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Hydrogels in Controlled Drug Delivery Systems

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ABSTRACT

Hydrogels are a unique class of macromolecular networks that can hold a large fraction of an aqueous solvent within their structures. They are particularly suitable for biomedical applications, including controlled drug delivery, because of their ability to simulate biological tissues. Many hydrogel-based networks have been designed and fabricated to meet the needs of pharmaceutical and medical fields. The objective of this paper is to give a brief review on the fundamentals and recent advances in the design of hydrogel-based drug delivery systems (DDS) as well as the description of the release mechanism of bioactive molecules from these hydrogels. The structure and classification of hydrogels, swelling behaviour of hydrogels, different mechanisms of solvent diffusion into and drug release from hydrogels and mathematical description of these phenomena are elucidated. The most important properties of hydrogels relevant to their biomedical applications are also identified, especially for use of hydrogels as drug delivery systems. Kinetics of drug release from hydrogels and the relevant mathematical modelling are also reviewed in this manuscript.

Key Words:

hydrogels;
drug delivery;
swelling;
thermodynamics;
mathematical modelling.

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CONTENTS

INTRODUCTION

In recent years, extensive efforts have been devoted to the use of potential pharmaceutical devices such as novel drug delivery systems (DDS), since it proposes a suitable means of site-specific and/or time-controlled delivery of therapeutic agents [1,2]. Among various kinds of polymeric systems, which have been used as drug containers or release rate controlling barriers, hydrogels have gained considerable interest [3-11]. Hydrogels are cross-linked, three-dimensional hydrophilic networks that swell but not dissolve when brought into contact with water. Hydrogels can be formulated in a variety of physical forms, including slabs, microparticles, nanoparticles, coatings, and films. As a result, they are commonly used in clinical practice and experimental medicine for a wide range of applications, including biosensors, tissue engineering and regenerative medicine, separation of biomolecules or cells and barrier materials to regulate biological adhesions [7,12,13]. Among these applications, hydrogel-based drug delivery devices have become a major area of research interest. Hydrogels can protect drugs from hostile environments, e.g. the presence of enzymes and low pH in the stomach. Their porosity permits loading of drugs into the gel matrix and subsequent drug release at a pre-designed rate. Hydrogels can also control drug release by changing the gel structure in response to environmental stimuli, such as pH [14], temperature [10], ionic strength [15], and electric field [16].

This article provides an overview of current research in the fields of synthesis and application of hydrogels in the pharmaceutical field, hydrogels characterization and their use as intelligent carriers for novel pharmaceutical formulations. Swelling behaviour of hydrogels, different mechanisms of solvent diffusion into and drug release from hydrogels and mathematical description of these phenomena are also presented. In spite of numerous published review papers, books and encyclopedias which focus directly or indirectly on biomedical application of hydrogels, this review aims to throw light on the specific applications that hydrogels have in the drug delivery areas.

HYDROGELS

Hydrogels are water swollen polymer matrices, with a huge tendency to absorb water. Their ability to swell, under physiological conditions, makes them an ideal material for biomedical applications [17]. The hydrophilicity of the network is due to the presence of chemical residues such as hydroxylic, carboxylic, amidic, primary amidic, sulphonic and others that can be found within the polymer backbone or as lateral chains. It is also possible to produce hydrogels containing a significant portion of hydrophobic polymers, by blending or copolymerizing hydrophilic and hydrophobic polymers, or by producing interpenetrating networks (IPN) or semi-interpenetrating polymer networks (s-IPN) of hydrophobic and hydrophilic polymers.

Hydrogels can be classified as neutral or ionic, based on the nature of the side groups. In neutral hydrogels, the driving force for swelling is due to the water-polymer thermodynamic mixing contribution to the overall free energy, along with elastic polymer contribution [6]. Hydrogels can be classified as affine or phantom, based on their mechanical and structural characteristics. Hydrogels are also classified as homopolymers or copolymers, based on the methods of preparation. Additionally, they can be classified based on the physical properties of the network as amorphous, semi-crystalline, hydrogen bonded structures, super-molecular structures and hydrocolloidal aggregates [6]. An important class of hydrogels is the stimuli responsive gels. These gels show swelling behaviour dependent on their physical environment, allow for usage in a number of applications [18].

Hydrogels can be prepared from natural or synthetic polymers (Table 1). Several techniques have been reported for the synthesis of biomedical hydrogels [19,20]. Chemically cross-linked gels have ionic or covalent bonds between polymer chains.

Table 1. Natural polymers and synthetic monomers used in hydrogel fabrication [25].

Natural polymers	Synthetic monomers/polymers
Chitosan	Hydroxyethylmethacryate (HEMA)
Alginate	*N*-(2-Hydroxy propyl)methacrylate (HPMA)
Fibrin	*N*-Vinyl-2-pyrrolidone (NVP)
Collagen	*N*-Isopropylacrylamide (NIPAMM)
Gelatin	Vinyl acctate (VAc)
Hyaluronic acid	Acryolic acid (AA)
Dextran	Methacrylic acid (MAA)
	Polyethylene glycol acrylate/methacrylate (IPEGA/PEGMA)
	Polyethylene glycol diacrylate/dimethacrylate (PEGDA/PEGDMA)

Copolymerization [21,22], suspension polymerization [23], polymerization by irradiation [24], chemical reaction of complementary groups [25-27], and cross-linking using enzymes [28] are some common examples. Chemically cross-linked gels imply the use of a cross-linking agent which is often toxic. This requires that the cross-linking agent be removed from the gel, which can affect the gel integrity. For these reasons, physically cross-linked gels are now coming into prominence. Several cross-linking methods such as ionic interactions [29-32], crystallization [33], hydrogen bonds [34,35], protein interaction [36], and cross-linking by hydrophobic interactions [7,20] have been investigated exploring preparation of physically cross-linked gels [37].

SWELLING BEHAVIOUR OF HYDROGELS

When a hydrogel in its initial state is placed in an aqueous solution, water molecules will penetrate into the polymer network. The entering molecules are going to occupy some space, and as a result some meshes of the network will start expanding, allowing other water molecules to enter within the network. Evidently, swelling is not a continual process, the elasticity of the covalently or physically cross-linked network will counter-balance the infinite stretching of the network to prevent its destruction. Thus, by balancing these two opposite forces, a net force, known as the swelling pressure (P_{sw}) is produced, which is equal to zero at equilibrium obtained with pure water, and that can be expressed as [7]:

$$P_{sw} = k \times C^n \quad (1)$$

where, k and n are constants, and C is the polymer concentration. At the equilibrium there is no additional swelling. Swelling can be described as the increase in weight, volume, or length. Thus, the amount of water up-taken by the hydrogel (m_w) is given by [7]:

$$m_w = \frac{m_{HG,w} - m_{HG,d}}{m_{HG,w}} \quad (2)$$

where, $m_{HG,w}$ and $m_{HG,d}$ are the wet and dry hydrogel weights, respectively. In addition, while the percent of swelling does not exceed 100, the percent of hydration does. Then, the degree of swelling (D_{sw}) is given by [7]:

$$D_{sw} = \frac{m_{HG,w}}{m_{HG,d}} \qquad D_{sw} \geq 1 \quad (3)$$

whereas, the swelling ratio (R_{sw}) is [7]:

$$R_{sw} = D_{sw} \frac{\rho_0}{\rho_{sw}} = \frac{V_s}{V_r} \quad (4)$$

where, ρ_0 is the density of the hydrogel in the dry

state, ρ_{sw} is the density of the swollen gel, whereas V_s and V_r are the volumes of the hydrogel in the wet and dry states, respectively.

Thermodynamics of Gel Swelling

The structure of hydrogels that do not contain ionic moieties can be analyzed by the Flory-Rehner theory [38]. The combination of thermodynamic and elasticity theories states that a cross-linked polymer gel that is immersed in a fluid and allowed to reach equilibrium with its surroundings is subject only to two opposing forces: the thermodynamic force of mixing and the retractive force of the polymer chains. The change of chemical potential due to mixing can be expressed using heat and the entropy of mixing. The change in chemical potential due to the elastic retractive forces of the polymer chains can be determined from the theory of rubber elasticity. Upon equal contributions of these two, the expression for determining the molecular weight between two adjacent cross-links of a neutral hydrogel prepared in the absence of a solvent can be derived [1].

In the case of ionic polymers, the swelling equilibrium of the polymeric matrix is more complicated as it heavily depends also on the ionic strength (Figure 1). The free energy change of ionic hydrogel, corresponding to the volume change during swelling, ΔG, is the sum of contributions due to mixing of pure solvent with an initially pure, amorphous, unstrained gel network, ΔG_1, due to configurational changes of the gel structure, ΔG_2, and due to mixing of ions with solvent, ΔG_3. An ionic gel is subjected to a swelling pressure, π, which is expressed as the sum of three components corresponding to each contribution to ΔG [39,40].

A molecular theory of swollen gels by including free volume as a third component in the binary mixture of solvent and polymer was developed by Marchetti et al. [41]. This theory could predict the phase behaviour such as near-critical lower consolute boundaries, low-temperature upper consolute boundaries and closed-loop miscibility gaps. The theory was further applied to correlate the experimental data of poly(isopropylacrylamide) and poly(diethylacrylamide) gels. The predicted values by the theory agree closely with those measured experimentally.

