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Hydrogels in controlled release formulations: Network design and mathematical modeling☆

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Abstract

Over the past few decades, advances in hydrogel technologies have spurred development in many biomedical applications including controlled drug delivery. Many novel hydrogel-based delivery matrices have been designed and fabricated to fulfill the ever-increasing needs of the pharmaceutical and medical fields. Mathematical modeling plays an important role in facilitating hydrogel network design by identifying key parameters and molecule release mechanisms. The objective of this article is to review the fundamentals and recent advances in hydrogel network design as well as mathematical modeling approaches related to controlled molecule release from hydrogels. In the first section, the niche roles of hydrogels in controlled release, molecule release mechanisms, and hydrogel design criteria for controlled release applications are discussed. Novel hydrogel systems for drug delivery including biodegradable, smart, and biomimetic hydrogels are reviewed in the second section. Several mechanisms have been elucidated to describe molecule release from polymer hydrogel systems including diffusion, swelling, and chemically-controlled release. The focus of the final part of this article is discussion of emerging hydrogel delivery systems and challenges associated with modeling the performance of these devices.
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Keywords: Hydrogel; Drug delivery; Modeling; Controlled release; Diffusion; Degradation

Contents

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1. Introduction

1.1. Overview of manuscript/scope of this review

Since the establishment of the first synthetic hydrogels by Wichterle and Lim in 1954 [1], the growth of hydrogel technologies has advanced many fields ranging from food additives [2] to pharmaceuticals [3] to biomedical implants [4]. In addition, the development of an ever-increasing spectrum of functional monomers and macromers continue to broaden the versatility of hydrogel applications. Hydrogels now play a critical role in many tissue engineering scaffolds, biosensor and BioMEMS devices, and drug carriers. Among these applications, hydrogel-based drug delivery devices have become a major area of research interest with several commercial products already developed [5]. A successful drug delivery device relies not only on intelligent network design but also on accurate a priori mathematical modeling of drug release profiles. An ordered polymer network composed of macromers with well-understood chemistries yields hydrogels with well-defined physicochemical properties and reproducible drug-release profiles. In a complimentary fashion, a quantitative mathematical understanding of material properties, interaction parameters, kinetic events, and transport phenomena within complex hydrogel systems assists network design by identifying the key parameters and mechanisms that govern the rate and extent of drug release. In addition, mathematical modeling accelerates device design by limiting the number of experiments researchers must perform to understand the release mechanisms governing a particular delivery system.

Many excellent review articles have been published detailing the modeling of drug release from polymeric devices including hydrogels. This review builds on the established literature by not only tracking recent advances in the development of mathematical models for quantitatively predicting drug delivery from hydrogel systems, but also highlights how these models are playing a critical role in the design of novel hydrogel networks for future applications. In addition to describing the mechanisms

governing drug release from conventional hydrogels, the fabrication and modeling of several emerging and intelligently designed hydrogel systems for drug delivery applications are discussed. Specifically, these novel systems aim to incorporate advanced drug delivery strategies into tissue engineering scaffolds and other biomedical implants and require rigorous methods for quantifying multiple phenomena influencing molecule release.

1.2. Hydrogel — definition, classification, and network structure

Hydrogels are polymeric networks that absorb large quantities of water while remaining insoluble in aqueous solutions due to chemical or physical crosslinking of individual polymer chains. Differing from hydrophobic polymeric networks such as poly(lactic acid) (PLA) or poly(lactide-co-glycolide) (PLGA) which have limited water-absorption capabilities (<5–10 wt.%), hydrophilic hydrogels exhibit many unique physicochemical properties that make them advantageous for biomedical applications including drug delivery. For example, hydrogels are excellent candidates for encapsulating biomacromolecules including proteins and DNA due to their lack of hydrophobic interactions which can denature these fragile species [6]. In addition, compared to commonly used hydrophobic polymers such as PLGA, the conditions for fabricating hydrogels are relatively mild. Gel formation usually proceeds at ambient temperature and organic solvents are rarely required. In-situ gelation with cell and drug encapsulation capabilities further distinguishes hydrogels from the other hydrophobic polymers.

Hydrogels can be prepared from natural or synthetic polymers [7]. Although hydrogels made from natural polymers may not provide sufficient mechanical properties and may contain pathogens or evoke immune/inflammatory responses, they do offer several advantageous properties such as inherent biocompatibility, biodegradability, and biologically recognizable moieties that support cellular activities. Synthetic hydrogels, on the other hand, do not possess these inherent bioactive properties. Fortunately, synthetic polymers usually have well-defined structures that can be modified to yield tailorable degradability and functionality. Table 1 lists natural polymers as well as synthetic monomers that are commonly used in hydrogel fabrication.

Table 1
Natural polymers and synthetic monomers used in hydrogel fabrication [6,7]

Natural polymer	Synthetic monomer
Chitosan	Hydroxyethyl methacrylate (HEMA)
Alginate	*N*-(2-hydroxypropyl) methacrylate (HPMA)
Fibrin	*N*-vinyl-2-pyrrolidone (NVP)
Collagen	*N*-isopropyl acrylamide (NIPAAm)
Gelatin	Vinyl acetate (VAc)
Hyaluronic acid	Acrylic acid (AA)
Dextran	Methacrylic acid (MAA)
	Polyethylene glycol acrylate/methacrylate (PEGA/PEGMA)
	Polyethylene glycol diacrylate/dimethacrylate (PEGDA/PEGDMA)

Since the favorable properties of hydrogels stem from their hydrophilicity, the characterization of their water-sorption capabilities is the first step towards understanding the nanoscopic structure of hydrogel networks. Generally, three parameters are critical in describing the nanostructure of crosslinked hydrogel networks: (1) polymer volume fraction in the swollen state, $v_{2,s}$, (2) number average molecular weight between crosslinks, $\bar{M}_c$, and (3) network mesh size, ξ [8]. For non-porous hydrogels, the amount of liquid being retained in the hydrogel, the distance between polymer chains, and the flexibility of those chains together determine the mobility of encapsulated molecules and their rates of diffusion within a swollen hydrogel matrix.

The polymer volume fraction in the swollen state ($v_{2,s}$) describes the amount of liquid that can be imbibed in hydrogels and is described as a ratio of the polymer volume (V_p) to the swollen gel volume (V_g). It is also a reciprocal of the volumetric swollen ratio (Q) which can be related to the densities of the solvent (ρ_1) and polymer (ρ_2) and the mass swollen ratio (Q_m) as described by Eq. (1):

$$v_{2,s} = \frac{V_p}{V_g} = Q^{-1} = \frac{1/\rho_2}{Q_m/\rho_1 + 1/\rho_2} \quad (1)$$

The average molecular weight between two adjacent crosslinks ($\bar{M}_c$) represents the degree of

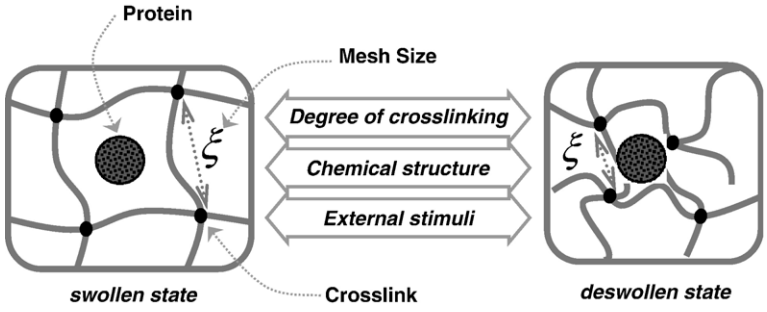

Fig. 1. Schematic of mesh size in hydrogels at swollen or shrunken states. Adapted from Ref. [12].

crosslinking of the hydrogel networks. $\bar{M}_c$ in a neutral, divinyl crosslinked network can be expressed as the following Flory–Rehner Equation [9].

$$\frac{1}{\bar{M}_c} = \frac{2}{\bar{M}_n} - \frac{\left(\frac{\bar{v}}{V_1}\right)\left[\ln(1-v_{2,s}) + v_{2,s} + \chi_{12} v_{2,s}^2\right]}{v_{2,s}^{1/3} - \frac{v_{2,s}}{2}} \quad (2)$$

Here, $\bar{M}_n$ is the average molecular weight of the linear polymer chains, $\bar{v}$ is the specific volume of the polymer, V_1 is the molar volume of water, and χ_{12} is the polymer–water interaction parameter. More complex versions of the Flory–Rehner expression have been developed by Peppas and others to describe the swelling behavior of ionic gels or gels crosslinked during polymerization [8]. For neutral gels at highly swelling conditions ($Q > 10$), Eq. (2) can be simplified to illustrate how gel swelling scales with the average molecular weight between crosslinks ($\bar{M}_c$) [10]:

$$Q = \left[\frac{\bar{v}(1/2 - 2\chi_{12})\bar{M}_c}{V_1}\right]^{3/5} = \beta\left(\bar{M}_c\right)^{3/5} \quad (3)$$

Another important parameter used to describe hydrogel swelling is the network mesh size (ξ) which can be described as follows [11]:

$$\xi = v_{2,s}^{-1/3}\left(\bar{r}_o^2\right)^{1/2} = Q^{1/3}\left(\bar{r}_o^2\right)^{1/2} \quad (4)$$

Here, $\left(\bar{r}_o^2\right)^{1/2}$ is the root-mean-squared end-to-end distance of network chains between two adjacent crosslinks in the unperturbed state. It can be determined using the following relationship [11]:

$$\left(\bar{r}_o^2\right)^{1/2} = l(C_n N)^{1/2} = l\left(C_n \frac{2\bar{M}_c}{M_r}\right)^{1/2} \quad (5)$$

where C_n is the Flory characteristic ratio, l is the bond length along the polymer backbone, N is the number of bonds between adjacent crosslinks, and M_r is the molecular weight of the repeating units of the composed polymer.

Combining Eqs. (4) and (5), one can easily calculate the mesh size of a hydrogel network and further compare it with the hydrodynamic radii of the molecules to be delivered. Theoretically, no solute diffusion is possible within the hydrogel matrix when mesh size approaches the size of the solute as shown in Fig. 1 [12]. Mesh size is affected by several factors including (1) degree of crosslinking of the gel; (2) chemical structure of the composing monomers; and (3) external stimuli such as temperature, pH and ionic strength. Mesh size is important in determining the physical properties of the hydrogels including mechanical strength, degradability, and diffusivity of the releasing molecule [10,13]. Typical mesh sizes reported for biomedical hydrogels range from 5 to 100 nm in their swollen state [10,14]. These size scales are much larger than most small-molecule drugs and therefore diffusion of these drugs are not significantly retarded in swollen hydrogel matrices. However, the release of macromolecules such as peptides, proteins, and oligonucleotides can be sustained from swollen hydrogels due to their significant hydrodynamic radii. When designed appropriately, the structure and mesh size of swollen hydrogels can be tailored to obtain

desired rates of macromolecule diffusion [15]. Alternatively, the rate and degree of gel swelling or degradation can also be tailored to control the release of molecules much smaller than the gel mesh size.

