolving poly(acrylate) and controlled drug-releasing capsule formulations with trypsin inhibiting properties, Int. J. Pharm. 138 (1996) 13–23.
[119] A.M. Lowman, M. Morishita, M. Kajita, T. Nagai, N.A. Peppas, Oral delivery of insulin using pH-responsive complexation gels, J. Pharm. Sci. 88 (1999) 933–937.
[120] H. Brøndsted, L. Hovgaard, L. Simonsen, Dextran hydrogels for colon-specific drug delivery. II. Synthesis and characterization, Eur. J. Pharm. Biopharm. 42 (1996) 85–89.
[121] O. Munjeri, J.H. Collett, J.T. Fell, Hydrogel beads based on amidated pectins for colon-specific drug delivery: the role of chitosan in modifying drug release, J. Control. Release 46 (1997) 273–278.
[122] I. Gliko-Kabir, B. Yagen, A. Penhasi, A. Rubinstein, Low swelling, crosslinked guar and its potential use as colon-specific drug carrier, Pharm. Res. 15 (1998) 1019–1025.
[123] L. Vervoort, G. Van den Mooter, P. Augustijns, R. Busson, S. Toppet, R. Kinget, Inulin hydrogels as carriers for colonic drug targeting. I. Synthesis and characterization of methacrylated inulin and hydrogel formation, Pharm. Res. 14 (1997) 1730–1737.
[124] L. Vervoort, G. Van den Mooter, P. Augustijns, R. Kinget, Inulin hydrogels. I. Dynamic and equilibrium swelling properties, Int. J. Pharm. 172 (1998) 127–135.
[125] L. Vervoort, P. Rombout, G. Van den Mooter, P. Augustijns, R. Kinget, Inulin hydrogels. II. In vitro degradation study, Int. J. Pharm. 172 (1998) 137–145.
[126] L. Vervoort, I. Vinckier, P. Moldenaers, G. Van den Mooter, P. Augustijns, R. Kinget, Inulin hydrogels as carriers for colonic drug targeting. Rheological characterization of the hydrogel formation and the hydrogel network, J. Pharm. Sci. 88 (1999) 209–214.
[127] E.P. Kakoulides, J.D. Smart, J. Tsibouklis, Azocross-linked poly (acrylic acid) for colonic delivery and adhesion specificity: synthesis and characterization, J. Control. Release 52 (1998) 291–300.
[128] E.P. Kakoulides, J.D. Smart, J. Tsibouklis, Azocross-linked poly (acrylic acid) for colonic delivery and adhesion specificity: in vitro degradation and preliminary ex vivo bioadhesion studies, J. Control. Release 54 (1998) 95–109.
[129] J.-M. Ryu, S.-J. Chung, M.-H. Lee, C.-K. Kim, C.-K. Shim, Increased bioavailability of propranolol in rats by retaining thermally gelling liquid suppositories in the rectum, J. Control. Release 59 (1999) 163–172.
[130] S. Miyazaki, F. Suisha, N. Kawasaki, M. Shirakawa, K. Yamatoya, D. Attwood, Thermally reversible xyloglucan gels as vehicles for rectal drug delivery, J. Control. Release 56 (1998) 75–83.
[131] K. Watanabe, S. Yakou, K. Takayama, K. Isowa, T. Nagai, Rectal absorption and mucosal irritation of rectal gels containing buprenorphine hydrochloride prepared with water-soluble dietary fibers, xanthan gum and locust bean gum, J. Control. Release 38 (1996) 29–37.
[132] S. Cohen, E. Lobel, A. Trevgoda, T. Peled, A novel in situ-forming ophthalmic drug delivery system from alginates undergoing gelation in the eye, J. Control. Release 44 (1997) 201–208.
[133] J. Carlfors, K. Edsman, R. Petersson, K. Jörnving, Rheological evaluation of Gelrite® in situ gels for ophthalmic use, Eur. J. Pharm. Sci. 6 (1998) 113–119.
[134] P. Chetoni, G.D. Colo, M. Grandi, M. Morelli, M.F. Saettone, S. Darougar, Silicone rubber/hydrogel composite ophthalmic inserts: preparation and preliminary in vitro/in vivo evaluation, Eur. J. Pharm. Biopharm. 46 (1998) 125–132.
[135] Y.-M. Sun, J.-J. Huang, F.-C. Lin, J.-Y. Lai, Composite poly(2-hydroxyethyl methacrylate) membranes as rate-controlling barriers for transdermal applications, Biomaterials 18 (1997) 527–533.