In 2001, a multi-component, one and two-dimensional model for the transient and equilibrium swelling of polyelectrolyte gels was developed by Achilleosa et al. [42]. The model accounts for the effect of network stress, osmotic pressure, and electrical potential on the species diffusive flux. The osmotic pressure and the network stress were derived from the Helmholtz free energy of the system. They try to simulate one and two dimensional swelling in unconstrained and constrained geometries for a salt-solvent-polymer system. Through solving their mathematical model numerically, one can obtain the transient and equilibrium fields of electrical potential, concentrations, deformation, and stress.

The swelling behaviour of cross-linked ionic

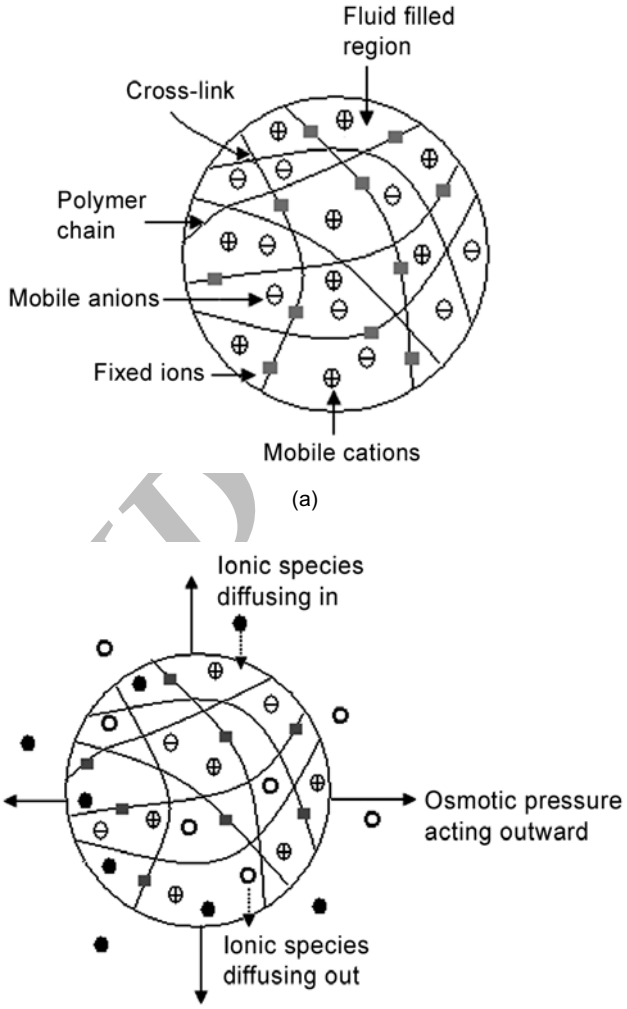

Figure 1. Schematic of an ionic polymeric hydrogel (a), and the swelling phenomena of an ionic hydrogel in a buffered pH solution (b).

hydrogels has been studied by Oliveira et al., by using a quasi-chemical thermodynamic model [43]. The calculated volume transition temperature of PNIPAm gel is 0.8ºC lower than the experimental value and the predicted solvent volume fraction in the collapsed and swollen gel states are about 2% larger than the corresponding experimental data measured at the transition point. Applying the same energy parameters obtained from regressing PNIPAm gel swelling pressure data, their model has also been capable to correctly represent the major features found in the swelling behaviour of linear poly(*N-tert*-butylacrylamide) and poly(*N-tert*-butylacrylamide) gels, after the model parameters that characterize the molecular structure were changed in accordance to each polymer repetitive unit.

Yang et al. [44] developed a lattice model for the binary polymer solutions based on statistical associating theory. In this work, a new molecular thermodynamic model for thermo-sensitive hydrogels was proposed through combining Yang et al.'s lattice model and an elastic term. When the energy parameter is expressed as a quadratic of inverse temperature, this model can describe the swelling behaviour of neutral thermo-sensitive hydrogels. The experimental swelling curves of two kinds of polyacrylamide based gels were correlated.

The swelling equilibrium of IPAAm/NaMA hydrogels in aqueous solutions of the single salts, NaCl and Na_2HPO_4, was investigated experimentally and described mathematically by developing a new thermodynamic model [45]. This new model combines an extension of Pitzer's model for aqueous electrolyte solutions for the excess Gibbs energy of an aqueous phase with an extension of the phantom network theory. Orlov et al. indicated that such an extension is necessary to account for the large volume changes observed when ionic hydrogels are dissolved in water and salt solutions at low salt concentrations. Wallmersperger et al. assumed that the swelling mechanism results from the equilibrium of different forces and can be triggered by chemical, thermal or electrical stimulations [46]. The chemical field could describe by a convection-diffusion equation, while the electric field was directly obtained by solving the Poisson equation in the gel and solution domain. The mechanical field was formulated by the momentum equation. To model the global macroscopic behaviour, they just used the statistical theory which is capable to describe the overall swelling ratio. By refining the scale, the mesoscopic coupled multi-field theory was applied. Their mesoscopic formulation is capable to capture the whole gel and solution domain for chemical, thermal and electrical stimulations without prescribing any jumps of concentration or electric potential at the interface.

A new molecular thermodynamic model for describing the swelling behaviour of thermo-sensitive hydrogels was developed by Huang et al. [47]. They assumed that a neutral hydrogel system contains only polymer network and water. The Gibbs energy inside the hydrogel is defined as: $\Delta G = \Delta G_m + \Delta G_e$, where ΔG_m is the mixing term of hydrogel network and water and ΔG_e is the elastic term deriving from the network elasticity. Their model consists of two terms: the contribution of the mixing of hydrogel network and water, which is dependent on the local polymer concentration and the interaction between polymer segment and solvent, and the elastic contribution derived from the network elasticity, which is dependent on the cross-linking degree of gel network. Their important parameters are ε (energy parameter, reflecting the interaction between water and gel network) and V^* (a size parameter which represents the cross-linking degree of the hydrogel). When the energy parameter is expressed as a quadratic of inverse temperature, this model can describe the swelling equilibrium behaviour of neutral thermo-sensitive hydrogels quite well.

Kinetics of Gel Swelling

It is well known that sorption processes for polymer-solvent systems frequently do not conform to the behaviour expected from the classical theory of diffusion [48]. The slow reorientation of polymer molecules can lead to a wide variety of anomalous effects for both permeation and sorption experiments. The four basic categories of the sorption phenomena in polymers may be described as follows.

Fickian or Case I transport is characterized by the single parameter D, the diffusion coefficient.

Penetrants in rubbery polymers and at low activities in glassy polymers typically exhibit Fickian behaviour. Molecular relaxation is either faster than

diffusion (well above glass transition temperature, T_g) or so slow that is not observed on the time scale of the experiment (well below T_g). In slab samples, Case I diffusion is characterized by a linear increase of polymer weight gain as a function of the square root of sorption time. It asymptotically approaches a fixed equilibrium value.

Case II transport is characterized by the single parameter V, the velocity of the advancing penetrant front. Diffusion is very rapid compared to relaxation, with relaxation occurring at an observation rate. Here, the rate of mass uptake is directly proportional to time.

Diffusion behaviour which is intermediate between that of Case I and Case II is regarded as Non-Fickian behaviour. Therefore, non-Fickian or anomalous transport is observed when the diffusion and relaxation rates are comparable.

Super Case II diffusion is characterized by an acceleration of absorption rate towards the end of the front penetration process. This change is attributed to the expansion forces exerted by the swollen gel on the glassy core.

The role of Case II diffusion as another limiting case of diffusion may be debated because of the controversy over the existence of Super Case II diffusion, and the fact that Case I diffusion generally precedes the onset of Case II diffusion. In addition, Case I behaviour may reoccur in Case II diffusion when the sample dimension is large. Therefore, Case II diffusion may be more appropriately named as Case II transport or Case II sorption. Case II sorption is uniquely characterized by a constant movement of penetration front after a glassy polymer is immersed in a non-dissolving liquid penetrant.

Numerous mathematical models have been proposed describing the kinetics of hydrogel swelling. The models may be divided into three categories [49]. The Fickian diffusion models apply Fick's laws to the distribution of solvent in a gel sample during swelling or collapse. These models predict that the fractional approach to equilibrium increases linearly with the square root of time up to roughly 0.4 and that the swelling curve, the fractional approach to equilibrium vs. square root of time, is not sigmoidal even if the diffusion coefficient is a function of composition. The collective diffusion models, developed by Tanaka et al., treat the swelling of a gel as the expansion of a network driven by a gradient of stress [50]. These models describe small volume changes, but they fail to predict the sigmoidal swelling curves resulting from large volume change. Sigmoidal experimental swelling curves are often taken to indicate non-Fickian behaviour. Deviations from the fixed boundary Fickian behaviour are usually attributed to some of the following phenomena: (i) variable surface concentration, (ii) a history dependent diffusion coefficient, (iii) stresses between parts of the gel swollen to different extents and (iv) polymer relaxation. The first three have been discussed by Crank et al. [51], while the last has been modelled by Joshi et al. [52]. However, it has been shown that the sigmoidal swelling behaviour can be well described by Fickian diffusion when the movement of the gel surface is taken into account correctly [53]. Although these models predict the swelling curves for large volume changes reasonably well, they are subject to three objections: (i) they do not allow for the movement of the gel boundary, (ii) they require three or more parameters to fit experimental data, and (iii) the diffusion coefficients may show unusual composition dependence, e.g. a maximum at an intermediate composition.