1.3. Niche roles of hydrogels in drug delivery

The advance in recombinant protein technology has identified numerous protein and peptide therapeutics for disease treatment. However, the effective delivery of these biomolecules is challenging mainly because of their large molecular weights and unique three-dimensional structures. Intravenous or subcutaneous injection is by far the most commonly used route for drug administration. However, these biomolecules are prone to proteolytic degradation and therefore experience extremely short plasma circulation times and rapid renal clearance, leading to multiple daily injections or increased dosage to maintain the drug concentration in the therapeutic window. Multiple daily injections decrease patient compliance while high doses may induce local toxicity and serious systemic immune responses. Polymeric controlled release formulations such as PLGA offer a sustained release mechanism in which the drug release rates can be controlled by changing polymer molecular weight and composition. However, it is well recognized that these hydrophobic polymers induce detrimental effects to the encapsulated proteins or peptides during network preparation and delivery [16] as well as trigger the host immune response [17]. Hydrophilic hydrogels, on the other hand, provide relatively mild network fabrication and drug encapsulation conditions that make them suitable for protein delivery [6]. The common niche for hydrogels in controlled release is the encapsulation (and subsequent release) of bioactive materials. Therefore, the systems we will focus on in this review deal with delivery from matrix devices rather than membrane devices. Through proper design, hydrogels can be used in a variety of applications including sustained, targeted, or stealth biomolecule delivery.

Several unique properties that hydrogels possess make them useful in delivering biomolecules. For example, stimuli responsiveness can be easily tailored into hydrogel networks during fabrication [18]. This enables sustained or bolus drug delivery corresponding to external stimuli such as pH or temperature. For example, pH-sensitive hydrogels are useful in oral drug delivery as they can protect peptide/protein drugs in the digestive track [19]. The pH responsiveness of hydrogels also facilitates lysosomal escape during gene delivery [20,21]. Such responsiveness changes the mode of drug administration from merely passive release to active delivery. These exclusive properties of hydrogels can be attributed to the variety of available network precursors. Acrylic acid (AA) and methacrylic acid (MAA) [19,22,23] are the most commonly used monomers to fabricate anionic pH-sensitive hydrogels while 2-(dimethylamino)ethyl methacrylate (DMAEMA) [24,25] is used for cationic hydrogel fabrication. *N*-isopropylacrylamide (NIPAAM) [26–28] and polypropylene oxide–polyethylene oxide–polypropylene oxide (PPO–PEO–PPO) block copolymers [28–30] are well-suited for the fabrication of temperature-sensitive hydrogels. The reversible swell-collapse transition modulates drug release rates and largely enhances the therapeutic efficacy of biomolecules.

Hydrogels can also be engineered to exhibit bioadhesiveness to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration [31–34]. Both natural polymers (e.g. chitosan) and synthetic monomers (e.g. AA) provide this advantageous property. Some bioadhesive polymers have been used to fabricate hydrogels for oral [6] and buccal drug delivery [35,36].

Hydrogels offer an important “stealth” characteristic in vivo owing to their hydrophilicity which increases the in vivo circulation time of the delivery device by evading the host immune response and decreasing phagocytic activities [37,38]. For example, Hubbell and coworkers developed poly(ethylene glycol)-based hydrogel nanoparticles as colloidal drug carriers [39]. Several other stealth delivery systems, such as PEGylated gold nanoparticles [37,40], have also been developed utilizing a PEG shell as a means of steric hindrance. This strategy exploits the hydrophilicity of PEG in excluding enzymatic degradation of the drug to be delivered. When conjugated with other protein therapeutics such as tumor necrosis factor (TNF), these PEGylated gold nanoparticles are good carriers for tumor-targeted delivery [41].

Another prospect of hydrogels is their role as scaffolding materials in tissue engineering applications [42–44]. Excellent examples are cartilage [45,46] and nerve [47] tissue engineering. The mild gelling conditions and in-situ polymerization capabilities of

hydrogels enable the simultaneous encapsulation of cells and growth factors. Controlled release of encapsulated growth factors and other agents from these tissue constructs is critical to providing the necessary cues for cell migration, differentiation, angiogenesis, and upregulation of extracellular matrix production required for neotissue growth or regeneration [48,49].

1.4. Drug release mechanisms from hydrogel devices

As discussed in the previous sections, hydrogels have a unique combination of characteristics that make them useful in drug delivery applications. Due to their hydrophilicity, hydrogels can imbibe large amounts of water (>90 wt.%). Therefore, the molecule release mechanisms from hydrogels are very different from hydrophobic polymers. Both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the rate-limiting step for controlled release and are therefore categorized as follows:

1. Diffusion-controlled
2. Swelling-controlled
3. Chemically-controlled.

Diffusion-controlled is the most widely applicable mechanism for describing drug release from hydrogels. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modeling diffusion-controlled release [13]. Drug diffusivities are generally determined empirically or estimated a priori using free volume, hydrodynamic, or obstruction-based theories [13].

Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels [50]. The release of many small molecule drugs from hydroxypropyl methylcellulose (HPMC) hydrogel tablets is commonly modeled using this mechanism. For example, Methocel® matrices, a combination of methylcellulose and HPMC, from Dow Chemical Company are commercially available for preparing swelling-controlled drug delivery formulations exhibiting a broad range of delivery timescales [50,51].

Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface-erosion or bulk-degradation of the polymer backbone. A more thorough discussion of these mechanisms can be seen in a later section of this review as well as in several other excellent reviews [6,13,52].

1.5. Design criteria for hydrogels in drug delivery formulations

Materials selection and network fabrication governs the rate and mode of drug release from hydrogel matrices. Several design criteria are crucial for drug delivery formulations and have to be evaluated prior to hydrogel fabrication and drug loading. These criteria are also important in mathematical modeling of drug release. Table 2 lists these important criteria and variables for designing hydrogel-based drug carriers. Within the realm of transport properties, the most notable variable is the drug diffusion coefficient, which is affected by the molecular size of the drug and characteristics of the polymer network. Hydrogel crosslinking density affects diffusivity to a large extent as shown in Fig. 1 and as discussed previously. If special functionalities, such as ionic groups, are introduced into the hydrogel networks, interactions between these functionalities and encapsulated drugs certainly affect drug diffusivity. Physical properties of the hydrogel also affect drug release. For example, polymer molecular weights, composition, and polymer/initiator concentrations influence hydrogel swelling and

Table 2
Design criteria for hydrogels in drug delivery formulations

Design criteria	Design variables
Transport properties	• Molecular weight and size of protein
Molecule diffusion	• Molecular weight of polymer
	• Crosslinking density
	• Polymer–protein interactions
	• Hydrogel degradation rate
	• Additional functionalities
Physical properties	• Polymer/crosslinker/initiator concentrations
Gelling mechanisms / conditions	• Temperature, pH, ionic strength
Structural properties	• Molecular weight of polymer
Biodegradability	• Mechanical strength
Stimuli-responsiveness	• Concentration of degradable groups
	• Concentration of responsive groups
Biological properties	• Cytotoxicity of the hydrogel
Biocompatibility	• Capsule formation

degradation. Finally, the stimuli-responsiveness of a hydrogel network can also mediate the amount and rate of drug delivery. The understanding of transport and physical properties is especially crucial in modeling molecule release.

Even if a hydrogel delivery formulation is designed with the appropriate physical and transport properties, it may still fail to perform its therapeutic role when implanted in vivo due to a localized inflammatory response. The formation of a fibrous capsule surrounding the delivery device creates additional diffusion barriers that may limit drug release rates while increased proteolytic activity may increase rates of matrix and drug degradation. Proper material selection, fabrication process, and surface texture of the device are therefore always critical in designing biocompatible hydrogel formulations for controlled release.

2. Novel engineering of hydrogels for drug delivery

2.1. Biodegradable hydrogels

For most biomedical applications, biodegradable hydrogels are favored over non-degradable gels since they degrade in clinically relevant time-scales under relatively mild conditions. Compared to non-degradable hydrogels, degradable carriers eliminate the need for additional surgeries to recover the implanted gels. However, proper techniques for predicting hydrogel degradation rates are critical for successful application of these degradable systems as they facilitate the design of implants with optimal degradation profiles that result in proper rates of drug release or tissue regeneration and hence maximize therapeutic effects.

The fabrication and modeling of hydrolytically degradable hydrogels are well-developed. For example, West and Hubbell fabricated PLA-*b*-PEG-*b*-PLA hydrogels composed of poly(lactic acid) (PLA) and poly(ethylene glycol) (PEG) block copolymers for protein release applications [53]. Metters et al. developed scaling laws to predict the degradation rates of PLA-*b*-PEG-*b*-PLA hydrogels based on macroscopic properties such as compressive modulus and volumetric swelling ratio [54–56]. Mason et al. further applied these scaling laws to predicting protein diffusion and release during bulk network degradation [10]. Using a more rigorous approach, Hennink and coworkers recently utilized a Monte Carlo simulation technique to microscopically predict the degradation and protein delivery behaviors of hydroxyethyl methacrylated dextran (dex-HEMA) microspheres [57].

In addition to hydrolytically degradable hydrogels, synthetic gels incorporating biological moieties that can be degraded enzymatically are also under intensive investigation. One way to fabricate this type of hydrogel is to incorporate peptide substrates for enzymatic hydrogel formation [58] and degradation [59,60]. Alternatively, polymers that can be naturally degraded by enzymes (e.g. polycaprolactone can be degraded by lipase) can be copolymerized with PEG to form enzymatically degradable gels [61]. Although hydrogels derived from natural sources (such as chitosan, gelatin, dextran, etc.) can also be degraded enzymatically, in many cases synthetic hydrogels containing defined biological moieties are more favorable because of their tunable physicochemical properties. For example, the degradation behavior can be more accurately tailored to obtain better control over gel degradation and drug release rates. Hubbell and colleagues have developed a hydrogel system containing integrin-binding sites for cell attachment and peptide substrates for matrix metalloproteinases (MMPs) or plasmin to mimic the natural bidirectional communication between extracellular matrix and migrating cells. Cells can only infiltrate the designer matrices once the gels are locally degraded in response to secretion of MMPs by invading cells [59,60].

2.2. Smart hydrogels

"Smart" hydrogels, or stimuli-sensitive hydrogels, are very different from inert hydrogels in that they can "sense" changes in environmental properties such as pH and temperature and respond by increasing or decreasing their degree of swelling. These sensing capabilities are attractive in many biomedical applications and several review papers have been published in this field [18,28]. The volume-changing behavior of 'smart' hydrogels is particularly useful in drug delivery applications as drug release can be triggered upon environmental changes [18,29,62]. For non-ionic hydrogels, the degree of swelling only depends on the chemical compositions of the polymers and does not respond to external pH change. When ionic moieties are incorporated into hydrogels, the swelling depends not only on the chemical composition of the gel but also on the pH of the surrounding medium. Generally, anionic hydrogels deprotonate and swell more when external pH is higher than pK_a of the ionizable groups tethered on polymer chains while cationic hydrogels protonate and swell more when external pH is lower than the pK_b of the ionizable groups. Depending on the ionic monomers used to fabricate the gel, the pH-dependent swelling curves exhibit one or more inflection points near the pK_a/pK_b of the ionizable groups as shown in Fig. 2. Many modeling efforts have been devoted to predicting the dynamic and equilibrium swelling of ionic hydrogels [23,63–66]. Because the swelling/deswelling behavior of the ionic hydrogels is closely related to ion movement, the swelling kinetics depends not only on the pH but also on the compositions of the external solutions. Hydrogels with pH-responsiveness have been used in a number of applications including oral peptide delivery [67–71], valves for microfluidic devices [72], and artificial muscles [73–75].