[136] M.-K. Kim, S.-J. Chung, M.-H. Lee, A.-R. Cho, C.-K. Shim, Targeted and sustained delivery of hydrocortisone to normal and stratum corneum-removed skin without enhanced skin absorption using a liposome gel, J. Control. Release 46 (1997) 243–251.
[137] J.-C. Gayet, G. Fortier, High water content BSA–PEG hydrogel for controlled release device: evaluation of the drug release properties, J. Control. Release 38 (1996) 177–184.
[138] J.A. Hubbell, Hydrogel systems for barriers and local drug delivery in the control of wound healing, J. Control. Release 39 (1996) 305–313.
[139] A.K. Banga, S. Bose, T.K. Ghosh, Iontophoresis and electroporation: comparisons and contrasts, Int. J. Pharm. 179 (1999) 1–19.
[140] L.-L.H. Chen, Y.W. Chien, Transdermal iontophoretic permeation of luteinizing hormone releasing hormone: characterization of electric parameters, J. Control. Release 40 (1996) 187–198.
[141] J.-Y. Fang, Y.-B. Huang, H.-H. Lin, Y.-H. Tsai, Transdermal iontophoresis of sodium nonivamide acetate. IV. Effect of polymer formulations, Int. J. Pharm. 173 (1998) 127–140.
[142] O.M. Conaghey, J. Corish, O.I. Corrigan, Iontophoretically assisted in vitro membrane transport of nicotine from a hydrogel containing ion exchange resins, Int. J. Pharm. 170 (1998) 225–237.
[143] J.-Y. Fang, L.-R. Hsu, Y.-B. Huang, Y.-H. Tsai, Evaluation of transdermal iontophoresis of enoxacin from polymer formulations: in vitro skin permeation and in vivo microdialysis using Wistar rat as an animal model, Int. J. Pharm. 180 (1999) 137–149.
[144] I. Zhang, K.K. Shung, D.A. Edwards, Hydrogels with enhanced mass transfer for transdermal drug delivery, J. Pharm. Sci. 85 (1996) 1312–1316.
[145] V.R. Sinha, L. Khosla, Bioabsorbable polymers for implantable therapeutic systems, Drug Dev. Ind. Pharm. 24 (1998) 1129–1138.
[146] G. Giammona, G. Pitarresi, V. Tomarchio, S. Spampinato, P. Govoni, T. Campana, New hydrogel matrices based on chemical crosslinked α,β-polyasparthydrazide: synthesis, characterization and in vivo biocompatibility studies, Int. J. Pharm. 127 (1996) 165–175.
[147] J.M. Teijón, R.M. Trigo, O. García, M.D. Blanco, Cytarabine trapping in poly(2-hydroxyethyl methacrylate) hydrogels: drug delivery studies, Biomaterials 18 (1997) 383–388.
[148] E. Beyssac, C. Bregni, J.-M. Aiache, S. Gerula, E. Smolko, Hydrogel implants for methotrexate obtained by ionizing radiation, Drug. Dev. Ind. Pharm. 22 (1996) 439–444.
[149] M.D. Blanco, C. Gomez, O. García, J.M. Teijón, Ara-C release from poly(acrylamide-co-monomethyl itaconate) hydrogels: in vitro and in vivo studies, Polym. Gels Networks 6 (1998) 57–69.
[150] M.D. Blanco, O. García, R. Olmo, J.M. Teijón, I. Katime, Release of 5-fluorouracil from poly(acrylamide-co-monopropyl itaconate) hydrogels, J. Chromatogr. B680 (1996) 243–253.
[151] M.D. Blanco, O. García, R.M. Trigo, J.M. Teijón, I. Katime, 5-Fluorouracil release from copolymeric hydrogels of itaconic acid monoester. I. Acrylamide-co-monomethyl itaconate, Biomaterials 17 (1996) 1061–1067.
[152] C.-S. Cho, S.-Y. Han, J.-H. Ha, S.-H. Kim, D.-Y. Lim, Clonazepam

release from bioerodible hydrogels based on semi-interpenetrating polymer networks composed of poly(e-caprolactone) and poly(ethylene glycol) macromer, Int. J. Pharm. 181 (1999) 235–242.
[153] X. Zhao, J.M. Harris, Novel degradable poly(ethylene glycol) hydrogels for controlled release of protein, J. Pharm. Sci. 87 (1998) 1450–1458.