Singh and Fan developed a generalized mathematical model for the simultaneous transport of a drug and a solvent in a planar glassy polymer matrix [54]. The swelling behaviour of the polymer is characterized by a stress-induced drift velocity term ‘v’. The change of volume due to the relaxation phenomenon is assumed instantaneous. The model incorporates convective transport of the two species induced by volume expansion and by stress gradient.

Vasheghani-Farahani has already indicated that the NIPAm gels exhibit Fickian behaviour upon swelling, but their shirking at 35ºC is non-Fickian [55]. Also, the rate of swell is slower than the rate of collapse. He has developed a Fickian mathematical model, which describes the kinetics of swelling and collapse of ionic hydrogels, through the use of a material coordinate and a chemical potential driving force. In this way, explicit relationships between diffusion coefficients in polymer material coordinate and in laboratory coordinate for cylindrical and spherical geometries have been obtained.

Swelling of superabsorbent acrylamide/sodium acrylate hydrogels prepared using multifunctional cross-linkers have been studied by Karadag et al. [56]. The research involved the study of the influence of cross-linkers and the relative content of sodium acrylate on swelling, initial swelling rate, swelling rate constant, swelling coefficient and diffusional behaviour of water in the hydrogel. Results indicate that acrylamide-sodium acrylate hydrogels showed greater swelling in water compared to acrylamide hydrogels and the water intake of hydrogels followed non-Fickian type diffusion.

Swelling behaviour and drug release kinetics of ionic and non-ionic IPNs of PNIPAm and calcium alginate were studied by Khorram et al. [57]. They used calcium alginate as a mould to obtain uniform, large size, macroporous spherical beads of NIPPAm hydrogels. Their swelling observations indicated that the equilibrium swelling degree of homopolymer gel increased after calcium alginate extraction, while it had no effect on lower critical solution temperature (LCST). In addition, equilibrium swelling degree of copolymer composite hydrogels containing Na^+ and Ca^{2+} cations were greater than that of the extracted hydrogel containing only monovalent cations. It was also observed that, swelling kinetics of hydrogels as well as their drug release followed Fickian behaviour. Bouquerand et al. developed a model of flavour release from encapsulated flavour particles immersed in water by considering a pseudo-steady state condition in the swollen region of the particles [58]. Their model predicts a very different release with time from the encapsulated flavour if the particle develops a hydrogel at the surface (swelling) compared to gradual erosion. But, the proposed model contains some errors which are corrected by Vasheghani-Farahani [59].

Osmotic swelling and de-swelling studies have been performed on gelatin suspended in water-ethanol marginal solvent at room temperature, where the alcohol concentration was changed from 0 to 100% (v/v) [60]. Boral et al. reported that the osmotic pressure of polymer-solvent mixing (π_m) is much smaller than the osmotic pressure due to network elasticity (π_e). In addition, the osmotic pressure arising from ionic contributions, π_{ion} was found to play a significant role in controlling volume phase transitions. For gelatin hydrogels, total swelling pressure of gel, π_{tot} could be related to gelatin volume fraction (φ_2), relaxed volume of network (V_0), and cross-link density (v_e) while it is independent of gel pH and swelling time.

BIOMEDICAL APPLICATIONS OF HYDROGELS

Hydrogels have been successfully used in biomedical fields due to their high water content and the consequent biocompatibility. Potential applications of hydrogels in tissue engineering, synthetic extracellular matrix (ECM) and three dimensional scaffolds are well highlighted in a recent work. The proliferation and differentiation of mesenchymal stem cells (MSC) in a three dimensional (3-D) network of nanofibres formed by self-assembly of peptide-amphiphile (PA) molecules was investigated by Hosseinkhani et al. [61]. A 3-D network of nanofibres was formed by mixing cell suspensions in media with dilute aqueous solution of PA. In another work, a hybrid scaffold consists of two biopolymers, a hydrogel formed through self-assembly of peptide-amphiphile with cell suspensions in media and a collagen sponge reinforced with poly(glycolic acid) fibre incorporation, were used successfully to enhance bone formation [62]. A novel injectable 3-D scaffolds with encapsulated growth factor was formed by mixing of PA aqueous solution with basic fibroblast growth factor (bFGF) suspension [63]. Hosseinkhani et al. showed that when aqueous solution of PA was subcutaneously injected together with bFGF suspension into the back of mice, a transparent 3-D hydrogel was formed at the injected site and induced significant angiogenesis around the injected site, in marked contrast to bFGF injection alone or PA injection alone.

Materials controlling the activity of enzymes, phospholipids bilayer destabilizing agents, materials controlling reversible cell attachment, nanoreactors with precisely placed reactive groups in three-dimensional space, smart microfluidics with responsive hydrogels, and energy-conversion systems are the promising applications of hydrogels in biomedical and pharmaceutical areas [64-67]. The soft and hydrophilic nature of hydrogels makes them particularly suitable as novel drug delivery systems [68].

Control of hydrogel swelling properties can be used as a method to trigger drug release. Through proper design, hydrogels can be used in a variety of applications including sustained, targeted, or stealth biomolecule delivery. Hydrogels can be engineered to exhibit bioadhesiveness to facilitate drug targeting, especially through mucus membranes, for non-invasive drug administration [69]. 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 [70]. Dinarvand's group developed poly(lactide-*co*-glycolide)-based hydrogel nanoparticles with modified surface properties to increase the blood circulating half life of drug carriers [71].

INTELLIGENT HYDROGELS IN DDS

The intelligent response of environmentally responsive hydrogels allows for release that is controlled by the conditions of the environment. Temperature-responsive and pH-responsive hydrogels have been widely used to create drug delivery systems that exhibit a pulsatile release in response to temperature or pH changes [72]. By incorporating enzymes within environmentally responsive hydrogels, researchers have created drug delivery systems that are responsive to biological analytes [73]. Another area of drug delivery where hydrogels have proven beneficial is in systems where molecular recognition is utilized for enhanced residence times, sustained delivery, and/or targeted drug delivery [74].

Temperature Responsive Hydrogels in DDS

Temperature sensitive hydrogels can be classified as negatively thermosensitive, positively thermosensitive, and thermally reversible hydrogels. Negatively thermosensitive hydrogels are those showing lower critical solution temperature (LCST) behaviour, while positively thermosensitive gels are known to have an upper critical solution temperature (UCST) [75]. The LCST polymers exhibit a hydrophilic-to-hydrophobic transition with increasing temperature, whereas the UCST systems undergo the opposite transition. Thermally reversible hydrogels are those that can experience cyclic phase transitions (sol-gel transition), such as poloxamers, gelatin and other natural polymers.

Negatively Thermosensitive Hydrogels

The LCSTs of several typical negatively thermosensitive polymers are listed in Table 2 [9]. Negatively thermosensitive hydrogels tend to shrink or collapse as the temperature is increased above the LCST, and swell upon lowering the temperature below the LCST. The change in the hydration state, which causes the volume phase transition, reflects competing hydrogen bonding properties, where intra- and inter-molecular hydrogen bonding of the polymer molecules are favoured compared to a solubilization by water [10]. Thermodynamics can explain this with a balance between entropic effects due to the dissolution process itself and due to the ordered state of water molecules in the vicinity of the polymer. Enthalpic effects are due to the balance between intra- and inter-molecular forces and due to solvation, e.g. hydrogen bonding and hydrophobic interaction. The transition is then accompanied by coil-to-globule transition. By controlling the polymer composition and topology, the coil-to-globule transition could be kinetically and thermodynamically controlled [76]. Control of deswelling kinetics was achieved by using graft copolymer structure. The comb-type grafted hydrogels of cross-linked P(NIPAAm) grafted with oligo-NIPAAm and poly(NIPAAm-*g*-PEG) exhibited fast response to temperature changes [77]. Grafted short chains of oligo-NIPAAm in the former case contributed to fast dehydration, whereas in the latter case the hydrophilic PEG chains provided a water channel

Table 2. Lower critical solution temperatures (LCST)s of several typical thermosensitive polymers [9].

Polymer	LCSTs (ºC)
Poly(*N*-isopropylacrylamide) (PNIPAM)	32
Poly(*N,N*-diethylacrylamide) (PDEAM)	25
Poly(*N*-ethylmethacrylamide) (PNEMAM)	58
Poly(methyl vinyl ether) (PMVE)	34
Poly(2-ethoxyethyl vinyl ether) (PEOVE)	20
Ploy(*N*-vinylcaprolactam (PNVCa)	30-35
Poly(*N*-vinylisobutyramide) (PNVIBAM)	39
Poly(*N*-vinyl-*n*-butyramide) (PNVIBAM)	32

for a fast deswelling mechanism. Copolymerization of NIPAAm with hydrophobic butylmethacrylate decreases the LCST of aqueous copolymer solution and copolymerization with hydrophilic comonomers, such as acrylic acid or hydroxy ethyl methacrylate, results in an increase in LCST.