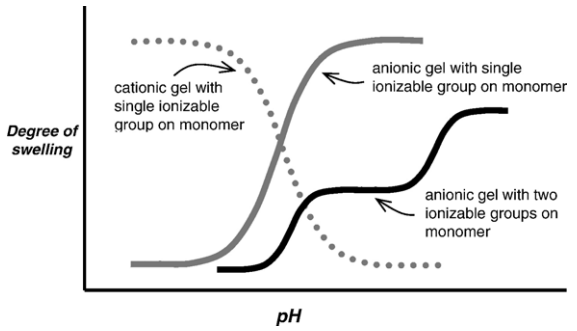

Fig. 2. Schematic of relative ionic hydrogel swelling as a function of pH.

Another important stimulus for causing hydrogel responsiveness is temperature. The most commonly used synthetic polymer for fabricating temperature-sensitive hydrogels is poly(*N*-isopropylacrylamide) (poly(NIPAAM)), which possesses a lower critical solution temperature (LCST) at around 32 °C. The value of the LCST can be increased or decreased by copolymerizing hydrophilic or hydrophobic polymers with poly(NIPAAM). When the bulk temperature is higher than the LCST of the polymer, the polymer chains lose their bound-water. Hydrophobic interactions between the polymer chains lead to a rapid collapse (deswelling) of the gel [76]. Readers are directed to other more thorough reviews discussing the mechanisms and applications of thermo-sensitive hydrogels [28,30]. Temperature-responsiveness is particularly useful for in-situ formation of drug-delivery devices since it allows handling of the formulation in the sol-phase at room temperature and solidification of the carrier upon injection [28].

More recently, studies have been conducted to fabricate and characterize hydrogels with dual-sensitivities. This was accomplished by copolymerizing a temperature-sensitive monomer, usually *N*-isopropylacrylamide, and a pH-sensitive monomer such as acrylic acid or methacrylic acid [21,77–82]. For example, Stayton's group has investigated a series of copolymers containing propylacrylic acid (PAA) and *N*-isopropylacrylamide pendant chains as pH- and thermo-sensitive moieties, respectively [20]. This new class of copolymers can sense environmental changes in the physiological range and has found usefulness in intracellular drug delivery in which subtle pH differences across the endosomal membrane triggers the delivery of protein or DNA.

2.3. Biomimetic hydrogels

One drawback of using synthetic and some natural hydrogels for in vivo applications is that they do not possess biological recognition sites for supporting cellular activities. For this reason, relatively inert polymer chains can be tailored with select biological moieties to yield bioactive hydrogels for tissue engineering applications. The Arginine–Glycine–Aspartic acid (RGD) tri-peptide derived from fibronectin is the

most commonly used biological moiety in this regard as it mediates the adhesion of many cell types through integrin-binding without the need for protein adsorption on a hydrogel surface [83–86]. Through the selective presentation of bioactive ligands on otherwise bioinert hydrogel background, researchers are able to better control cell–hydrogel interactions to fulfill specific biomedical applications.

The controlled incorporation and presentation of biological cues within hydrogel matrices has also played a role in the development of novel controlled delivery devices. For example, in vivo observations of the sequestering and protection of proteins by the extracellular matrix (ECM) have inspired the design of novel biomimetic hydrogels with specific and reversible protein-binding capabilities [87–89]. This approach is especially useful in controlled release of growth factors for tissue regeneration as it mimics the mechanism and temporal profiles of endogenously produced growth factors. Through judicious selection of network-immobilized ligands with desired protein-binding affinities or by adjusting the molar ratio of protein to protein-binding ligand, researchers can readily manipulate protein release rates form these bioactive matrices.

Another biomimetic hydrogel system used in controlled release applications is the enzymatically-cleavable prodrug system. The main advantage of this approach is that the degradation rate of the prodrug linkage is directly proportional to the concentration of specific enzymes secreted by local cells. Therefore the rate of drug release self-adjusts to the rate of cellular infiltration and cell-mediated matrix remodeling. Therapeutic proteins such as vascular endothelial growth factor (VEGF) have been covalently immobilized within hydrogel networks by enzyme-sensitive oligopeptides [90]. VEGF release is mediated by proteases (e.g. matrix metalloproteinases or MMPs) secreted by migrating fibroblast and endothelial cells and is therefore made available only when specific cellular processes occur. This cell-demanded VEGF release has been shown to not only preserve growth factor bioactivity but also promote localized angiogenesis.

3. Molecule release mechanisms for hydrogel formulations

The physicochemical properties of the hydrogel network as well as the selection of drug-loading method will determine the mechanism(s) by which the loaded drug is released from the crosslinked matrix. The incorporation of drugs into hydrogel delivery matrices can be performed via one of the following ways: (1) *Post-loading*: absorption of drugs is achieved after hydrogel networks are formed. If an inert hydrogel system is used, diffusion is the major driving force for drug uptake and release will be determined by diffusion and/or gel swelling. In the presence of hydrogels containing drug-binding ligands, terms accounting for drug–polymer interaction and drug diffusion must both be included in any model description of release; (2) *in-situ loading*: drugs or drug–polymer conjugates are mixed with polymer precursor solution and hydrogel network formation and drug encapsulation are accomplished simultaneously. In these systems, the release of drugs can be controlled by diffusion, hydrogel swelling, reversible drug–polymer interactions, or degradation of labile covalent bonds.

3.1. Diffusion-controlled delivery systems

Understanding the mechanisms and identifying the key parameters that govern drug release from hydrogels are the first step toward accurately predicting the entire release profile. For porous hydrogels, when pore sizes are much larger than the molecular dimensions of the drug, the diffusion coefficient can be related to the porosity and the tortuosity of the hydrogels [91]. However, for non-porous hydrogels and for porous gels with pore sizes comparable to the drug molecular size, drug diffusion coefficients are decreased due to steric hindrance provided by polymer chains within the crosslinked networks [13,91,92]. In these cases, the average free volume per molecule available to the drug is decreased and the hydrodynamic drag experienced by the drug is increased, leading to increased drug diffusion path length compared to porous hydrogels with pore sizes much larger than the encapsulated drug [93–95]. Due to the usually high permeabilities of hydrogel networks and the advantages of in-situ fabrication, most research efforts are focused on understanding diffusion-controlled release of encapsulated drugs from three-dimensional hydrogel matrices.

Drug diffusion within highly swollen hydrogels is best described by Fick's law of diffusion or Stefan–Maxwell equations [8]. Diffusion-controlled hydrogel delivery systems can be either reservoir or matrix

systems [96]. For a reservoir system where the drug depot is surrounded by a polymeric hydrogel membrane, Fick's first law of diffusion can be used to describe drug release through the membrane:

$$J_A = -D\frac{dC_A}{dx} \tag{6}$$

Here, J_A is the flux of the drug, D is the drug diffusion coefficient, and C_A is drug concentration. In many cases, the drug diffusion coefficient is assumed constant to simplify the modeling. However, in the general case it is a function of drug concentration and a special correlation incorporating the concentration-dependent drug diffusivity must be utilized to accurately predict drug flux. Another assumption of this expression is that J_A is the drug flux corresponding to the mass average velocity of the system.

For a matrix system where the drug is uniformly dispersed throughout the matrix, unsteady-state drug diffusion in a one-dimensional slap-shaped matrix can be described using Fick's second law of diffusion:

$$\frac{dC_A}{dt} = D\frac{d^2C_A}{dx^2} \tag{7}$$

Here, the drug diffusion coefficient is again assumed as a constant. Other assumptions include sink condition and a thin planar geometry where the release through slab edges is neglected. When diffusivity is concentration-dependent the following equation is used:

$$\frac{\partial C_A}{\partial t} = \frac{\partial}{\partial x}\left(D(C_A)\frac{\partial C_A}{\partial x}\right) \tag{8}$$

Many previous attempts to model diffusion-controlled drug delivery from hydrogels rely largely on empirically determined diffusion coefficients. Once the diffusion coefficient is determined, Eqs. (6)–(8) can be solved, together with proper initial and boundary conditions, to yield drug concentration profiles that dictate the release kinetics. For example, an exact analytical solution to Eq. (7) can be obtained using separation of variable technique. The ratio of the amount of molecule released up to any time t (M_t) to the final amount of molecule release (M_∞) can be expressed as:

$$\frac{M_t}{M_\infty} = 1 - \sum_{n=0}^{\infty} \frac{8}{(2n+1)^2\pi^2} \cdot \exp\left[\frac{-(2n+1)^2\pi^2 D}{L^2}t\right] \tag{9}$$

This equation can be used to predict the diffusion of a broad range of molecules including small molecular weight drugs and biomacromolecules like proteins and DNA once an appropriate diffusion coefficient is obtained. Although this simple solution applies to many diffusion-controlled drug release systems, model complexity will increase as other mechanisms, polymer–drug interactions, and when non-spherical drugs are used [15].

Another empirical equation developed by Peppas et al. assumes a time-dependent power law function [6,50]:

$$\frac{M_t}{M_\infty} = k \cdot t^n \tag{10}$$

Here, k is a structural/geometric constant for a particular system and n is designated as release exponent representing the release mechanism. Table 3 lists the n values for delivery matrices with different geometries and release mechanisms [50]. It is noteworthy that in a purely swelling-controlled slab-based delivery system, the drug fractional release (M_t/M_∞) appears to be zero-order as the release exponent equals unity. The power law is easy to use and can be applied to most diffusion-controlled release systems. However, it is too simple to offer a robust prediction for complicated release phenomena. For example, in diffusion-controlled systems where $n=0.5$, the power law is only valid for the first 60% of the release profile. These empirical models can only predict the release profile after certain release experiments are conducted and have limited capability to predict how the release profiles will change as the chemical or network properties of the system are varied.

Analytical solutions to Fick's law are not available when more complex geometries or non-constant drug diffusivities are incorporated into the model descriptions. Except in extremely dilute systems, drug diffusion

Table 3
Release exponent values (n) in the empirical power law model

Matrix Geometry	Diffusion-controlled delivery system (Case I)	Swelling-controlled delivery system (Case II)
Slab	$n=0.5$	$n=1$
Cylinder	$n=0.45$	$n=0.89$
Sphere	$n=0.43$	$n=85$

Adapted from Ref. [50].

coefficients will be a function of drug concentration. Additionally for hydrogel systems diffusivities of encapsulated molecules will depend on the degree of swelling and crosslinking density of the gels. Therefore the diffusion coefficient used to describe drug release will be sensitive to environmental changes or degradation of the polymer network and may vary over the time-scale of release. Several theoretical models have been developed to relate molecule diffusion coefficients to fundamental hydrogel characteristics and have been reviewed elsewhere [6,13]. Generally, theoretical models for predicting molecule diffusion coefficients have the following general form:

$$\frac{D_g}{D_o} = f(r_s, v_{2,s}, \xi) \tag{11}$$

Here, D_g and D_o are the drug diffusion coefficients in the swollen hydrogel network and in pure solvent, respectively. r_s is the size of the drug to be delivered. This general expression takes into account factors affecting drug release such as the structure of the gel, the polymer composition, the water content, and the size of the molecules. For a degradable hydrogel, D_g changes as the network degrades due to an increase in gel mesh size and a decrease in polymer volume fraction over time.

