Hydrogels: from controlled release to pH-responsive drug delivery

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Hydrogels are one of the upcoming classes of polymer-based controlled-release drug delivery systems. Besides exhibiting swelling-controlled drug release, hydrogels also show stimuli-responsive changes in their structural network and hence, the drug release. Because of large variations in physiological pH at various body sites in normal as well as pathological conditions, pH-responsive polymeric networks have been extensively studied. This review highlights the use of hydrogels (a class of polymeric systems) in controlled drug delivery, and their application in stimuli-responsive, especially pH-responsive, drug release.

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▼ The design of a drug delivery system is usually based on the drug's physicochemical and pharmacokinetic properties. Conventional delivery systems suffer from the limitations of minimal synchronization between the required time for therapeutically effective drug plasma concentrations and the actual drug-release profile exhibited by the dosage form. An increased understanding of the concept of chronopharmacokinetics and variations in disease symptoms because of diurnal rhythms has upraised the importance of drug delivery systems mimicking the symptomatic requirement of disease [1]. These considerations have shifted the focus of pharmaceutical scientists towards idealized drug delivery, wherein the required amount of active agent is made available at the desired time and site of action in the body.

Hydrogels have emerged as a promising option in this regard. The existence of hydrogels dates back to 1960, when Wichterle and Lim first proposed the use of hydrophilic networks of poly(2-hydroxyethyl methacrylate) (PHEMA) in contact lenses [2]. Since then, the use of hydrogels has extended to various biomedical [3] and pharmaceutical [4] applications. In comparison to other synthetic biomaterials, hydrogels resemble living tissues closely in their physical properties because of their relatively high water content and soft and rubbery consistency. Hydrogels show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out of (drug release) hydrogels allows the possible use of dry or swollen polymeric networks as drug delivery systems for oral, nasal, buccal, rectal, vaginal, ocular and parenteral routes of administration.

Several terms have been coined for hydrogels, such as 'intelligent gels' or 'smart hydrogels' [5]. The smartness of any material is the key to its ability to receive, transmit or process a stimulus, and respond by producing a useful effect [6]. Once acted on, stimuli can result in changes in phases, shapes, optics, mechanics, electric fields, surface energies, recognition, reaction rates and permeation rates. Hydrogels are 'smart' or 'intelligent' in the sense that they can perceive the prevailing stimuli and respond by exhibiting changes in their physical or chemical behaviour, resulting in the release of entrapped drug in a controlled manner [7].

In the current niche of drug delivery technologies, hydrogels have made an irreplaceable space because of their unique characteristics. This review presents a brief introduction to hydrogels, their application for controlled drug delivery and their use as pH-responsive drug delivery systems.

Gels versus hydrogels

A common misinterpretation in polymer science is the use of the terms 'gel' and 'hydrogel' synonymously. As polymeric networks, both gels and hydrogels might be similar chemically, but they are physically distinct. Dorothy Jordan Lloyd aptly described gels as,