Bulmus et al. used the PNIPAAm polymers for on/off control of avidin-biotin binding [78]. Below the transition temperature of 32ºC, NIPAAm copolymers are in a fully extended conformation in water because of favourable polymer-water interactions. The PNIPAAm with fully extended conformation interferes with the biotin-binding site on the avidin, whereas above the transition temperature, the polymers are collapsed and cannot interfere with the binding sites.

Cellulose nitrate and cellulose acetate monolayer membranes containing *n*-heptyl-cyanobiphenyl were developed as thermoresponsive barriers for drug permeation [79]. Methimazole and paracetamol as hydrophilic and hydrophobic drug models were used, respectively. Atyabi's group found that upon changing the temperature of the system around 41.5ºC, both cellulose membranes without cyanobiphenyl showed no temperature sensitivity to drug permeation, whereas the results for cyanobiphenyl entrapped membranes exhibited a distinct jump in permeability when temperature was raised to above the 41.5ºC for both drug models. Drug permeation through the membranes was reversible, reproducible and followed zero order kinetics. The pattern of on/off permeation through these membranes was more distinguished for methimazole compared to that of paracetamol, seemingly due to its lower molecular weight.

Positively Thermosensitive Hydrogels

Certain hydrogels formed by IPNs show positive thermosensitivity, i.e. swelling at high temperature and shrinking at low temperature. IPNs of poly(acrylic acid) and polyacrylamide (PAAm) or P(AAm-*co*-BMA) perform as positively thermosensitive hydrogels [80]. Increasing the BMA content shifted the transition temperature to higher temperature. The swelling of those hydrogels was reversible, responding to stepwise temperature changes. This resulted in reversible changes in the release rate of a model drug, ketoprofen, from a monolithic device.

Another UCST system was fabricated by Aoki et al., based on a combination of acrylamide (AAm) and acrylic acid (AAc) [81]. The obtained IPNs were very stable at 70ºC in an aqueous solution. Dissociation temperatures of the hydrogels shifted to higher values with increasing AAm content. These IPNs showed limited swelling ratios between their swelling transition temperatures and lower swelling ratios above these transition temperatures. Transition temperatures shift to higher values with increasing AAm content. Reversible and pulsatile solute release, reflecting the "on" state at higher temperatures and the "off" state at lower temperatures, was recorded by Aoki et al.

A positively thermosensitive drug-release microcapsule was fabricated by Ichikawa et al. [82]. The microcapsule had a core layered with carbazochrome sodium sulphonate (a water-soluble model drug) particles and a thermosensitive coat composed of an ethylcellulose matrix containing nano-sized thermosensitive hydrogels (Figure 2). The hydrogel particles consisted of newly synthesized composite latex with a PNIPAAm shell that could reversibly change the shell thickness in water with response to an environmental temperature change. This microcapsule demonstrated a positively thermosensitive on-off pulsatile drug release around 32ºC, suggesting that the shrinkage of PNIPAAm shells most likely created many voids in the coat and thereby imparted the higher water-permeability to the coat.

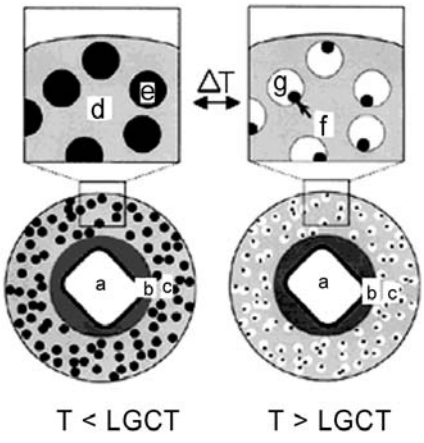

Figure 2. Ideal structure of microcapsules with positively thermosensitive drug release. (a) Calcium carbonate core; (b) drug; (c) thermosensitive coat; (d) Aquacoat; (e) & (f) swollen and shrunken hydrogel particles; (g) void. Adopted from ref [80].

A novel family of monodisperse thermosensitive core-shell microspheres has been developed by Xiao et al. [83]. The microspheres were fabricated in a three-step process. First, monodisperse poly(acrylamid-*co*-styrene) seeds were prepared by emulsifier free emulsion polymerization. Then, poly(acrylamide) or poly[acrylamid-*co*(butylate)] shells were fabricated on the microsphere seeds by free radical polymerization. Finally, the core-shell microspheres with poly(acrylamide)/poly(acrylic acid) based IPN shells were finished by a method of sequential IPN synthesis. The swelling ratio of the microspheres could be tuned by controlling the hydrophobic monomer (BMA) or cross-linker (MBA) dosage in the PAAM shell fabrication and IPN synthesis.

Thermally Reversible Hydrogels

Aqueous solutions of some polymers undergo sol to gel transition in response to a certain stimulus (Figure 3) [84]. Among them, thermally reversible hydrogels are of most interest and will be discussed in this section.

Polymers with hydrophobic domains can cross-link in aqueous environments via reverse thermal gelation. Hydrophobicity-driven gelation often occurs via the mechanism shown in Figure 4. The hydrophobic segment is coupled to a hydrophilic polymer segment by post-polymerization grafting or by directly synthesizing a block copolymer to create a polymer amphiphile. Such amphiphiles are water soluble at

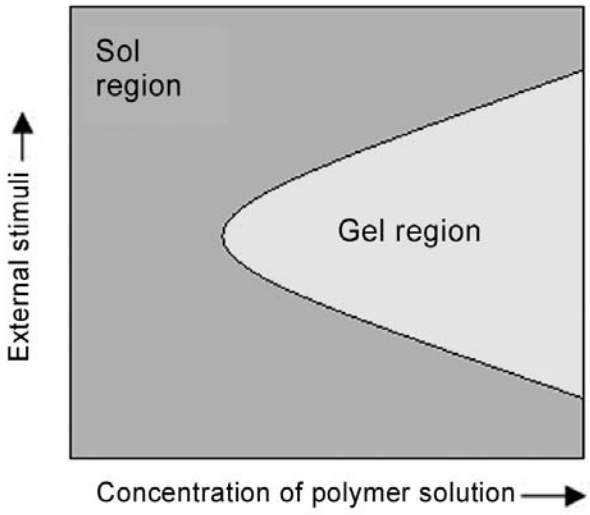

Figure 3. Schematic representation of sol-to-gel transition in stimuli-sensitive polymers.

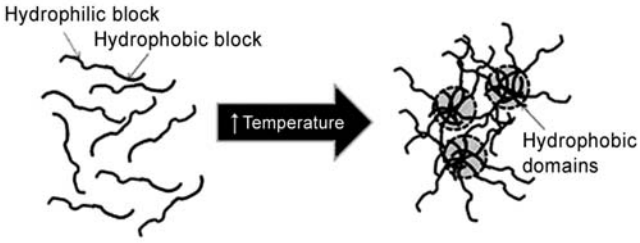

Figure 4. Mechanism of in situ physical gelation driven by hydrophobic interactions. Adopted from ref [4].

low temperature. As the temperature is increased, hydrophobic domains aggregate to minimize the hydrophobic surface area contacting the bulk water, reducing the amount of structured water surrounding the hydrophobic domains and maximizing the solvent entropy. The temperature at which gelation occurs depends on the concentration of the polymer, the length of the hydrophobic block, and the chemical structure of the polymer [4].

The chemical structures of some common hydrophobic blocks which can undergo reverse thermal gelation at or near physiological temperature are shown in Figure 5.

Triblock copolymers of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO-PPO-PEO, the Poloxamers/Pluronics) are the most widely used thermally reversible hydrogels [85]. Aqueous solution of poloxamers demonstrates phase transitions from sol to gel at 5-30ºC and gel to sol at 35-50ºC with the temperature increasing monotonically over the polymer concentration range of 20 to 30 wt% [76]. The transition mechanism from gel-to-sol is related to the shrinkage of PEO corona of the micelles because of temperature effects on PEO solubility and interaction of PEO chains with the PPO hard core. A recent small angle neutron scattering study proposed the transition of micelle structure from spherical to cylindrical, thus releasing micelle-packing constraints, as the cause of the high temperature gel-sol transition [76]. A sol-gel transition behaviour was also observed for an altered triblock structure in which poly(butylenes oxide) (PBO) was used in place of PPO in the middle block or with PEO-PBO diblock copolymers.