Several theories have been developed to correlate the relationship between drug diffusivity in the gels and in the solution [13]. For example, the following equation using a free-volume approach proposed by Lustig and Peppas can be used to describe the relationship between drug diffusivity and network structure [15]:

$$\frac{D_g}{D_o} = \left(1-\frac{r_s}{\xi}\right)\exp\left(-Y\left(\frac{v_{2,s}}{1-v_{2,s}}\right)\right) \tag{12}$$

Here, Y is defined as the ratio of the critical volume required for a translational movement of the encapsulated drug molecule and the average free volume per molecule of solvent. A good approximation for Y is unity. For highly swollen ($Q>10$) hydrogels with degradable crosslinks the diffusivity correlation shown in Eq. (12) can be simplified during the initial stages of degradation to [10,97]:

$$1-\frac{D_g}{D_o} = \frac{r_s}{\xi} \sim e^{-7/5jk_E't} \tag{13}$$

Here, the lumped parameter jk_E' is the pseudo-first-order reaction rate constant for the hydrolysis of a labile crosslink. From this expression one can realize that mesh size is time-dependent due to network degradation. It is clear that D_g increases as degradation proceeds and approaches D_o. The rate of increase in drug diffusivity depends on network structure and bond cleavage kinetics [10,98].

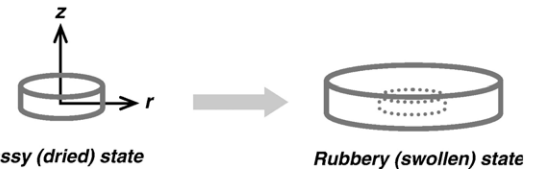

Fig. 3. Schematic of HPMC hydrogel tablet in the glassy (left) and rubbery (right) state.

3.2. Swelling-controlled delivery systems

Another mechanism for drug delivery is swelling-controlled delivery. As shown in Fig. 3, hydrogels may undergo a swelling-driven phase transition from a glassy state where entrapped molecules remain immobile to a rubbery state where molecules rapidly diffuse. In these systems, the rate of molecule release depends on the rate of gel swelling. One example of swelling-controlled drug delivery systems is hydroxypropyl methylcellulose (HPMC). Drug loaded HPMC tablets are three-dimensional, hydrophilic matrices that are usually stored in a dry, glassy state. After oral administration, HPMC polymer absorbs liquid and a rapid glassy-to-rubbery phase-transition occurs once the glass transition temperature (T_g) is reached, causing the systematic release of loaded drugs. The drug release rates are modulated by the rate of water transport and the thickness of the gel layer.

Drug diffusion time and polymer chain relaxation time are two key parameters determining drug delivery from polymeric matrices. In diffusion-controlled delivery systems, the time-scale of drug diffusion, t, (where $t=\delta(t)^2/D$ and $\delta(t)$ is the time-dependent thickness of the swollen phase) is the rate-limiting step while in swelling-controlled delivery systems the time-scale for polymer relaxation (λ) is the rate-limiting step. The Deborah number (De) is used to compare these two time-scales [99,100]:

$$\mathrm{De} = \frac{\lambda}{t} = \frac{\lambda D}{\delta(t)^2} \tag{14}$$

In diffusion-controlled delivery systems ($De \ll 1$), Fickian diffusion dominates the molecule release process and diffusion equations described in the previous section can be used to predict molecule release. In swelling-controlled delivery systems ($De \gg 1$), the rate of molecule release depends on the swelling rate of polymer networks.

The empirical power law (Eq. (9)) used to describe diffusion-controlled drug release from hydrogel matrices can also be used comprehensively in swelling-controlled delivery systems. A modification of Eq. (9) takes into account both the drug diffusion and polymer relaxation [101]:

$$\frac{M_t}{M_\infty} = k_1 t^m + k_2 t^{2m} \tag{15}$$

where k_1, k_2, and m are constants. The two terms on the right side represent the diffusion and polymer relaxation contribution to the release profile, respectively.

The above empirical relationship does not account for "moving-boundary" conditions in which the gel expands heterogeneously as water penetrates and swells the gels. For this more rigorous description, Korsmeyer and Peppas introduced a dimensionless swelling interface number, Sw, to correlate the moving boundary phenomena to hydrogel swelling [102–104]:

$$\mathrm{Sw} = \frac{V\delta(t)}{D} \tag{16}$$

Here, V is the velocity of the hydrogel swelling front and D the drug diffusion coefficient in the swollen phase. For a slab system when $\mathrm{Sw} \ll 1$, drug diffusion is much faster than the movement of glassy-rubbery interface and thus a zero-order release profile is expected.

Building on several modeling iterations [11,15,105–107], a more rigorous method for predicting molecule release from swelling-controlled systems is provided by a sequential layer model developed by Siepmann and Peppas [50,108–112]. In this model, drug diffusion, polymer relaxation and dissolution are all taken into account. Drug transport in both radial and axial directions is accounted for using Fick's second law of diffusion in a cylindrical geometry with concentration-dependent diffusion coefficients as shown below [110,111]:

$$\frac{\partial C_k}{\partial t} = \frac{\partial}{\partial r}\left(D_k \frac{\partial C_k}{\partial r}\right) + \frac{D_k}{r}\frac{\partial C_k}{\partial r} + \frac{\partial}{\partial z}\left(D_k \frac{\partial C_k}{\partial z}\right) \tag{17}$$

Here, C_k and D_k are the concentration and diffusivity of the diffusible species (1: water; 2: drug), respectively. Concentration-dependent diffusivities derived by a "Fujita-like" free-volume model can be expressed as [113]:

$$D_1 = D_{1\mathrm{eq}} \exp\left(-\beta_1\left(1-\frac{C_1}{C_{1\mathrm{eq}}}\right)\right) \tag{18}$$

$$D_2 = D_{2\mathrm{eq}} \exp\left(-\beta_2\left(1-\frac{C_1}{C_{1\mathrm{eq}}}\right)\right) \tag{19}$$

where β_1 and β_2 are dimensionless constants and "eq" represents the equilibrium drug concentration at the water/matrix interface where polymer disentanglement occurs.

Due to the concentration-dependent diffusion coefficients, Eqs. (17)–(19) can only be solved numerically. Siepmann et al. demonstrated that these numerical solutions agreed well with experimental results [50,108]. This model is therefore useful in predicting the shape and dimensions of HPMC tablets needed to acquire desired release profiles [109].

Stemming from the work of Siepmann and Peppas, Wu and coworkers [114] recently developed a mathematical model to describe swelling-controlled release. They introduced additional boundary conditions derived from a volume balance and accounted for two-dimensional movement of the swelling front in the radial or axial directions. This model assumes a homogeneous mixture of drug and polymer at $t=0$, perfect sink conditions, and geometrical symmetry of the tablet. Model predictions were verified using compressed poly(ethylene oxide) (PEO) hydrogel tablets with different molecular weights. The results of water uptake, swelling and dissolution of PEO matrices as well as drug release are shown to agree well with the mathematical model [114].

3.3. Chemically-controlled delivery systems

In addition to diffusion and swelling-controlled delivery systems discussed previously, a third type of molecule release mechanism is chemically-controlled delivery. The latter can be further classified as (1) purely kinetic-controlled release where polymer degradation (bond-cleavage) is the rate-determining step and diffusion term is assumed to be negligible; and (2) reaction-diffusion-controlled release in which both reaction (e.g. polymer degradation, protein–drug interaction) and diffusion terms must be included in the model to accurately predict drug release. The reaction-diffusion-controlled release is particularly intriguing as more synthetic hydrogel systems designed with drug-binding capacity are utilized in drug delivery [87,88,115] and tissue engineering [89].

3.3.1. Kinetic-controlled release — pendant chain systems

There are two types of kinetic-controlled-release systems: pendant chain (prodrugs) and surface-eroding systems. In pendant chain systems, drugs are covalently linked to the hydrogel network via cleavable spacers and drug release is controlled by the rate of spacer-bond cleavage. In surface-eroding systems, drug release is mediated by the rate of surface erosion. Drug diffusion does not determine the rate of drug release in either system.

Prodrugs or polymer–drug conjugates are designed to enhance the therapeutic efficacy of the drug. This strategy is especially useful when growth factors are to be delivered as most of them are susceptible to rapid proteolytic degradation. The design of prodrugs has attracted much attention and extensive reviews on the design and therapeutic application of these systems can be found elsewhere [116,117].

Generally, the release of covalently tethered prodrugs is determined by the degradation rate of the polymer–drug linkage [118–121]. Most of these linkages have been designed to be hydrolytically degradable allowing degradation and release rates to be characterized by fairly simple first-order kinetic relationships [59]. However, in particular applications, for example where a more targeted delivery profile is desired, it is advantageous to design enzymatically cleavable spacer bonds [122]. These chemistries lead to more complex release kinetics. Furthermore, in cases where the prodrugs are tethered to degradable hydrogel matrices, the kinetics of gel degradation may also play a significant role in determining overall drug release profiles [118–123].

Ehrbar et al. recently developed fibrin matrices tethered with pendant vascular endothelial growth factor (VEGF) variants linked by plasmin-sensitive peptidyl substrates [122]. These covalently bound VEGF

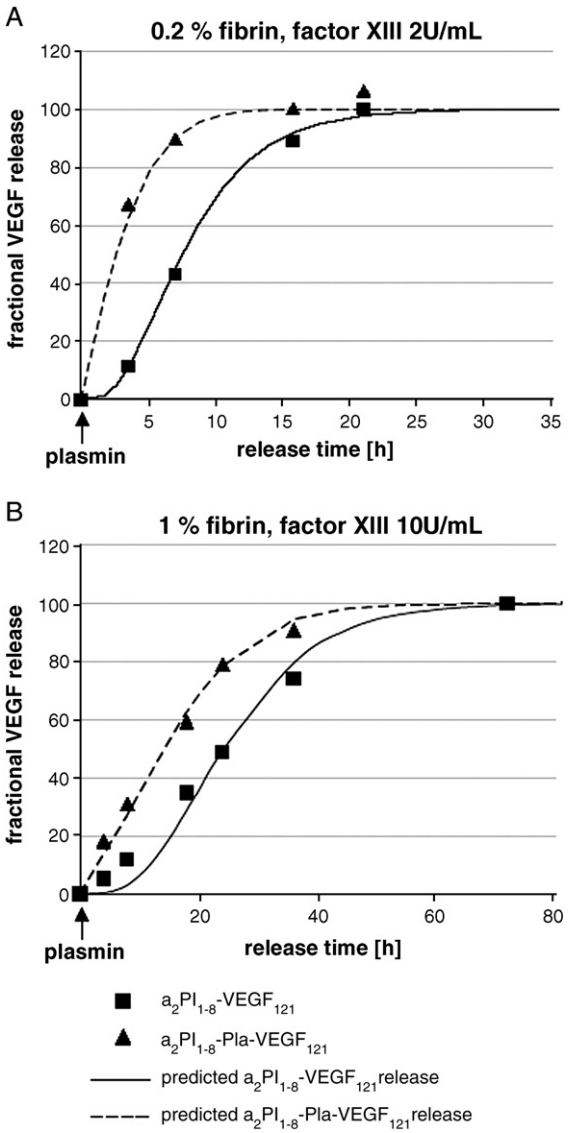

Fig. 4. Mathematical modeling predicts experimental observations of proteolysis-mediated release of fibrin-bound $VEGF_{121}$ variants from low- or high-density fibrin gel networks. Reproduced from Ref. [122], Copyright (2005), with permission from Elsevier.

variants can only be liberated from the insoluble matrix through plasmin-mediated cleavage of the engineered peptide substrates. First-order cleavage kinetics were used to model the time-dependent VEGF release. Accurate prediction of VEGF release profiles also required a description of VEGF-release via matrix-mediated degradation. Two adjustable parameters were therefore used to accurately predict complete VEGF release profiles. The first parameter was the pseudo first-order degradation rate constant, k. The degradation of bonds within the fibrin network and the plasmin-sensitive substrates used to link VEGF to the fibrin were assumed to follow the same first-order kinetics. The second adjustable parameter, N, represented the number of fibrin repeat units between two crosslinks and was an indication of fibrin network structure. As shown in Fig. 4, the developed model accurately predicted release of cleavable and non-cleavable VEGF variants from both low and high-density fibrin matrices by accounting for both network structure and kinetics of individual bond cleavage.