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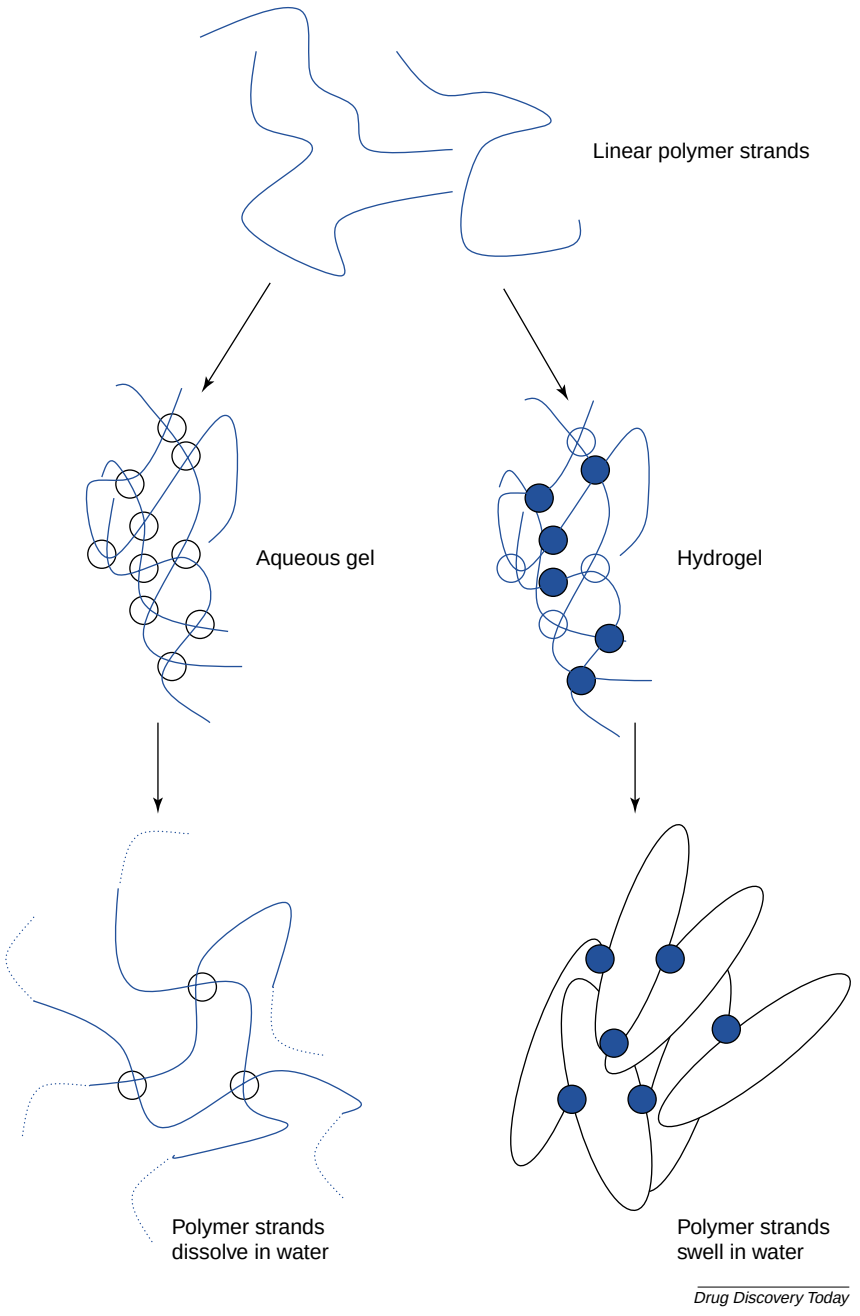

Figure 1. Polymer strands forming a gel and a hydrogel, showing different behaviour in an aqueous environment. Solid circles represent covalent cross-links and hollow circles represent virtual cross-links formed by entanglements.

'The colloidal condition, the gel, is one which is easier to recognize than to define' [8].

Technically, gels are semi-solid systems comprising small amounts of solid, dispersed in relatively large amounts of liquid, yet possessing more solid-like than liquid-like character [9]. Sometimes, hydrogels are also described as aqueous gels because of the prefix 'hydro'. Although the term 'hydrogel' implies a material already swollen in water, in a true sense hydrogels are a cross-linked network of hydrophilic polymers. They possess the ability to absorb large amounts of water and swell, while maintaining their three-dimensional (3D) structure [10]. This definition differentiates hydrogels from gels, which are polymeric networks already swollen to equilibrium, and the further addition of fluids results only in dilution of the polymeric network (Fig. 1). Although some of the gels are rigid enough to maintain their structure under a small stress, after exceeding the yield-value, gel fluidity is observed with loss of polymer structure. A hydrogel exhibits swelling in aqueous media for the same reasons that an analogous linear polymer dissolves in water to form an ordinary polymer solution. Thus, the feature central to the functioning of a hydrogel is its inherent cross-linking. Conventional gels can also develop small levels of cross-links as a result of a gain in energy under the influence of shear forces, but this is reversible because of the involvement of weak physical forces.