[154] W.E. Hennink, H. Talsma, J.C.H. Borchert, S.C. De Smedt, J. Demeester, Controlled release of proteins from dextran hydrogels, J. Control. Release 39 (1996) 47–55.
[155] O. Franssen, O.P. Vos, W.E. Hennink, Delayed release of a model protein from enzymatically-degrading dextran hydrogels, J. Control. Release 44 (1997) 237–245.
[156] W.E. Hennink, O. Franssen, W.N.E. van Dijk-Wolthuis, H. Talsma, Dextran hydrogels for the controlled release of proteins, J. Control. Release 48 (1997) 107–114.
[157] O. Franssen, R.J.H. Stenekes, W.E. Hennink, Controlled release of a model protein from enzymatically degrading dextran microspheres, J. Control. Release 59 (1999) 219–228.
[158] O. Franssen, L. Vandervennet, P. Roders, W.E. Hennink, Degradable dextran hydrogels: controlled release of a model protein from cylinders and microspheres, J. Control. Release 60 (1999) 211–221.
[159] K. Moriyama, N. Yui, Regulated insulin release from biodegradable dextran hydrogels containing poly(ethylene glycol), J. Control. Release 42 (1996) 237–248.
[160] B. Narasimhan, N.A. Peppas, The role of modelling studies in the development of future controlled release devices, in: K. Park (Ed.), Controlled Drug Delivery: Challenges and Strategies, American Chemical Society, Washington, DC, 1997, pp. 529–557.
[161] R.S. Langer, N.A. Peppas, Chemical and physical structure of polymers as carriers for controlled release of bioactive agents: a review, J. Macromol. Sci., Rev. Macromol. Chem. Phys. C23 (1983) 61–126.
[162] B. Narasimhan, S.K. Mallapragada, N.A. Peppas, Release kinetics: data interpretation, in: E. Mathiowitz (Ed.), Encyclopedia of Controlled Drug Delivery, Wiley, New York, 1999, pp. 921–935.
[163] J. Crank, The Mathematics of Diffusion, 2nd ed, Oxford University Press, New York, 1975.
[164] H. Eyring, Theory of rate processes, J. Chem. Phys. 4 (1936) 283–289.
[165] H. Fujita, Diffusion in polymer–diluent systems, Fortschr. Hochpolym.–Forsch. 3 (1961) 1–47.
[166] H. Yasuda, C.E. Lamaze, Permselectivity of solutes in homogeneous water-swollen polymer membranes, J. Macromol. Sci. Phys. B5 (1971) 111–134.
[167] N.A. Peppas, C.T. Reinhart, Solute diffusion in swollen membranes. I. A new theory, J. Membr. Sci. 15 (1983) 275–287.
[168] N.A. Peppas, H.J. Moynihan, Solute diffusion in swollen membranes. IV. Theories for moderately swollen networks, J. Appl. Polym. Sci. 30 (1985) 2589–2606.
[169] R.S. Harland, N.A. Peppas, Solute diffusion in swollen membranes. VII. Diffusion in semicrystalline networks, Colloid. Polym. Sci. 267 (1989) 218–225.
[170] E.N. Lightfoot, Transport Phenomena and Living Systems, Wiley, New York, 1974.
[171] H. Faxen, Die bewegung einer starren kugel langs der achse eines mit zaherer flussigkeit fefullten rohres, Arkiv. Mat. Astronom. Fys. 17 (1923) 27–32.
[172] P.L. Ritger, N.A. Peppas, A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs, J. Control. Release 5 (1987) 23–26.
[173] J. Crank, Free and Moving Boundary Problems, 2nd ed, Oxford University Press, New York, 1975.
[174] R.W. Korsmeyer, S.R. Lustig, N.A. Peppas, Solute and penetrant diffusion in swellable polymers. I. Mathematical modeling, J. Polym. Sci., Polym. Phys. 24 (1986) 395–408.
[175] S.R. Lustig, J.M. Caruthers, N.A. Peppas, Theories of penetrant transport in glassy polymers, J. Membr. Sci. 48 (1990) 281–307.
[176] E.W. Merril, Poly(ethylene oxide) star molecules: synthesis, characterization and applications in medicine and biology, J. Biomater. Sci. Polym. Ed. 1 (1993) 1.
[177] K.B. Keys, F.M. Andreopoulos, N.A. Peppas, Poly(ethylene glycol) star polymer hydrogels, Macromolecules 31 (1998) 8149–8156.