Unique release profiles unattainable with diffusion-controlled release mechanisms have also been demonstrated from hydrolytically degradable hydrogels with tethered agents. Dubose et al. covalently incorporated fluorescently labeled probe molecules within the three-dimensional network structure of PEG-based hydrogels formed via step-growth polymerizations [123]. As shown in Fig. 5, they demonstrated that hydrolytic degradation of covalent bonds within the step-crosslinked PEG network as well as the cleavage of immobilized probe molecules resulted in a biphasic release profile in which a constant molecular release profile is obtained prior to gel dissolution and an almost instantaneous burst release following gel dissolution. The authors demonstrated that the slope of the approximate zero-order delivery regime as well as the extent of the latent burst could be controlled by crosslinker functionality (tetra-functional versus octa-functional PEG, Fig. 5A) and degradation kinetics (varying temperature, pH, or chemistry of the degradable bond, Fig. 5B).

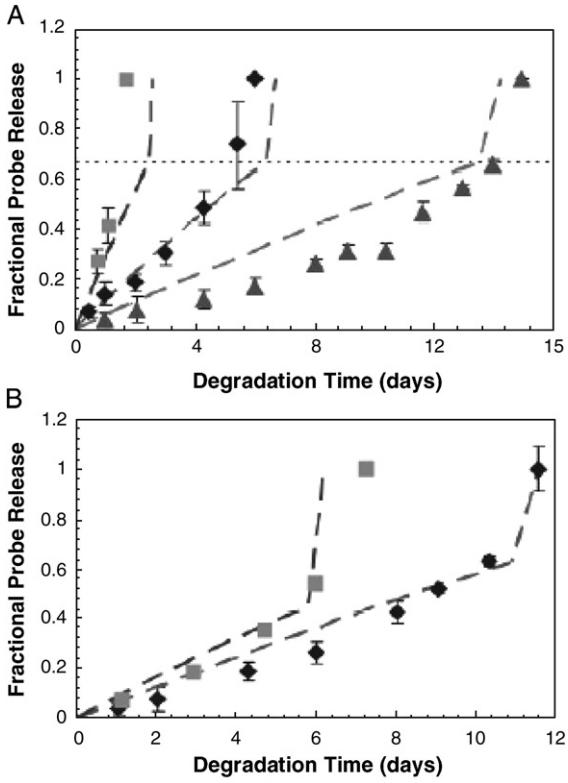

Fig. 5. Fractional probe release from degradable PEG-acrylate/dithiol gels formed via step-growth polymerization (**A**) gels fabricated from 30 wt.% eight-armed PEG-acrylate/DTT precursor solutions and degraded at varying temperatures: 37 °C (▲), 46 °C (◆), and 57 °C (■). (**B**) Gels fabricated with either four-arm/10-kDa (■) or eight-arm/20-kDa (◆) PEG were measured and compared with model predictions (– – –). Reproduced with permission from [123]. Copyright 2005, John Wiley and Sons.

3.3.2. Kinetic-controlled release — surface-eroding systems

Other kinetic-controlled systems occur when drug release is mediated by surface erosion of the polymer matrix. For hydrophobic polymer networks, surface erosion occurs when the rate of water transport into the polymer is much slower than the rate of bond hydrolysis. However, due to the inherently high water content of hydrogels, surface erosion only occurs in enzymatic-degrading systems where the transport of enzyme into the gel is slower than the rate of enzymatic degradation. While no hydrogels have been specifically designed to degrade in this fashion, surface erosion of enzymatically degradable poly(ethylene glycol)-polycaprolactone (PCL-*b*-PEG-*b*-PCL) block copolymer hydrogels has been observed in vitro by Rice et al. when exposed to relatively high concentrations of lipase [61].

Most of the models focusing on surface-eroding polymers are based on hydrolytic-degrading polymers. These relationships, however, can also be applied to

enzymatically degradable, surface-eroding hydrogel systems. Surface-eroding matrices are advantageous for drug delivery applications as the structural integrity of the carrier device is maintained during delivery and zero-order release of the encapsulated molecules can be readily obtained by appropriate choice of device geometry [7].

Hopfenberg initially developed a drug delivery model where the release only depends on matrix erosion rates. Eq. (22) describes the release from surface-eroding devices with an initial dimension a_0 (radius for a spherical or cylindrical geometry and half-thickness for slab geometry) and drug concentration C_0 [124]:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{C_0 a_0}\right)^n \tag{20}$$

In this equation, n is a geometrical factor and a number of 1, 2, or 3 is used for a slab, cylinder, or sphere, respectively. It is clear that when a slab-shaped device is used ($n=1$), drug release appears to be a zero-order profile.

Following Hopfenberg's work, Katzhendler, Hoffman, and coworkers further developed a general mathematical model for heterogeneous eroding networks accounting for different radial and vertical erosion rate constants for a flat tablet (k_a and k_b for radial and vertical degradation constant, respectively) [125]:

$$\frac{M_t}{M_\infty} = 1 - \left(1 - \frac{k_a t}{C_0 a_0}\right)^2 \left(1 - \frac{2K_b t}{C_0 b_0}\right) \tag{21}$$

Here, a_0 is the initial radius of the tablet and b_0 is the thickness of the tablet. By changing the radius to thickness ratio of the device, one can easily obtain various drug release rates. It is noteworthy that in these models, swelling of the matrices is either not considered or is assumed to occur prior to erosion and drug release. Stemming from these initial efforts, several additional models have been developed to predict molecule release via surface-erosion [108,126,127].

3.3.3. Reaction-diffusion-controlled release — bulk-degrading systems

Many of the approaches for modeling drug release from hydrogel networks assume only one mechanism, either diffusion, swelling, or degradation, dominates the release process. Although not realistic for many cases, this is one way to simplify the model and, in many cases, obtain a reasonable fit to experimental results. As more complicated drug delivery systems are designed to fulfill the ever-increasing needs for advanced drug delivery and tissue engineering, the assumption of a single dominant release mechanism will no longer be suitable. Overlooking the coupled effects of diffusion and matrix degradation within hydrogel matrices will result in significant deviations when comparing modeling and experimental results.

The coupling of reaction and diffusion phenomena is already notable in bulk degrading networks where drug release profiles are governed by both network degradation and molecule diffusion. Macroscopically, this degradation–diffusion coupling phenomena can be observed through the swelling characteristics and mechanical properties. The degradation behavior of chain-polymerized hydrogels with hydrolytically or enzymatically labile bonds can be tailored through a variety of parameters. Sawhney's pioneering work incorporated degradable PLA moieties within hydrophilic PEG macromers [128]. The resulting PLA–PEG–PLA block copolymers can be polymerized to form hydrolytically degradable hydrogels. Metters et al. further described the release of encapsulated macromolecules from bulk-degrading, covalently crosslinked PLA–PEG–PLA hydrogels considering network structure as well as degradation kinetics [55,56]. Generally, molecule diffusivity decreases as crosslinking density increases ($\bar{M}_c$ decreases), as the molecular size (r_s) increases, and as the polymer volume fraction of the gel ($v_{2,s}$) increases [91,129,130]. In PLA–PEG–PLA hydrogel systems, molecule diffusivity can be correlated to gel degradation kinetics and can be used to predict drug release corresponding to gel degradation as shown in Fig. 6 [10,97]. The diffusion coefficient of a solute from the degrading network with time-dependent mesh size can then be obtained using Eq. (13) described in the previous section. As shown in Fig. 6, the scaling model agreed well with the volumetric swelling ratio of the degrading gels while for solute release only a qualitative agreement was obtained.

The degradation behaviors described above are only valid for hydrogels made from di-vinyl macromers. For hydrogels formed via chain-polymerization of multifunctional macromers such as acrylated poly(vinyl alcohol) (PVA), Martens et al. developed a generalized

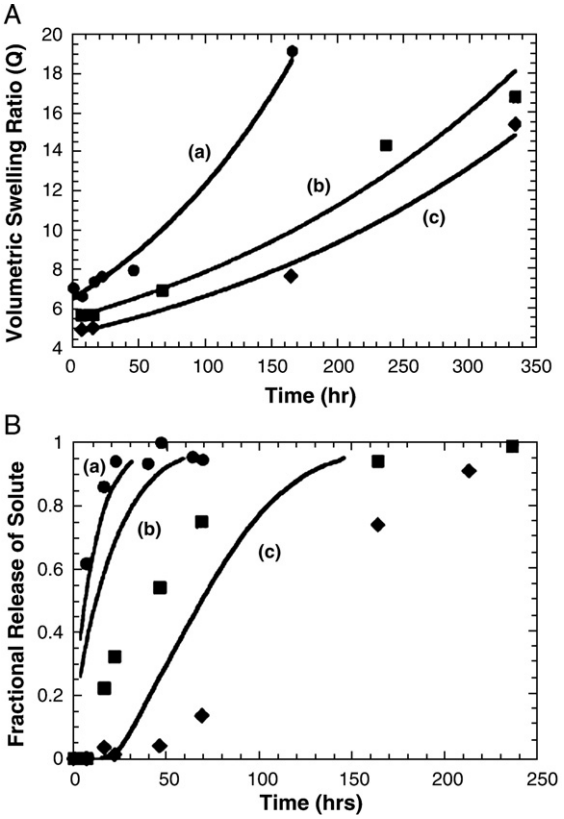

Fig. 6. (A) Volumetric swelling ratio and (B) fractional release of BSA as a function of degradation time from a series of PLA-*b*-PEG-*b*-PLA hydrogels polymerized from increasing concentrations of macromer: (●) 25 wt.%, (■) 35 wt.%, and (◆) 50 wt.%. Lines represent exponential fits to the swelling data (A) and solute release predictions based on scaling equations (B). $D_0 = 1.0 \times 10^{-5}$ mm^2/s for all curves. Reproduced with permission from Ref. [10]. Copyright 2001 American Chemical Society.

statistical-co-kinetic model to predict their degradation behaviors [131–133]. In this model, a statistical approach was used to predict the different configurations of the crosslinking molecules and kinetic chains. It also accounts for the probability of an intact degradable linkage. The model was verified by experimental observation of gel swelling, mass loss and compressive modulus [133]. Combining the degradation kinetics provided by this model and the diffusivity estimated by Eq. (13), the release of a model protein, bovine serum albumin (BSA), was verified [97].

For hydrogels formed via step-growth polymerization, Metters and Hubbell have shown that the degradation rates of networks depend on molecular weight, hydrophilicity, and degree of functionality of the starting monomers [134].