Because the basic framework of both gels and hydrogels is the polymer network, these polymers produce systems that span a range of rigidities, beginning with a sol and increasing to mucilage, jelly, gel and hydrogel [9]. Thus, hydrogel, sometimes referred to as xerogel, is a more rigid form of gel. Hydrogels are usually prepared to a measurable dimensional configuration. Sometimes, polymers such as Carbopol® (BF Goodrich Specialty Chemicals, Cleveland, OH, USA), are also referred to as hydrogels because of their cross-linked configuration. Although, these polymers exhibit swelling in an aqueous environment, at equilibrium their swelling contributes to a gain in solution viscosity, leading to aqueous gel formation.

Because polymeric systems are analogous to each other, several misrepresentations exist in their nomenclature, which can be prevented by a thorough understanding of their physical, chemical, mechanical and behavioural characteristics.

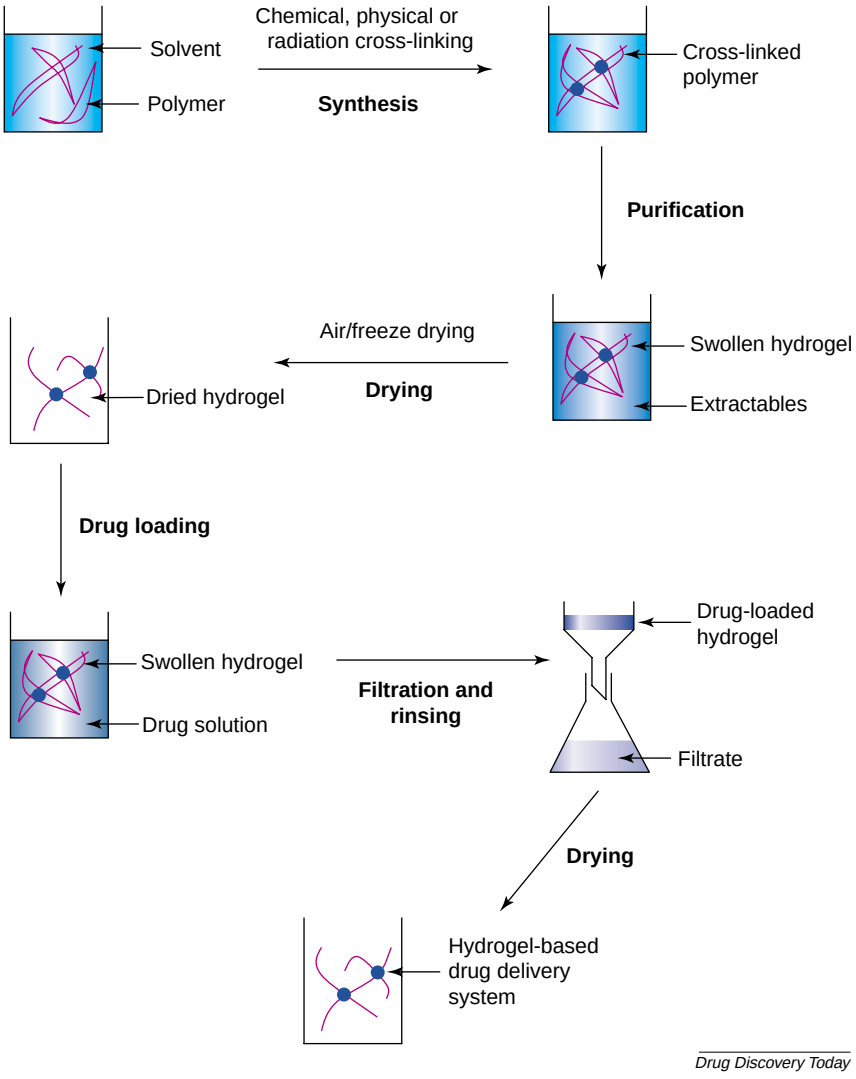

Figure 2. Schematic representation of the steps involved in preparation of a hydrogel-based drug delivery system.