Poloxamers can also be modified by adding an additional polymer block at each chain terminus,

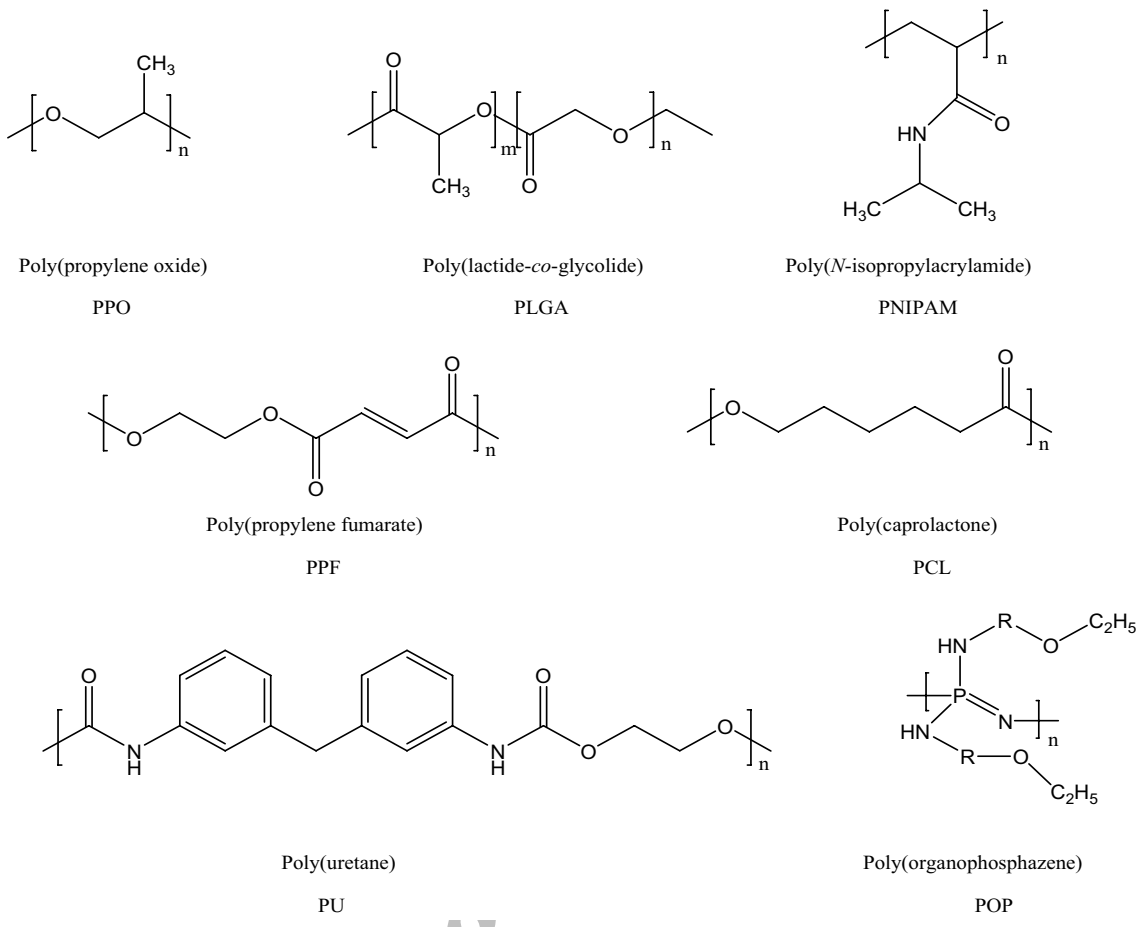

Figure 5. Chemical structures and abbreviations of common thermogelling hydrophobic blocks; R = any thermogelling polymer. Adopted from ref [4].

forming multi-block copolymer with improved properties for drug delivery [86,87]. PL(G)A-based gelators typically exhibit better biodegradability, higher gelation temperatures, and longer periods of sustained drug release compared to poloxamer systems. Release of hydrophilic compounds from PLGA-PEG-PLGA copolymers was found to be diffusion controlled, while release of hydrophobic compounds showed an initial diffusion-controlled stage followed by a prolonged polymer degradation-controlled stage [88].

Some natural polymers also undergo reverse thermal gelation. Chitosan-glycerol phosphate-water system is an interesting example, which has being investigated for protein delivery, gene delivery and tissue engineering applications [89]. Recently, novel di-block copolymers of chitosan and PEG were synthesized were synthesized by block copolymerization of monomethoxy-PEG onto chitosan backbone, using potassium persulphonate as a free radical initiator [90]. The obtained hydrogels undergo a thermosensitive transition from a free flowing solution at room temperature to a gel around body temperature. Their gelation time varied from 6 to 11 min. Figure 6 illustrates viscosity of a 2% w/v of chitosan-*b*-PEG copolymer in an aqueous solution versus temperature. A sharp increase in viscosity around 35°C indicates the beginning of the gelation process. It is also found that solutions with high polymer concentrations and low PEG content gel faster than those with low polymer concentrations or high PEG content. Similar trends were observed by Bhattarai et al. for their thermosensitive PEG-grafted chitosan copolymers [91]. Their hydrogel is synthesized by grafting an appropriate amount of PEG onto the chitosan backbone and used for drug release of bovine serum albumin (BSA) as a model protein. Chitosan was first modified with a PEG-aldehyde to yield an imine (Schiff base) that was subsequently converted into

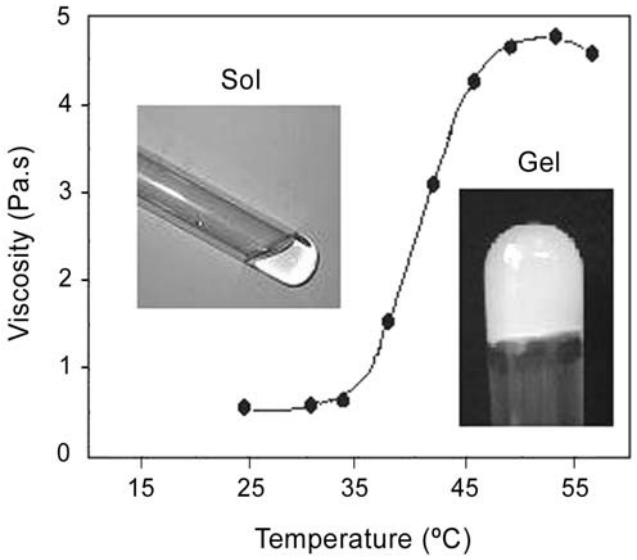

Figure 6. Viscosity of chitosan-*b*-PEG copolymer versus temperature for 2% w/v polymer solution.

PEG-*g*-chitosan through reduction with sodium cyanoborohydride ($NaCNBH_3$). The required time for gelation of their PEG-*g*-chitosan copolymers varied from 10 min to 1 h, depending on polymer concentration. They have found that the required amount of grafted PEG for an injectable thermosensitive copolymer is approximately 36-55 wt%. Below the 36 wt% of grafted PEG, the obtained copolymers were found to be hardly soluble in water [92].

Grafting PNIPAM linear chains onto natural polymers can also convert those polymers into physically cross-linkable hydrogels. For example, PNIPAM-grafted hyaluronic acid formed a gel in vivo which showed a burst release of riboflavin for 12 h and sustained release thereafter [91]; NIPAM-grafted chitosan has also been used to control the release of 5-fluorouracil [94].

pH Sensitive Hydrogels in DDS

Since the pH change occurs at many specific or pathological body sites, it is one of the important environmental parameter for drug delivery systems. For non-ionic hydrogels, the degree of swelling only depends on the chemical compositions of the polymers. However, for ionic hydrogels the swelling depends not only on the chemical composition but also on the pH of the surrounding medium. Therefore, the pH-sensitive polymers show dramatic changes on the pH

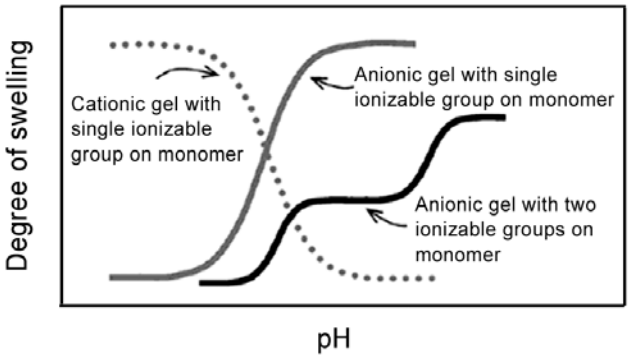

Figure 7. Schematic of relative ionic hydrogel swelling as a function of pH. Adopted from ref [24].

and on the compositions of the external solutions.

The pH-sensitive polymers can be classified as acidic weak polyelectrolytes and basic weak polyelectrolytes according to the method of ionization i.e., donating or accepting protons. Anionic hydrogels deprotonate and swell more when external pH is higher than pK_a of the ionizable groups bonded on polymer chains, while cationic hydrogels protonate and swell more when external pH is lower than the pK_b of the ionizable groups [18]. Depending on the ionic monomers used to fabricate the hydrogel, the pH-dependent swelling curves exhibit one or more inflection points near the pK_a/pK_b of the ionizable groups as shown in Figure 7.

Typical acidic pH-sensitive polymers for drug delivery are based on the polymers containing carboxylic groups, such as poly(acrylic acid) [95], poly(methacrylic acid) [96], poly(*L*-glutamic acid) [97], and polymers containing sulphonamide groups [98]. Typical examples of the basic polyelectrolytes include poly(tertiary amine methacrylate) such as poly(2-(dimethylamino) ethyl methacrylate) and poly(2-(diethylamino)ethyl methacrylate) [99], poly(2-vinylpyridine) [100] and biodegradable poly(β-amino ester) [101].

Kamada et al. synthesized a pH-sensitive polymeric carrier, in which a poly(vinylpyrrolidone-*co*-dimethyl maleic anhydride) (PVD) was conjugated to doxorubicin (DOX), that could gradually release free drug in response to changes in pH, from near neutral to slightly acidic pH [102]. The superior anticancer activity of PVD-DOX conjugate is mainly due to controlled release and enhanced tumor accumulation of

the drug.