In addition to the statistical modeling approaches assuming homogeneous changes in gel properties, Monte Carlo simulations have also been used to predict protein release from degradable polymer networks at the microscopic level. Gopferich and Langer developed Monte Carlo simulations to predict polymer erosion and monomer release. Although this work was not for hydrogel systems, it allowed the calculation of porosity distributions within the polymer and was useful in predicting drug and degraded monomer release [135–138]. Monte Carlo simulation is good for describing network morphological changes, however it does not provide any information regarding molecule release. Diffusion equations (Fick's law) must be incorporated in order to link the network degradation to molecule diffusion [138]. The following modified diffusion equation can be used to describe one-dimensional diffusion in porous polymers:

$$\frac{\partial}{\partial t} C(x,t)\varepsilon(x,t) = \frac{\partial}{\partial x} D_{\text{eff}}(C)\varepsilon(x,t)\frac{\partial C(x,t)}{\partial x} \qquad (22)$$

Here, $C(x,t)$ is the concentration of diffusing monomer, $\varepsilon(x,t)$ is the porosity along the diffusion path, and $D_{\text{eff}}(C)$ is the effective concentration-dependent diffusion coefficient.

Recently, Vlugt-Wensink et al. developed kinetic Monte Carlo simulations to predict protein release from crosslinked dextran microspheres [57]. Although this approach, reasonably predicts protein release from degrading networks and incorporates spatial variations in the network microstructure that are not accounted for in the previously described macroscopic models of network degradation, some predictive limitations still exist. Most importantly, swelling of the hydrophilic microspheres and changes in swelling with matrix degradation were not accounted for in the described model.

The macroscopic models used to correlate solute release (diffusion) with gel degradation (reaction) provide a powerful tool for predicting protein release with changing network structure. However, macroscopic observations in gel swelling and mass erosion are not sufficient to obtain precise predictions due to the averaging of microscopic events. On the other hand, models describing network changes at a

microscopic level may provide more accurate release predictions. However, gel swelling, a very important characteristic of hydrogel drug carriers, must be included during the simulation since solute diffusivity is tightly coupled to water content.

3.3.4. Reaction–diffusion-controlled release — affinity hydrogel systems

Inspired by the reversible sequestering of proteins to the extracellular matrix (ECM), researchers have developed biomimetic hydrogel carriers bearing reversible binding capacities to decrease release rates of target protein therapeutics. These so-called 'affinity' hydrogels can also be classified as reaction–diffusion-controlled hydrogel delivery systems. The release kinetics of a molecule from affinity gels can be depicted by a model developed by Crank [139] where protein–ligand (P–L) binding equilibrium is described using simple binding kinetics:

$$P + L \underset{k_r}{\overset{k_f}{\rightleftharpoons}} P \cdot L \tag{23}$$

Here, k_f and k_r are association and dissociation rate constants, respectively. In this model, binding of proteins to immobilized elements is considered reversible and a time-independent equilibrium constant $K_b = C_{PL}/C_P$ is used to represent the concentration equilibrium between bound (PL) and free (P) proteins. K_b can be therefore also described as a ratio of free-receptor concentration to dissociation constant ($K_b = [L]/K_d$). Assuming that the reaction is fast compared to protein diffusion, the following equation can be obtained for the transport of reversibly bound protein within an affinity hydrogel [140]:

$$\frac{D}{K_b + 1} \nabla^2 C_p = \frac{\partial C_p}{\partial t} \tag{24}$$

Compared to the standard form of Fick's law of diffusion (Eq. (7)) the above equation illustrates that the presence of rapid and reversible protein–ligand binding retards the release of free protein by decreasing the apparent protein diffusivity by a factor of ($K_b + 1$).

From this simple reaction–diffusion model described above, one can easily obtain the concentration profile of free proteins in the affinity gels available for diffusion. However, due to the fact that this model assumes a time-independent equilibrium constant (K_b) and a rapid binding equilibrium, the model is limited to describing systems with simple yet rapid binding mechanisms with high ratios of ligand to protein. These assumptions may not be valid in the hydrogel matrix where the mobility of therapeutic macromolecules and therefore the intrinsic reaction constants are retarded by their size and limited free volume.

Heparin, a highly sulfated glycosaminoglycan (GAG), is known to serve as a growth factor depot *in vivo* owing to its electrostatic affinity to various basic growth factors including NGF, bFGF, VEGF, etc. Matrices containing heparin have been used as delivery depots to modulate the release rates of these growth factors through affinity binding [141,142]. For example, Sakiyama-Elbert and Hubbell have developed affinity hydrogels composed of fibrin gels copolymerized with peptides that bind to heparin [87,88,115]. This system has been applied to deliver several growth factors including NGF [87], basic fibroblast growth factor (bFGF) [88], and neurotrophin-3 (NT-3) [89]. In order to incorporate heparin into the fibrin network and modulate growth factor release, a group of short peptide sequences with different affinities for heparin have been identified and copolymerized into the fibrin gel networks. To model growth factor release from this tri-component delivery system, six partial differential equations based on diffusion–reaction kinetics were solved simultaneously [88]:

$$\frac{\partial C_G}{\partial t} = D_G \frac{\partial^2 C_G}{\partial x^2} - k_F C_G C_H + k_R C_{GH} - k_F C_G C_{HP} + k_R C_{GHP} \tag{25}$$

$$\frac{\partial C_H}{\partial t} = D_H \frac{\partial^2 C_H}{\partial x^2} - k_F C_G C_H + k_R C_{GH} - \kappa_F C_H C_P + \kappa_R C_{HP} \tag{26}$$

$$\frac{\partial C_P}{\partial t} = -\kappa_F C_H C_P + \kappa_R C_{HP} - \kappa_F C_{GH} C_P + \kappa_R C_{GHP} \tag{27}$$

$$\frac{\partial C_{GH}}{\partial t} = D_{GH} \frac{\partial^2 C_{GH}}{\partial x^2} + k_F C_G C_H - k_R C_{GH} - \kappa_F C_{GH} C_P + \kappa_R C_{GHP} \tag{28}$$

$$\frac{\partial C_{HP}}{\partial t} = \kappa_F C_H C_P - \kappa_R C_{HP} - k_F C_G C_{HP} + k_R C_{GHP} \quad (29)$$

$$\frac{\partial C_{GHP}}{\partial t} = k_F C_G C_{HP} - k_R C_{GHP} + \kappa_F C_{GH} C_P - \kappa_R C_{GHP} \quad (30)$$

In these equations C_G, C_H, and C_P represent the concentrations of growth factor (G), heparin (H), and heparin-binding peptide (P), respectively. Similarly C_{GH}, C_{HP}, and C_{GHP} represent the concentrations of the possible biomolecule complexes.

Assuming the system is in equilibrium between the species initially, these equations, in conjunction with proper initial and boundary conditions, can be solved numerically and used to predict the fraction of growth factor present in its freely diffusible and bound state (Fig. 7, [89]) and the ratio of heparin to growth factor needed to obtain sustained growth factor release (Fig. 8, [88]). As can be seen from the above equations, there are four kinetic constants (k_F, k_R, κ_F, κ_R) and three diffusion coefficients (D_G, D_H, D_{GH}) required to solve the equations which largely complicate this modeling approach. Furthermore, while experimental results and model predictions agree qualitatively, these results were never directly compared to the theoretical predictions obtained from this model [87–89].

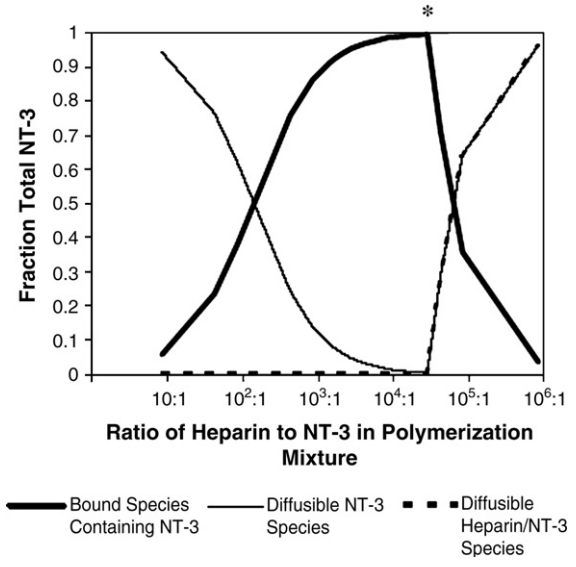

Fig. 7. Predicted initial equilibrium fractions of NT-3-containing species versus initial heparin to NT-3 ratio. Reproduced from Ref. [89], Copyright (2004), with permission from Elsevier.

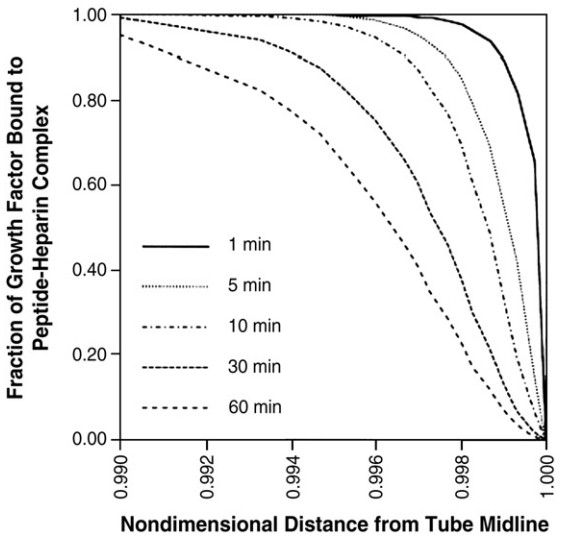

Fig. 8. Theoretical concentration of matrix-bound bFGF as a function of distance from the midline of a model tubular nerve growth guide, 6 mm long and open at both ends. Concentration is shown as percentage of the initial bound concentration, which was 5.7×10^{-8} M. The ratio of heparin to growth factor modeled was ~ 500. The decreasing concentration profile propagates inward over time, as one would expect. Reproduced from Ref. [88], Copyright (2000), with permission from Elsevier.

4. Emerging systems and remaining challenges

Although mathematical simulations have been performed extensively to predict and design better hydrogel systems, there are still many challenges associated with the modeling of drug delivery phenomena and accurate prediction of release profiles from complex hydrogel systems. Creating a fundamental understanding of drug transport processes is the first step towards developing a suitable mathematical model. Mass transport governs the translocation of drug from the interior of hydrogels to the surrounding environments. Multiple factors affect the mass transport of encapsulated molecules including the network crosslinking density, extent of swelling, gel degradation, the size and charge of the encapsulated molecules, and the physical interactions these molecules exhibit for themselves and for the polymer

matrix. If specific drug-binding motifs are present within the hydrogels, the kinetics and/or thermodynamics of drug–ligand binding must also be understood and quantified to predict the controlled release of the encapsulated molecules. In this final section, the network design and mathematical modeling of several emerging hydrogel-based delivery systems as well as the challenges associated with these systems are discussed.

4.1. Dynamic hydrogel delivery systems

4.1.1. Degradable hydrogels

Previous sections have detailed the fabrication, degradation, and molecule release from degradable hydrogels. Understanding degradation mechanisms is critical in designing hydrogels for drug delivery applications since the rates of matrix swelling and degradation govern the diffusion of encapsulated or tethered molecules. Via appropriate design of polymer chemistries and network structure, degradable hydrogel matrices can be engineered with proper degradation profiles for achieving previously unattainable molecule release regimes.

Mathematical modeling of molecule release has provided much information to facilitate the design of degradable hydrogels and identify key parameters dictating molecule release profiles. However, to accurately predict the unique molecule release profiles that occur with many degradable hydrogels, additional parameters not commonly found in previous release models must be included. For example, as discussed in the previous section, enzymatically degradable hydrogels are becoming more important in controlled release applications. One challenge for this novel class of hydrogel is how to model the rate of enzyme (e.g. MMPs) production by invading cells. As discussed before, enzyme concentration determines whether gel degradation occurs via surface-erosion (rate of enzyme/substrate reaction greater than rate of enzyme transport) or bulk-degradation (rate of enzyme transport greater than rate of enzyme/substrate reaction). Therefore, the accuracy of predicting gel degradation and molecule release from enzymatically degradable hydrogels largely depends on correctly understanding cellular physiology and cell–material interactions and properly incorporating these phenomena in a quantitative model along with molecule transport and enzyme-substrate kinetics.