Hydrogels: swelling-controlled drug delivery systems

A hydrogel is considered to be a polymeric material that has the ability to absorb >20% of its weight of water and still maintain a distinct 3D structure. The hydrophilicity of the polymer imparts water-attracting properties to the system. Their characteristic water-insoluble behaviour is attributed to the presence of chemical or physical cross-links, which provide a network structure and physical integrity to the system. Hydrogels are elastic in nature because of the presence of a memorized reference configuration to which they return even after being deformed for a long time [11]. In a true sense, hydrogels consist of polymers combined with water to create a solid with certain water-like properties, such as permeability for many water-soluble substances. Hydrogels are available in various structural and chemical forms, on which basis they have been broadly classified in the literature [12].

Traditionally, controlled release polymeric systems have been classified into 'matrix' and 'reservoir' types [13]. Matrix systems are most commonly employed because of their ease in development, cost-effectiveness and better performance. However, these systems tend to follow Higuchi's model, wherein drug release is proportional to the square root of time ($t^{1/2}$). This leads to non-uniform release rates, continuously decreasing in the beginning and more rapidly thereafter. The key benefit of hydrogels for controlled drug delivery lies in the near constant release rates [14].

Development of hydrogel-based drug delivery system

Preparation of hydrogel-based drug product involves either cross-linking of linear polymers or simultaneous polymerization of monofunctional monomers and cross-linking with polyfunctional monomers [15,16]. Further, the mechanical strength of poorly cross-linked hydrogels can be adequately enhanced by various methods [10]. Polymers from natural, synthetic or semi-synthetic sources can be used for synthesizing hydrogels. Usually, polymers containing hydroxyl, amine, amide, ether, carboxylate and sulfonate as functional groups in their side chains are used. A detailed list of various monomers and cross-linkers is available in the literature [10]. A stepwise methodology common to the preparation of hydrogel-based drug delivery systems is shown in Fig. 2 [10].

The design of hydrogel-based dosage forms depends on the route of administration. The synthesis of hydrogels usually involves cross-linking of polymers within a mould to impart the desired shape suitable for administration into the body. Different shapes of hydrogels developed for various routes of administration include:

- peroral route – spherical beads [17], cylinders [18] and discs [19];
- implants – drum-shaped [20], disc-shaped [21] and cylindrical preparations [22];

- rectal route – cylinders [23]; and
- vaginal administration – cylindrical [24] and torpedo-shaped devices [25].

The function of a hydrogel is central to its properties [8,10], namely equilibrium swelling, swelling kinetics, permeability and biocompatibility, which are characteristic for a particular polymeric network. A suitable way of characterization is required for efficient product performance and quality assurance of produced batches. Table 1 highlights some of the crucial characterization parameters for hydrogels and the methods used to measure them.

Table 1. Characterization parameters for hydrogels

Parameter	Techniques of measurement	Refs
Network pore size	Quasi-elastic laser-light scattering, electron microscopy, mercury porosimetry, rubber elasticity measurements, equilibrium swelling experiments	[30]
Cross-linking and mechanical strength	Ultimate compressive strength, change in polymer solubility with time	[42,55,57,58]
Drug distribution	Fourier transform infrared (FTIR) microscopy, scanning electron microscopy (SEM)	[59]
Drug diffusion	Membrane permeability, controlled release experiments, nuclear magnetic resonance, FTIR spectroscopy, SEM, quasi-elastic laser-light scattering	[30]
Degree of swelling	Dimensional changes with time, volume or mass degree of swelling, equilibrium water content	[10,17,60,61]

Drug-release mechanism

Most of the hydrogels are glassy in their dehydrated state, and drug release generally involves simultaneous absorption of water and desorption of drug via a swelling-controlled mechanism [26]. The rate-controlling factor mediating drug delivery is the resistance of the polymer to an increase in volume and change in shape [15]. A glassy hydrogel, on coming into contact with water or any other thermodynamically compatible medium, allows solvent penetration into free spaces on the surface between the macromolecular chains. When enough water has entered the matrix, the glass transition temperature of the polymer drops to the experimental temperature. The presence of solvent in a glassy polymer causes the development of stresses that are accommodated by an increase in the radius of gyration and end-to-end distance of polymer molecules, which is seen macroscopically as swelling. The movement of solvent molecules into the dry (glassy) polymer matrix takes place with a well-defined velocity front and a simultaneous increase in the thickness of the swollen (rubbery) region with time in the opposite direction. Such swelling and diffusion do not generally follow a Fickian diffusion mechanism. The existence of a slow macromolecular relaxational process in the swollen region is believed to be responsible for the observed non-Fickian behaviour [17]. Various approaches used for predicting these mechanisms are:

- fitting of release data with a power function of time [27];
- determination of various dimensionless parameters, such as Deborah number (D_{eb}) and swelling interface number (S_w) [28]; and
- moving boundary analysis of drug release from swellable polymers with constant or concentration-dependent diffusion coefficients, using microscopic imaging under polarized light [29].

Hydrogels: the stimuli-responsive drug delivery systems

The past few years have witnessed enormous advances in polymer-based controlled-release drug delivery systems. Several products displaying constant or decreasing release rates have progressed from the laboratory to the clinic in this short period of time. Most of these systems are therapeutically advantageous over conventional systems, but are insensitive to changing metabolic states in the body. To synchronize the drug-release profile with physiological conditions, mechanisms responding to physiological variations must be provided. An ideal drug delivery system should respond to physiological requirements, sense the changes and accordingly alter the drug-release profile. The symptoms of most of the disease states follow a rhythmic pattern and require drug delivery as per the rhythms. Above all, if the drug possesses some side effects, drug release when not required poses an extra burden on the body's metabolic system. Thus, drug delivery patterns need to be optimized for pulsed or self-regulated mechanisms.

Hydrogels can exhibit dramatic changes in their swelling behaviour, network structure, permeability or mechanical strength in response to different stimuli, both internal and external to the body [30]. Various stimuli that have been explored for modulating drug delivery are represented in Fig. 3 [7]. The mechanisms of action of these stimuli on structural changes in the polymer network and corresponding modulation in drug release have been well documented in the literature [6,7,31,32]. External stimuli have been produced with the help of different stimuli-generating devices, whereas internal stimuli are produced

within the body to control the structural changes in the polymer network and to exhibit the desired drug release.

Most of the time, drug release is observed during the swelling of the hydrogel. However, a few instances have been reported for drug release during syneresis of the hydrogel, as a result of a squeezing mechanism [33]. Another interesting characteristic about many responsive hydrogels is that the mechanism causing changes in network structure can be entirely reversible in nature. This imparts elastic deformability with 'shape-memory' behaviour so that hydrogels return back to their original shape at the end of triggering stimuli.

Much research has been directed towards single-stimulus-responsive hydrogels for drug delivery. This might not be advantageous in pathological conditions with more than one physiological stimulus present, where drug release is required in the presence of both stimuli rather than a single one. An interpenetrating network (IPN) of gelatin and dextran has been proposed as a dual-stimuli-responsive biodegradable hydrogel [34], wherein lipid microspheres (LM) have been incorporated as drug micro-reservoirs. The hydrogel prepared below the sol–gel transition temperature was found to release LM in the presence of both α-chymotrypsin and dextranase, whereas it hindered the release in the presence of either enzyme alone.

Table 2 summarizes various applications of stimuli-responsive drug delivery systems. Because of feasibility in therapeutic applications, product scale-up and cost considerations, internal stimuli-responding systems have gained wider attention compared with those governed by external stimuli. Among this category, the application and development of pH-responsive systems has been extensively studied for stimuli-responsive drug delivery.

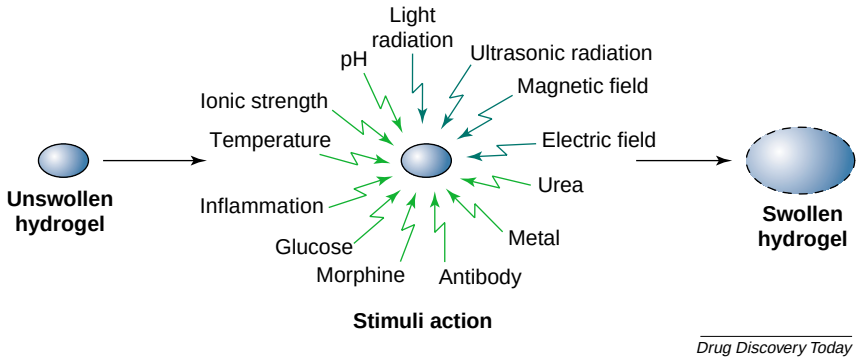

Figure 3. Stimuli responsive swelling of hydrogels.