Alginate-*N,O* carboxymethyl chitosan (NOCC) gel beads coated by chitosan were prepared for colon-specific drug delivery system and their swelling behaviour was investigated by Dolatabadi-Farahani et al. [103]. Their studies showed that swelling degree at pH 7.4 was considerably higher than that at pH 1.2, which indicates the pH sensitivity of these networks. Swelling degree of beads also decreased by chitosan coating and presence of NOCC due to the hydrogen bond formation and ionic interaction of functional groups of the polymer chains.

The synthesis and swelling behaviour of a superabsorbent hydrogel based on starch (St) and polyacrylonitrile (PAN) are investigated [104]. The absorbency of the hydrogels indicated that the swelling ratios decreased with increasing ionic strength. The hydrogels exhibited a pH-responsive swelling-deswelling behaviour at pHs 2 and 8. This on/off switching behaviour provides the hydrogel with the potential to control delivery of bioactive agents. Release profiles of ibuprofen from the hydrogels were studied under both simulated gastric and intestinal pH conditions. The release was much quicker at pH 7.4 than at pH 1.2. The swelling rates of the hydrogels with various particle sizes were investigated as well.

A biodegradable pH-sensitive hydrogel for potential colon-specific drug delivery was synthesized by Casadei et al. [14]. Their composite hydrogel, based on a methacrylated and succinic derivative of dextran, and a methacrylated and succinic derivative of poly(*N*-2-hydroxyethyl)-*DL*-aspartamide was produced by photo cross-linking polymerization. In vitro drug release studies, performed using 2-methoxyestradiol as a model drug, show that obtained hydrogel is able to release the drug in simulated intestinal fluid, due to its pH-sensitive swelling and enzymatic degradability.

Temperature/pH Sensitive Hydrogels in DDS

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 [105].

Stayton's group has investigated a series of copolymers containing propylacrylic acid (PAA) and NIPAAm pendant chains as pH- and thermosensitive moieties, respectively [71]. 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.

Hollow beads of IPN of PNIPAAm were synthesized using Ca-alginate as the polymerization mould [106]. Drug loading was carried out using injection of drug solution into the cores of hollow beads. Acetaminophen and diltiazem hydrochloride were used as low-water-soluble and water-soluble model drugs. Drug loading into this hydrogel based reservoir controlled release system indicated its advantage for loading of sparingly soluble drug in aqueous solutions.

Swelling behaviour of poly((2-dimethyl amino) ethyl methacrylate-*co*-BMA) was investigated by Emileh et al. [107]. These hydrogels demonstrated dual sensitivity to both pH and temperature. It was shown that the pH-sensitive or temperature-sensitive phase transition behaviour of the gels can be changed by changing the temperature or pH of the swelling medium at constant hydrogel composition. Increasing the temperature decreased the transition pH, while increasing the pH of the surrounding medium decreased the transition temperature of the temperature-sensitive phase transition. Increasing the BMA content reduced the transition pH and temperature of the pH and temperature-sensitive phase transition, respectively. The results of equilibrium swelling and compression-strain measurements were used to calculate the polymer-solvent interaction parameters of these hydrogels using the Flory-Rehner equation of equilibrium swelling.

The pH and temperature double responsive poly(*N*-isopropylacrylamide-*co*-IA) hydrogels were prepared by copolymerization in mixed solvents of water and dimethylsulphoxide (DMSO) [108]. The results indicated that only hydrogels prepared in the highest DMSO/water ratio media exhibited improved properties such as higher swelling ratios, faster deswelling and reswelling kinetics compared with traditional P(NIPAAm-*co*-IA) hydrogels. They have

proposed that there maybe an energy barrier existed for conformation transitions in the process of removal of DMSO by water. Only the gels which could overcome the energy barrier exhibited expanded network structures and improved properties while, the other gels maintained their contracted network structures and poor properties.

Bioresponsive Hydrogels in DDS

Bioresponsive hydrogels, which undergo structural and/or morphological changes in response to a biological stimulus, have been investigated for numerous applications in drug delivery, tissue regeneration, bioassays/biosensors, and biomimetic systems [109]. Much work on bioresponsive hydrogels for drug delivery relates to the release of insulin in response to raised blood sugar levels as a potential autonomous treatment of insulin-dependant diabetes [109,110]. Glucose oxidase molecules are immobilized onto a basic polymeric carrier. Following the enzyme reaction glucose is converted to gluconic acid and therefore the pH of the hydrogel is temporarily lowered. In this situation the basic groups on the polymer are protonated and induced swelling of the gel which enhancing the release profile of insulin (Figure 8). This system works as a feedback loop: upon release of insulin the sugar levels drop, resulting in a pH increase that stops the release of further insulin [110].

Bioresponsive hydrogels can be designed in a degradable form in response to external stimuli such as enzymes. Such systems deliver physically entrapped guest molecules, held freely within the carrier, and do not require chemical modification for targeted delivery. Plunkett et al. have developed a procedure to synthesize hydrogels with cross-links composed of different enzyme-cleavable peptides [111]. Law et al. described self-assembled peptide sequences that release therapeutic payloads upon specific interaction with disease-associated proteases [112]. The core peptide sequence consists of a protease cleavable region flanked by two self-assembly motifs. Successful enzyme cleavage results in drug release; however, the extent of cleavage is limited by the degree of cross-linker required to form a suitable gel.

A biochemically and stimulus responsive triblock copolymer is developed by Li et al. [113]. The polymer forms a micellar, dithiol cross-linked NIPAAm

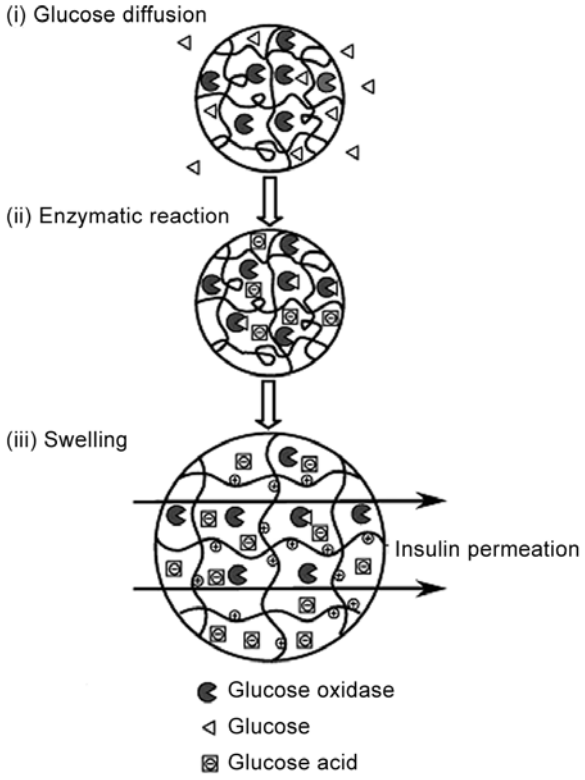

Figure 8. Schematic representation of the glucose-sensitive hydrogel membrane consisting of a poly(amine) and glucose-oxidase-loaded membrane. Adopted from ref [108].

gel at 37ºC that can be degraded by glutathione via cleavage of a central disulphoide bond. Thus, the system offers the possibility of payload release from a loaded gel following glutathione-stimulated degradation.

Kumashiro et al. have synthesized a temperature-responsive hydrogel that only allow enzyme-triggered polymer degradation above a lower critical solution temperature and below a higher critical solution temperature [114]. They anticipate that this technique will allow the release of drug molecules depending on both enzyme selectivity and changes in body temperature.

Kim et al. have prepared the PNIPAm-*co*-AAc hydrogels by photo-polymerization with the peptide cross-linker, which provides enzyme degradable capability of the hydrogels [115]. In the presence of collagenase the peptide cross-linked hydrogels were successfully degraded in dependence on the concentration of the enzyme and the initial cross-linking density.

By conjugating a bio-affinity pair to the hydrogels a new group of bioresponsive hydrogels were prepared, which have been used as a convenient construct for post-functionalization. One interesting example is in targeting cell as a potential drug carrier, where PNIPAm core-shell hydrogel nanoparticles are conjugated with the folic acid that is a ligand for targeting cancer cells. When the folic acid labelled hydrogel particles are incubated with cancer cells that over express the folate receptors, the hydrogel particles are incorporated into the cancer cells via receptor-mediated endocytosis [116].

KINETICS OF DRUG RELEASE FROM HYDROGELS

Hydrogels can be used in many different types of controlled release systems, as diffusion-controlled systems, swelling-controlled systems and chemically-controlled systems. In this section, the mechanism of drug release in each type of system is described.