4.1.2. Stimuli-sensitive hydrogels

Stimuli-sensitive hydrogels represent another advanced hydrogel system that, under intelligent design, can sense changes in complex in vivo environments and utilize these triggers to modify drug release rates. Since the swelling or deswelling of these hydrogels is controlled by external stimuli, it is critical to model the dynamic swelling response in order to predict solute release. Several review articles have been published detailing the fabrication and application of stimuli-sensitive hydrogels [18,62,143]. Ionic or pH-sensitive hydrogels are probably the most studied stimuli-sensitive gels. At a fixed pH and salt concentration, the swelling of ionic hydrogels is balanced by the osmotic pressure and the relaxation of the polymer chains. Thermodynamically, the total free energy can be expressed as:

$$\Delta G_T = \Delta G_e + \Delta G_m + \Delta G_o \quad (31)$$

Here, ΔG_T is the total Gibbs free energy, ΔG_e is the free energy contributed by elastic force of the polymer chains, ΔG_m is the free energy of mixing, and ΔG_o is the free energy due to osmotic pressure. When the swelling of an ionic hydrogel is in equilibrium ($\Delta G_T = 0$), the decreased elastic free energy is balanced by the free energy of mixing and osmotic pressure. Based on this concept, the simulations of ionic hydrogel swelling have been derived in many reports [66,144–146]. Grimshaw et al. developed a continuum model to describe the macroscopic behaviors of pH-responsive poly(methacrylic acid) (PMAA) hydrogel membranes accounting for charge density, ionic strength, stress, strain, and electric field [144]. The simulation results were used to compare experimentally determined PMAA swelling and shrinking. It was found that the membrane swelling was slower than shrinking. Following Grimshaw's work, De et al. derived an equilibrium model to predict the degree of hydrogel swelling at given pH and ionic strength and a kinetic model to predict the rate of swelling under changing pH. Their simulation results agreed well with experimental observations. The equilibrium swelling of anionic pH-responsive hydrogels appears to be proportional to the pH with a sharp increase around the pK_a of the charge group.

For molecule release from pH-sensitive hydrogels, Peppas and coworkers developed a series of models focusing on ionic hydrogel swelling, water transport,

and molecule release [106,107,147,148]. For example, a concentration-dependent solute diffusion coefficient D_i was used to predict cationic hydrogel swelling and solute release upon pH changes induced by the production of gluconic acids [148]:

$$D_i = D_{i,0} \exp(\alpha_d v_1) \tag{32}$$

where $D_{i,0}$ is the solute diffusion coefficient in the dry state. From this expression, it is clear that the diffusion coefficient changes exponentially with the water volume fraction v_1 and experimentally determined water–polymer interaction parameter α_d. The modeling of cationic hydrogel swelling agreed well with experimental data. For insulin release, however, no experimental results were compared to model predictions [148] indicating that verification of this modeling approach is still required.

While the benefits of using thermo-sensitive hydrogels are widely acknowledged, mathematical simulation of molecular release from these "smart" hydrogels is still very limited. A strategy correlating gel swelling and diffusion-controlled molecule release can be readily constructed using equations for estimating molecule diffusivity. Amsden [13] reviewed a variety of hydrogel diffusivity models related to fundamental characteristics such as hydrogel water content and molecule free volume. Andersson et al. applied one such expression for assessing glucose and insulin diffusivities in n-isopropylacrylamide gels [26]:

$$\frac{D_e}{D_0} = \frac{(1-\Phi)^3}{(1+\Phi)^2} \tag{33}$$

where D_e and D_0 are the effective molecule diffusivities in the gel and in pure solvent, respectively. Φ is the polymer volume fraction of the gel. Since the swelling of thermo-sensitive hydrogels depends on temperature changes, one can readily obtain the polymer volume fraction at the tested temperature. Using this equation, the effective diffusivities of molecules encapsulated within thermo-sensitive hydrogels can be estimated as a function of temperature. Once the molecule diffusivity is determined, a release profile can then be predicted using Fick's law of diffusion [26]. Fig. 9 shows one comparison of simulated and experimental results [26].

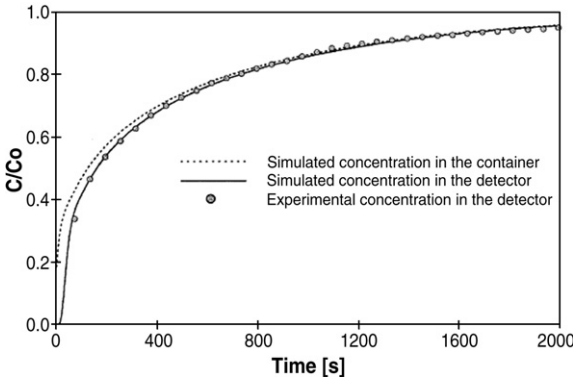

Fig. 9. Experimental and simulated concentration profiles for one of the glucose diffusion experiments at 10 °C. Reproduced from Ref. [26], Copyright (1997), with permission from Elsevier.

Finally, several groups have devoted significant efforts to the fabrication and characterization of dual-stimuli responsive hydrogels that respond to changes in pH and temperature [79–82]. Although the unique drug release profiles observed from these novel carriers have revealed the usefulness of this exciting new strategy of hydrogel design, mathematical modeling of drug release from these dual-responsive networks has yet to be developed.

4.2. Composite hydrogel delivery systems

Modeling drug release from composite hydrogel systems has proven to be challenging due to the fact that their material and molecule transport properties change dramatically with spatial location within the device. Two primary types of composite hydrogel delivery systems have been investigated, multi-layer and multi-phase systems. These composite systems have great potential in delivering multiple protein therapeutics for tissue engineering applications where temporal and spatial control over drug delivery is desirable. The simultaneous delivery of multiple proteins is known to occur in vivo during angiogenesis, bone remodeling, and nerve regeneration. For example, several angiogenic proteins including vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and matrix metalloproteinases (MMPs) are involved in the angiogenesis process. Marui et al. discovered that the dual delivery of bFGF and hepatocyte growth factor (HGF) from collagen

microspheres greatly increased blood vessel formation in an animal model [149]. Peattie et al. utilized cross-linked hyaluronan (HA) hydrogels to simultaneous deliver VEGF and keratinocyte growth factor (KGF) to enhance angiogenesis [150]. Simmons et al. used alginate hydrogels to deliver bone morphogenetic protein-2 (BMP2) and transforming growth factor-β (TGF-β3) and showed enhanced bone formation compared to delivery of either single protein [49]. Although *in vivo* tissue growth was improved in animal models using these dual-protein delivery systems, it is not clear whether tissue growth would be further enhanced if the proteins were delivered at optimized rates since no independent control over the release profiles has been shown in these studies. Therefore, the development of models that can relate drug transport and release in these composite systems to their fundamental properties would prove valuable and possibly lead to the engineering of devices capable of independently tunable delivery of multiple proteins for modulating cell behavior and tissue growth.

4.2.1. Multi-layer hydrogel delivery systems

In multi-layer systems, a basal polymer layer is fabricated, followed by lamination of subsequent layers. Different proteins can be encapsulated into each layer during fabrication and tunable multiple-protein release or unique single-protein release profiles are made possible by independently adjusting the crosslinking density of each layer. Many models have been developed for predicting drug release from multi-layer hydrogel composites. For example, Streubel et al. developed a multi-layer system to achieve bimodal drug release [151]. Fick's second law of diffusion was used to predict drug release profiles. They derived diffusion equations accounting for constant or non-constant diffusivities, as well as stationary or moving boundary conditions. Grassi et al. fit their experimental data into a semi-empirical model accounting for the resistance the drug experienced when diffusing through the multi-layer system [152]. They started the modeling with an equation governing the dissolution of solid drug and accounted for the gel layer resistance (R) and drug dissolution resistance ($1/K$):

$$\frac{dC}{dt} = -\frac{\varphi_d A}{V}\frac{C_S - C}{(1/K) + R} \tag{34}$$

where C is the drug concentration, t is the dissolution time, C_S is the solubility of the drug in the dissolution medium, φ_d is the drug volume fraction, A is the surface area at the solid/liquid interface, and V is the volume of the medium. The release of some small molecular weight drugs from partially coated matrices containing different drug to polymer fraction can be fit into the analytical solution of this model.

Sohier and colleagues developed a porous scaffold containing three hydrogel layers with different porosities to simultaneously deliver lysozyme and myoglobin [153]. The governing equations used to model this system were again based on Fick's second law with a time-dependent diffusion coefficient related to the rate of polymer degradation. Although this model successfully predicted the release of lysozyme from a multi-layer polymer construct, it did not provide an accurate description of dual-protein delivery.

In addition to multiple-protein delivery, multi-layer matrices can also be used to decrease the problematic burst release, a common challenge facing drug delivery. For example, Lu and Anseth developed a multi-laminated hydrogel system prepared by photopolymerization. A desirable, zero-order release profile was obtained through non-uniform initial drug loading in multi-laminated hydrogels and the results were verified by a diffusion model [154–156]. Their model was based on the well-known diffusion model first developed by Crank [139]. Assuming a constant diffusion coefficient and one-dimensional release under sink conditions, the fractional passive release of drug (M_t/M_∞) from these composite hydrogels can be analytically derived from Fick's second law of diffusion and expressed as the following equation:

$$\frac{M_t}{M_\infty} = 1 - \frac{\sum_{n=0}^{\infty} \frac{(-1)^{n+1}}{\lambda_n} e^{-\lambda_n^2 Dt}\left(\int_0^L f(x)\sin(\lambda_n x)dx\right)}{\sum_{n=0}^{\infty} \frac{1}{\lambda_n} e^{-\lambda_n^2 Dt}\left(\int_0^L f(x)\sin(\lambda_n x)dx\right)},$$
$$\text{where } \lambda_n = [(n+0.5)\pi]L \tag{35}$$

In this expression, $f(x)$ is the initial concentration profile, D is the molecule diffusion coefficient, and L is the thickness of the gel. As shown in Fig. 10, experimental results verified the accuracy of this model and indicate that the initial burst was nearly eliminated.

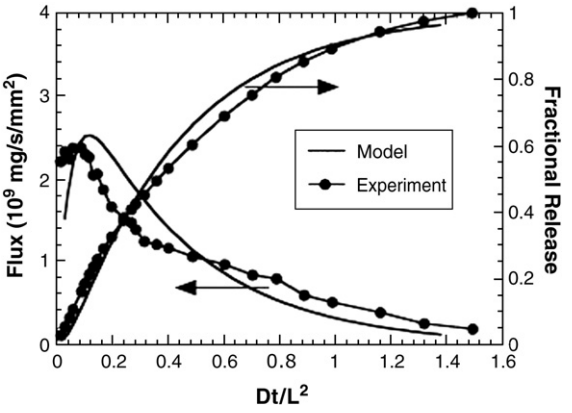

Fig. 10. Comparison of theoretical and experimental solute release. The initial concentration profile used, from center outward, was: 1.2 wt.%, 0.55 wt.%, 0.2 wt.%, and 0 wt.%, respectively. Model results (—), experimental results (–●–). Reproduced from Ref. [154], Copyright (1999), with permission from Elsevier.