Table 2. Stimuli-responsive hydrogels in drug delivery

Stimuli	Polymer	Drug	Refs
Magnetic field	Ethylene-co-vinyl acetate (EVAc)	Insulin	[62]
Ultrasonic radiation	EVAc, Ethylene-co-vinyl alcohol	Zinc bovine insulin, insulin	[7]
Electric field	Poly(2-hydroxyethyl methacrylate) (PHEMA)	Propranolol hydrochloride	[63]
Glucose	EVAc	Insulin	[64]
Urea	Methyl vinyl ether-co-maleic anhydride	Hydrocortisone	[65]
Morphine	Methyl vinyl ether-co-maleic anhydride	Naltrexone	[22]
Antibody	Poly(ethylene-co-vinyl acetate)	Naltrexone, ethinyl estradiol	[31]
pH	Chitosan–poly (ethylene oxide) (PEO)	Amoxicillin, metronidazole	[37]
	Poly(acrylic acid):PEO	Salicylamide, nicotinamide, clonidine hydrochloride, prednisolone	[19]
	Gelatin–PEO	Riboflavin	[66]
	PHEMA	Salicylic acid	[67]
	Poly(acrylamide-co-maleic acid)	Terbinafine hydrochloride	[68]
	N-vinyl pyrrolidone, polyethylene glycol diacrylate, chitosan	Theophylline, 5-fluorouracil	[69]
Temperature	Poly(*N*-isopropyl acrylamide)	Heparin	[70]
pH and temperature	Poly(*N*-isopropyl acrylamide-co-butyl methacrylate-co-acrylic acid)	Calcitonin	[45]

pH-Responsive hydrogels

Variations in pH are known to occur at several body sites, such as the gastrointestinal tract [35], vagina [36] and blood vessels, and these can provide a suitable base for pH-responsive drug release. In addition, local pH changes in response to specific substrates can be generated and used for modulating drug release. The pH-responsive drug delivery systems have been targeted for peroral controlled drug delivery [19,37], taste-masking of bitter drugs [38] and intravascular drug release during elevated blood pH in certain cardiovascular defects [21].

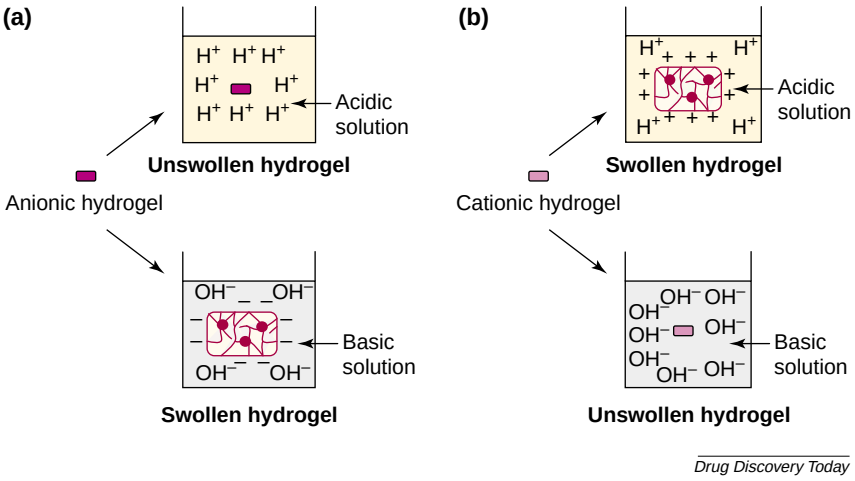

Figure 4. The pH-responsive swelling of **(a)** anionic and **(b)** cationic hydrogels.