Diffusion-controlled Delivery Systems

Diffusion-controlled is the most widely applicable mechanism for describing drug release from hydrogels, dividing in two major types: reservoir devices and matrix devices (Figure 9). Reservoir systems consist of a polymeric membrane surrounding a core containing the drug. In matrix devices, the drug is dispersed throughout the three-dimensional structure of the hydrogel. Drug release from each type of system occurs by diffusion through the macromolecular mesh or through the water filled pores. Fick's law of diffusion is commonly used in modelling diffusion-controlled release systems [18,37]. 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:

$$J_i = -D_{ip}\frac{dC_i}{dX} \tag{5}$$

where, J_i is the molar flux of the drug (mol/cm^{2}s), C_i is the concentration of drug, and D_{ip} is the diffusion coefficient of the drug in the polymer. For the case of a steady-state diffusion process, i.e. constant molar flux, and constant diffusion coefficient, eqn (5) can be integrated to give the following expression:

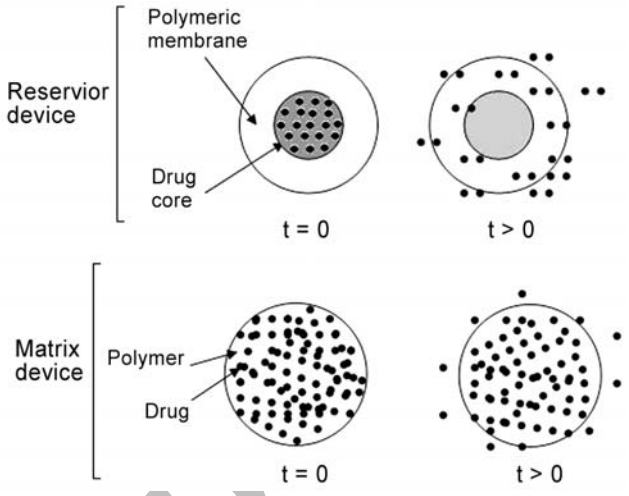

Figure 9. Schematic representation of diffusional controlled reservoir and matrix devices.

$$J_i = K\frac{D_{ip}\Delta C_i}{\delta} \tag{6}$$

where, δ is the thickness of the hydrogel and K is the partition coefficient, defined as the ratio of drug concentration in the gel per drug concentration in solution. To maintain a constant release rate or flux of drug from the reservoir, the concentration difference must remain constant. This can be achieved by designing a device with excess solid drug in the core. Under these conditions, the internal solution in the core will remain saturated. This type of device is an extremely useful device, allows for time-independent or zero-order release.

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 by the Fick's second law:

$$\frac{\partial C_i}{\partial t} = \frac{\partial}{\partial X}\left(D_{ip}\frac{\partial C_i}{\partial X}\right) \tag{7}$$

This form of the equation is for one-dimensional transport with non-moving boundaries and can be evaluated for the case of constant diffusion coefficients and concentration-dependent diffusion coefficients. For the case of concentration independent diffusion coefficients, eqn (6) can be analyzed by application of the appropriate boundary conditions. Upon

application of perfect-sink condition, the solution can be written in terms of the amount of drug released at a given time, M_t, normalized to the amount released at infinite times, M_∞ [37]:

$$\frac{M_t}{M_\infty} = 4\left(\frac{D_{ip}t}{\delta}\right)^{1/2}\left[\frac{1}{\pi^{1/2}} + 2\sum_{n=0}^{\infty}(-1)^n ierfc\frac{n\delta}{2(D_{ip}t)^{1/2}}\right] \quad (8)$$

And at short times, this solution can be approximated as [37]:

$$\frac{M_t}{M_\infty} = 4\left(\frac{D_{ip}t}{\pi\delta^2}\right)^{1/2} \quad (9)$$

Fu et al. obtained an analytical solution of Fick's law for cylindrical geometry considering mass transfer in three dimensions [117]:

$$\frac{M_t}{M_\infty} = 1 - \frac{8}{h^2r^2}\sum_{m=1}^{\infty}\alpha_m^{-2}\exp(-D\alpha_m^{-2}t)\times \sum_{m=1}^{\infty}\beta_n^{-2}\exp(-D\beta_n^2 t) \quad (10)$$

where M_3 and M_∞ are the amounts of drug released at time t and infinite, time respectively; and h denotes the half length, and r the radius of the cylinder; D is the constant diffusivity; $\beta_n = (2n+1)\pi/2h$ and $J_0(r\alpha) = 0$, such that J_0 a zero order Bessel function and m and n are integers. This model is applicable to tablets that range from the shape of a flat disk (radius > thickness) to that of a cylindrical rod (radius < thickness).

The exact solution for the release kinetics of a solute from an infinite spherical and rectangular reservoir with the burst effect initial condition into a finite external volume was developed by Abdekhodaie [118,119]. The governing diffusional equation for transport in the membrane is solved by the time Laplace transform method. Abdekhodaie concluded that the approximate solution is very accurate at late time but at early time deviations from the exact solution increase. His release kinetics results indicate that as the external fluid volume increases the cumulative release at any time and the releasable amount of the solute at infinite time increase. Based on the obtained models, the fractional release of model drugs decreases when the polymeric coating thickness increases Experimentally, cumulative release profiles of theophylline microspheres coated with ethylene vinyl acetate copolymer into different external volumes agreed with the mathematical predictions.

In most systems, the drug diffusion coefficient is dependent on the drug concentration as well as the concentration of the swelling agent. In order to analyze the diffusive behaviour of drug delivery systems in this case, one must choose an appropriate relationship between the diffusion coefficient and the drug concentration. Based on theories that account for the void space in the gel structure, known as free-volume, researchers have proposed relationships between the diffusion coefficient and to the gel property. One of the most widely used equations, proposed by Fujita in 1961, relates the drug diffusion coefficient in the gel to the drug concentration in the following manner [120]:

$$D_{ip} = D_{iw}\exp[-\beta(C_i - C_o)] \quad (11)$$

where, D_{iw} is the diffusion coefficient in the pure solution, β is a constant dependent on the system, and C_o is the concentration of drug in solution. Additionally, a similar equation was written to relate the diffusion coefficient to the concentration of the swelling agent (C_s) and the drug in the gel [120]:

$$D_{ip} = D_{iw}\exp[-\beta(C_s - C_i)] \quad (12)$$

The structure and morphology of a polymer network will also significantly affect the ability of a drug to diffuse through a hydrogel. 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 [121]:

$$D_{eff} = D_{iw}\frac{K_p\varepsilon}{\tau} \quad (13)$$

where D_{eff} is the effective diffusion coefficient, D_{iw} is the diffusion coefficient of the solute in the pure solvent, K_p is the partition coefficient, ε is network porosity and τ is its tortuosity.

In 1961, Higuchi developed a mathematical model aimed to describe drug release from a matrix system

[122]. This model is based on the several hypotheses, as: (1) initial drug concentration in the matrix is much higher than drug solubility, (2) drug diffusion takes place only in one dimension, (3) drug particles are much smaller than system thickness, (4) matrix swelling and dissolution is negligible, (5) drug diffusivity is constant and (6) perfect sink conditions are always attained in the release environment. Accordingly, model expression is given by [122]:

$$M_t = A\sqrt{D(2C_0 - C_s)C_s t} \qquad C_0 > C_s \tag{14}$$

where M_t is the amount of drug released until time t, A is the release area, D is the drug diffusion coefficient, C_0 is the initial drug concentration in the matrix while C_s is drug solubility. Interestingly, this model shows an M_t square root dependence on time as exact Fick's solution predicts when the amount released is less than the 60 percent. Another simple and useful empirical equation is the so-called power law equation:

$$\frac{M_t}{M_\infty} = kt^n \tag{15}$$

The constants, k and n, are characteristics of the drug-polymer system. Peppas et al. were the first to give an introduction to the use and the limitations of these equations [123]. The diffusional exponent, n, is dependent on the geometry of the device as well as the physical mechanism for release (Table 3). Based on the diffusional exponent, the drug transport in slab geometry is classified as Fickian diffusion, Case II transport, non-Fickian or anomalous transport and Super Case II transport. For systems exhibiting Case II transport, the dominant mechanism for drug transport is due to polymer relaxation as the gels swells. These types of devices, known as swelling-controlled release systems, will be described in more detail later. Anomalous transport occurs due to a coupling of Fickian diffusion and polymer relaxation.

For the case of anomalous transport, Peppas and Sahlin developed the following model to describe the release behaviour of dynamically swelling hydrogels [124]:

$$\frac{M_t}{M_\infty} = k_1 t + k_2 t^{1/2} \tag{16}$$

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

Shang et al. have shown that the partition coefficient can be controlled by immobilizing a certain amount of drug molecules in the membrane while maintaining diffusivity of the free drug of the same type [125]. One of the potential applications of this control scheme is for hydrogel-based pulsatile DDS, which requires sharp change in the drug permeation rate when the device is elicited on and off to better mimic the physiological release profile of certain hormones. Based on their hypothesis, the amount of immobilization needed for a required permeation rate can be calculated from [125]:

$$K_{eff} = \left[\frac{exp((\mu_{D,0} - \mu_{M,0})/RT)\gamma_{D,free}}{C_{D,free}^{\alpha-1}\ \gamma_{M,free}(bC_{M,immob})^{\beta}} \right]^{1/\alpha}$$

$$for\ C_{M,immob} > 0 \tag{17}$$

where K_{eff} is the partition coefficient of free drugs; $\mu_{D,0}$ and $\mu_{M,0}$ are the reference chemical potentials in the donor and membrane, respectively; $\gamma_{D,free}$ and $\gamma_{M,free}$ are the activity coefficients of free drugs in the donor and membrane, respectively; $C_{D,free}$ is the free drug concentration in the donor and $C_{M,immob}$ is the concentration of immobilized drug in the membrane;

Table 3. Drug transport mechanisms and diffusional exponents for hydrogel slabs [68].