4.2.2. Multi-phase hydrogel delivery systems

Another strategy for multiple-protein delivery is multi-phase systems. In this approach, prefabricated microspheres containing one or more proteins are uniformly embedded within a hydrogel containing a second protein [157–159]. The release of the microsphere-encapsulated protein is delayed due to the combined diffusional resistances of the microsphere polymer and surrounding gel. Richardson and colleagues prepared a composite polymeric scaffold containing PLGA microspheres embedded in porous PLGA matrices with different intrinsic viscosities to simultaneous deliver VEGF and PDGF. The in vitro and in vivo results using this approach have shown promising results in an animal model to enhance the maturation of vasculatures [48]. Although this multi-phase formulation is not considered to be a hydrogel system, it was the first heterogeneous polymeric system for delivering two proteins with distinct release profiles. Holland et al. also fabricated degradable oligo(poly (ethylene glycol) fumarate) hydrogels containing gelatin microspheres to independently control the delivery of insulin-like growth factor-1 (IGF-1) and transforming growth factor-β1 (TGF-β1). Release profiles can be adjusted by varying the protein loading in each polymer phase [157]. These multi-phase dual delivery systems have achieved substantial success, however, to date no rigorous mathematical models for predicting molecule release from these composite networks have been developed.

4.2.3. Challenges facing composite hydrogel delivery systems

The design and application of composite hydrogel delivery systems have attracted much attention due to their multi-faceted roles in advanced drug delivery and tissue engineering. However, many challenges facing the design and modeling of these novel systems remain largely unattended and need to be addressed to optimize their application as drug carriers. First, these systems have complex network geometries and phase morphologies that must be properly parameterized to quantify diffusion length scales in each phase. The individually tailored physicochemical properties of each layer, which results in heterogeneous transport properties within a single matrix, must also be evaluated in the context of the overall device. For example, as shown by Sohier et al. the swelling, and therefore permeability, of a highly hydrophilic layer can be limited by its attachment to layers exhibiting a lower degree of swelling [153]. Once identified, the positional dependence of drug diffusion coefficients as well as drug–polymer interaction parameters must be taken into account during the development of any rigorous mathematical model describing these composite systems.

4.3. Micro/nanoscaled hydrogel delivery systems

Over the past few decades, polymeric microspheres and, more recently, nanoparticles have been widely used for sustained or targeted drug delivery [160] as well as cell encapsulation [161–163]. Numerous studies have been conducted using PLGA as a matrix for encapsulating proteins, peptides, DNA, and small molecular weight drugs. However, the hydrophobicity, acidic degradation products, and harsh fabrication/encapsulation processes of PLGA micro/nanoparticles make them unfavorable as carriers for biomacromolecules such as protein and DNA [164]. Alternatively, micro/nanoparticles made from hydrophilic hydrogels are more suitable for encapsulating these fragile biomacromolecules. These miniaturized drug-containing vehicles can be fabricated in vitro and then administered via oral [165,166] or nasal route [167,168] or injected into the patients in a minimally

invasive manner to increase patient compliance. Protein-containing microparticles can also be fabricated and loaded into a bulk gel containing a second protein for dual-protein delivery as discussed in the previous section. It is beyond the scope of this review to thoroughly discuss the fabrication and application of micro/nanoparticles and readers are advised to look to the cited references for more information [169,170].

Two types of mathematical approaches have been used to predict molecule release from hydrogel microspheres: macroscopic diffusion models and microscopic Monte Carlo simulations. For macroscopic modeling, the most applicable models are still based on Fick's second law of diffusion. Particle size and geometry are the most important parameters in this type of modeling as well as surface area since this appears to correlate to observed burst effects. Additionally molecule diffusivities must be accurately determined. As with other diffusion-controlled delivery systems, simple empirical relationships have been used to estimate molecule diffusivity [171]. Other more rigorous expressions for molecule diffusivity such as those discussed in Section 3.1 for degradable gels, can also be applied to these systems. The accuracy of any diffusion model to predict molecule release from hydrogel-based microparticle systems will directly depend on the accuracy of the diffusivity estimation.

Another technique to model molecule release from hydrogel microspheres is Monte Carlo simulation. This method has proven itself valuable for describing the transport behavior of molecules within degradable microsphere systems and has been widely applied to hydrophobic polymer networks such as PLGA [172,173]. As mentioned earlier, Vlugt-Wensink et al. recently utilized Monte Carlo simulations to predict protein release from degradable dextran microspheres [57]. Unfortunately, the accuracy of the model is highly protein specific. For example, for larger proteins such as IgG, model predictions only agreed with experiments qualitatively in most cases. This may be due to the fact that swelling of the dextran gels was not accounted for in the Monte Carlo description of the degrading hydrogel network.

One of the unique challenges facing microscaled matrix delivery systems is burst release due to the high surface-to-volume ratio of these particulate systems [174,175]. Burst release may cause a "dose-dumping" effect and is potentially harmful to patients in clinical applications. Several possible causes of burst release have been identified including material/drug interactions, fabrication conditions, and sample geometry and/or morphology [174]. Although not completely understood, burst release has been taken into consideration during the design of delivery matrices as well as in modeling approaches [154–156,176,177]. Several methodologies have been developed in an attempt to decrease the degree of burst release. These include increasing cross-linking density of the matrix surface [178,179], coating additional drug-free layers [152,177,180], embedding the drug-containing particles within a bulk polymeric matrix [157–159,181], and loading drug unevenly with higher concentrations toward the center of the matrix [182,183].

The prediction of burst release is problematic as the exact mechanism has not been elucidated. Typically, diffusion-controlled release can be divided into two phases: a rapid burst phase and a prolonged diffusion-controlled phase. The later can be modeled by conventional diffusion theories while the prediction of initial burst release is not readily attainable. Models in this area are therefore very limited. Several attempts have been made to predict burst release in polymeric delivery matrices. For example, the simplest model employed to describe the impact of burst release on drug delivery profiles is to add an extra parameter, namely α, into the well-known fractional release equation [174]:

$$\frac{M_t}{M_\infty} = kt^n + \alpha \tag{36}$$

In previous applications of this expression, the experimental release data were simply shifted a certain fraction to fit the model prediction. If no burst release exists, α equals zero and the equation is reduced to the original fractional release equation. However, this empirical model fails to relate the extent of burst release to quantifiable system parameters. Thus, this simple model is not practical for extrapolating results between different device designs or optimizing delivery profiles.

4.4. In-situ forming hydrogels

Recent advances in polymer chemistry and hydrogel engineering have promoted the development of in-

situ forming hydrogels for drug delivery applications. Through intelligent design of monomers/macromers with desired functionalities, hydrogel precursor solutions can be injected and subsequently polymerized in-situ. This in-situ sol–gel transition enables the surgery or implantation procedure to be performed in a minimally invasive manner. Several physical or chemical crosslinking mechanisms have been used for in-situ network formation. Physically, in-situ forming gels are formed by one of the following mechanisms: hydrogen bonding, hydrophobic–hydrophobic interactions, or electrostatic interactions. Sodium alginate hydrogels, for example, can be physically crosslinked through the addition of calcium ions [160]. The common disadvantage of physical crosslinking, however, is that the gels thus formed are unstable and may disintegrate rapidly and unpredictably.

For long-term drug delivery applications, covalent crosslinking methods performed under physiological conditions, such as photopolymerization of multi-vinyl macromers, are more favorable compared to physical crosslinking methods as they produce relatively stable hydrogel networks with predictable degradation behaviors. The photocuring process, for example, is fast, usually taking only seconds to minutes to complete, and can be conducted at room temperature without organic solvents [53]. Photopolymerization of degradable hydrogels has been applied in protein [71,184,185] and gene delivery [186–188] and permits in-situ encapsulation of these species during network fabrication. These advantages overcomes the complexities and limitations associated with post-loading techniques and provides a convenient and efficient way of loading high concentrations of proteins and other releasable solutes for subsequent long-term delivery.

When in-situ forming hydrogels are used to deliver macromolecules such as DNA and protein, reduced or incomplete release of these biomolecules is commonly observed [185–188]. Incomplete protein release decreases the bioavailability of the therapeutic agent and alters the overall delivery profile. In addition, the protein trapped within the gel is generally modified or denatured, which can lead to undesirable antigenic responses when applied in vivo. The factors influencing incomplete biomolecule release from these hydrogel carriers has commonly been attributed to the fabrication processes. For example, several researchers have studied the effect of drug–polymer interactions on molecule release using thermally responsive poly (*N*-isopropylacrylamide) hydrogels [189,190] and alginate microparticles [191]. Although these studies observed and verified the incomplete release phenomena, no mathematical model was derived for predicting molecular release.

When in-situ forming gels are used to deliver proteins, irreversible interactions between the encapsulated proteins and polymerizing polymer chains decrease the efficacy of the therapeutic agent. van de Wetering et al. identified the modification of hGH by reactive thiol macromers in a PEG-based hydrogel system prepared via Michael-type addition reaction [192]. Additionally, Quick and Anseth specified free radicals as the major source of incomplete DNA release when photopolymerization was used to fabricate DNA-containing hydrogels [186–188]. According to the authors, free radicals produced from the photoinitiation process attacked DNA molecules during UV irradiation, leading to DNA damage. Based on similar observations during protein encapsulation, Lin and Metters utilized a metal-ion-chelating molecule, iminodiacetic acid (IDA), to block undesirable protein–polymer conjugation reactions mediated by free radicals. This protective agent increased the fractional release of target proteins such as bovine serum albumin (BSA) from 40% to 100% following in-situ photocuring of PEG-diacrylate hydrogels [185]. A mathematical model accounting for reversible protein–IDA binding directly correlated the extent of BSA release to the degree of protein–IDA binding.

Modeling drug release from in-situ forming hydrogels is challenging due to several reasons. First, the effects of reduced/incomplete protein release discussed above can only be taken into account after identifying the sources of protein destabilization and quantifying the extent of interaction. These interactions will greatly depend on the selected polymer and drug chemistries as well as the method of gel fabrication. Secondly, in-situ forming gels assume irregular geometries at the implant site which are difficult to predict prior to injection. This irregular geometry will increase model complexity and may also contribute to non-uniform drug distribution within the gels, which further increases the difficulty to accurately represent the real system in a mathematical construct. Finally, experimental measurement of release profiles is usually accomplished through in

vitro release studies. These in vitro systems must be designed to include as many complexities of the in vivo environment as possible if these experiments are to accurately represent what will occur during clinical application.

5. Conclusion

Hydrogels have played a very important role in biomedical applications. With increasing efforts devoted to controlled molecule release, the applications of hydrogels will continue to grow in the future. Proper network design and accurate mathematical modeling are keys to tuning the drug release rates as well as to modulating tissue regeneration. Although many fundamental studies have revealed the basic molecule release mechanisms from hydrogel-based controlled release devices, many parameters in the current models are unknown and/or change with time or position and need to be identified in order to accurately predict drug release profiles. Reduced release efficiency, burst effects, complex geometries, and unknown correlations between in vitro and in vivo release further complicate our understanding of these materials as delivery devices and present difficult challenges to developing mathematical models that accurately describe the transport and release of molecules from these systems. Furthermore, as more advanced release devices are developed such as affinity hydrogels, microparticle systems, and in-situ forming gels, more rigorous mathematical modeling approaches are needed to describe the coupled mechanisms governing molecule release from these systems.

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