Type of transport	Diffusional exponent (n)	Time dependence
Fickian diffusion	0.5	$t^{1/2}$
Anomalous transport	0.5 < n < 1	t^{n-1}
Case II transport	1	Time independent
Super case II transport	n > 1	t^{n-1}

R is the gas constant and T is the temperature; α, β and b are fitting parameters. This partition control scheme offers an opportunity to modify the drug release profile of reservoir drug delivery systems with greater flexibility, i.e. the difference in drug permeation rates between the 'off-state' and the 'on-state' can be increased and drug release profile can be modified after its membrane is synthesized.

Swelling-controlled Delivery Systems

Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modelling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels. The rate of drug release is controlled by the velocity and position of the front dividing the glassy (dry) and rubbery (swelled) portions of the polymer [126].

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 [18]:

$$D_e = \frac{\lambda}{t} = \frac{\lambda D}{\delta_{(t)}^2} \qquad (18)$$

In diffusion-controlled delivery systems ($De \leq 1$), 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 ($De \geq 1$), the rate of molecule release depends on the swelling rate of polymer networks. This type of transport is known as Case II transport and results in zero-order release kinetics. A dimensionless swelling interface number, S_w, correlates the moving boundary phenomena to hydrogel swelling [127]:

$$S_w = \frac{V\delta(t)}{D} \qquad (19)$$

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

Among the first models aimed to describe drug release from a swellable matrix are those presented by Peppas et al. [128]. The considerable volume extension due to matrix swelling is accounted by introducing a moving boundary diffusion problem and chemical potential for swelling of ionizable networks. Good agreement between experimental results and model calculations was obtained for drug concentration profiles within the polymer in a system of KCl distributed in HPMC matrix tablets.

Wu et al. [129] 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.

Vasheghani et al. developed mathematical models for drug release from swelling controlled systems [130]. Swelling process from rubbery state was described by taking into account the movement of interface position R(t) (Figure 10) as [131]:

$$\frac{dR(t)}{dt} = -\frac{D_m}{\varphi_p^{\infty}} \frac{\partial \varphi_p}{\partial r}\Big|_{r=R(t)} \qquad (20)$$

where, D_m is diffusion coefficient of solvent in rubbery polymer, r is distance and φ_p^{∞} is volume fraction of polymer at interface. It was shown that developed model is relatively accurate for describing simultaneous drug release and hydrogel dimensional change. Also, modelling of swelling controlled drug release from glassy polymers was developed by using Fick's law and considering movement of the interface of hydrogel surrounding solution and the moving front

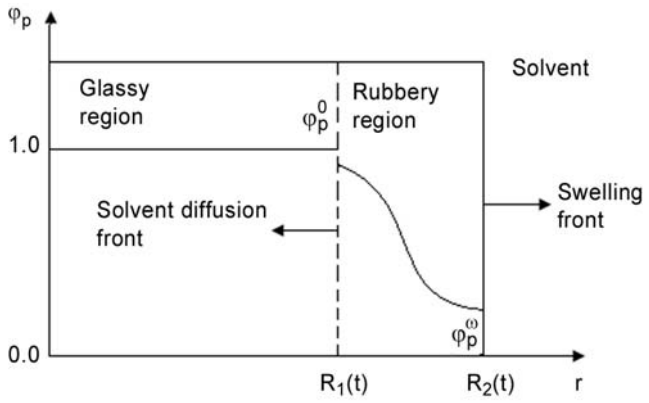

Figure 10. Schematic diagram representing the swelling of the hydrogels with the inward movement of diffusing front of the solvent.

of glassy gel interface, $R_1(t)$, as [131]:

$$\frac{dR_1(t)}{dt} = -\frac{D_m}{(1-\varphi_p^*)}\frac{\partial \varphi_p}{\partial r}\Big|_{r=R_1(t)} \quad (21)$$

where, the volume fraction of polymeric gel at diffusion front φ_p^*, is defined by:

$$\varphi_p^* = \frac{1}{C^*(\rho_p/\rho_s)+1} \quad (22)$$

where, C^* is the concentration of solvent in terms of g/g polymer at diffusion front and ρ_p and ρ_s are the density of polymer and solvent, respectively. The proposed model described accurately the dimensional changes of polymeric network (polymer-solvent and glassy-gel interfaces) and dichlofenac release from HPMC discs.

Chemically-controlled Delivery Systems

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

Erodible Drug Delivery Systems

In erodible drug delivery systems (either matrix or reservoir), also known as degradable or absorbable release systems, drug release is mediated by the rate of surface erosion. In reservoir devices, an erodible membrane surrounds the drug core. In matrix devices, the drug is dispersed within the three-dimensional structure of the hydrogel. Drug release is controlled by drug diffusion through the gel or erosion of the polymer. In true erosion controlled devices, the rate of drug diffusion will be significantly slower than the rate of polymer erosion and the drug is released as the polymer erodes [37]. One of the earliest mathematical models, where the release mechanism only depends on matrix erosion rates, was developed by Hopfenberg [132]:

$$\frac{M_t}{M_\infty} = 1-\left(1-\frac{k_a t}{C_0 a_0}\right)^n \quad (23)$$

where a_0 is the radius of a spherical or cylindrical geometry or half-thickness for slab geometry and C_0 is the drug concentration in the surface eroding device. In this equation, n is 1, 2, or 3 for slab, cylinder, or sphere, respectively. It is clear that only for a slab-shaped device the drug release must be a zero order profile.

Later, a general mathematical model for heterogeneous eroding networks developed by Katzhendler et al., accounting for different radial and vertical erosion rate constants for a flat tablet [133]:

$$\frac{M_t}{M_\infty} = 1-\left(1-\frac{k_a t}{C_0 a_0}\right)^2\left(1-\frac{2K_b t}{C_0 b_0}\right) \quad (24)$$

where k_a and k_b are radial and vertical degradation constant. 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 important to note that swelling of the matrices is either not considered or is assumed to occur prior to erosion and drug release in two above models. Also, these models just focused on the surface erosion of the hydrophobic polymers.

Martens et al. developed a generalized statistical-*co*-kinetic model to predict the degradation behaviours of acrylated poly(vinyl alcohol) (PVA) hydrogels [134]. In this model, a statistical approach was used to predict the different configurations of the cross-linking 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.

Monte Carlo simulation is used to predict protein release from cross-linked dextran microspheres [135]. 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. Based on Vlugt-Wensink et al. studies a kinetic Monte Carlo scheme for the degradation of a small domain inside the dextran microsphere was developed. The only processes included in their model are diffusion and degradation. The general effects of diffusion, cross-link density, protein loading, and clustering of proteins on the release were also studied in their report. However, swelling of the hydrophilic microspheres and changes in swelling with matrix degradation were not accounted for in the described model.

Pendant Chain Systems

In pendent chain system the drug molecule is chemically linked to the backbone of a polymer. In the presence of enzymes or fluids, chemical or enzymatic hydrolysis occurs with concomitant release of the drug as a controlled rate. The drug may be linked directly to the polymer or can be linked via a "spacer" group. In the biodegradable system, polymers gradually decompose and bring about a controlled release of drug. The drug is dispersed uniformly throughout the polymer and is slowly released as the polymer disintegrates. The release of covalently attached drugs is determined by the degradation rate of the polymer-drug linkage. Generally, these linkages degrade by hydrolysis allowing degradation and also release rates to be illustrated by simple first-order kinetic relationships [18]. However, in specific applications, the drug polymer linkages may design to be enzymatically degraded which lead to more complex release kinetics [136].

A statistical-*co*-kinetic model has been developed to predict the effects of hydrolytic or enzymatic degradation on the macroscopic properties of hydrogels [137]. Dubose et al. covalently incorporated fluorescently labelled probe molecules within the three-dimensional network structure of PEG-based hydrogels. Bond cleavage kinetics, microstructural network characteristics and detailed analysis of degradation products are the important parameters accounted in this study. They demonstrated that hydrolytic degradation of covalent bonds 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.

CONCLUSION

During past decades, hydrogels have played a very essential role in biomedical applications. New synthetic methods have been used to prepare homo- and copolymeric hydrogels for a wide range of drugs, peptides, and protein delivery applications. Recent enhancements in the field of polymer science and technology have led to the development of various stimuli sensitive hydrogels. Either pH-sensitive and/or temperature-sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. Polymer solutions in water (sol phase) that transform into a gel phase on changing the temperature (thermo-gelation) offer a very exciting field of research.

Recent advances in the development of novel hydrogels for drug delivery applications have focused on several aspects of their synthesis, characterization and behaviour. Obviously, drug release from hydrogel networks is controlled by a complex combination of different mechanisms, such as matrix swelling, drug dissolution/diffusion and hydrogel erosion. Successful design of drug delivery systems relies not only on proper network design but also on precise description of hydrogel behaviour as well as mathematical modelling of drug release profiles. As more advanced release devices, such as in-situ forming hydrogels are developed more rigorous mathematical modelling approaches are needed to describe the complete mechanisms governing drug release from these systems.

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