Structural framework

pH-responsive hydrogels are composed of polymeric backbones with ionic pendant groups. Most commonly studied ionic polymers for pH-responsive behaviour include poly(acrylamide) (PAAm), poly(acrylic acid) (PAA), poly(methacrylic acid) (PMAA), poly(diethylaminoethyl methacrylate) (PDEAEMA) and poly(dimethylaminoethyl methacrylate) (PDMAEMA) [30]. In aqueous media of appropriate pH and ionic strength, the pendant groups ionize and develop fixed charges on the polymer network, generating electrostatic repulsive forces responsible for pH-dependent swelling or deswelling of the hydrogel [7], thereby controlling the drug release. Small changes in pH can result in significant change in the mesh size of the polymeric networks. Pendant groups of anionic hydrogels are un-ionized below and ionized above the pK_a of the polymeric network, leading to swelling of the hydrogel at a pH above the polymer pK_a because of a large osmotic swelling force by the presence of ions. The reverse is the case for cationic hydrogels, which swell at lower pH. Differential swelling of ionic hydrogels in acidic and alkaline buffers is presented in Fig. 4.

The effect of drug product size on its swelling kinetics has been favourably exploited for rapid response to changing environments. The development of chemically modified polyacrylamide-g-guar-gum-based anionic spherical hydrogels of micron size has been tried as pH- and ionic strength-sensitive drug delivery systems for diltiazem hydrochloride and nifedipine [39]. The micron-sized spherical hydrogels were found to respond rapidly to a changing environment.

Various polymeric networks have also been studied to exhibit pH-sensitive bioerodible properties [40]. An enzyme–substrate reaction (urease–urea reaction) was used to cause pH change that modulated the erosion of a pH-sensitive polymer (copolymer of methyl vinyl ether and maleic anhydride) containing hydrocortisone in dispersed form. Although the device had no therapeutic relevance, it established the feasibility of creating self-responsive drug delivery systems.

The pH-sensitive polymeric networks have also been devised for insulin delivery, wherein enzymes glucose oxidase and catalase were immobilized in a pH-responsive hydrogel of hydroxyethyl methacrylate-based copolymer, enclosing a saturated solution of insulin [20]. The pH-responsive swelling of the hydrogel is triggered by the diffusion of glucose into the hydrogel, which results in the enzyme-catalyzed conversion of glucose to gluconic acid, thereby lowering the pH in the microenvironment of the hydrogel, and causing swelling. A decrease in glucose concentration in response to the released insulin causes the hydrogel to contract and, therefore, decreases the rate of insulin delivery. Such a self-regulated drug delivery device enabled drug release to meet the physiological necessity of the body.

Apart from the use of synthetic polymers, various natural polymers, such as albumin [41] and gelatin [42], have also shown pH-responsive swelling behaviour. Under appropriate conditions of pH and temperature, the linear polymers form helices in regions stabilized by extensive hydrogen bonding. These helices function as cross-links holding the amorphous regions together. These proteins with minimal surface charge at their isoelectric point (p*I*) show extensive swelling at a pH away from their p*I* because of the development of high surface net-charge and increased electrostatic repulsive force.

Various studies have proposed a novel class of hydrogels that exhibit both pH- and temperature-sensitive swelling

behaviour. These materials could prove extremely useful in enzymatic applications and protein drug delivery. Hydrogels made of poly(*N*-isopropylacrylamide) PNIPAAm and PAA exhibited dual sensitivities [43]: PNIPAAm is reported for its temperature-sensitivity, whereas PAA and PMAA show pH-sensitive swelling. These hydrogels were able to respond rapidly to both temperature and pH changes. Kim *et al.* proposed their use for the delivery of insulin [44] and calcitonin [45], and Chen and Hoffman prepared new graft copolymers of PAA and PNIPAAm that responded more rapidly to external stimuli than previously studied materials [46]. Such systems were evaluated for prolonged mucosal delivery of bioactive agents, specifically peptide drugs. PNIPAAm and PMAA hydrogels have also been studied for pH- and temperature-responsive release of streptokinase and heparin [21]. The system provided control over the drug release in a pulsatile pattern with a high swelling ratio of hydrogel in the presence of both stimuli.

Factors influencing pH-responsive swelling and drug release

Major factors that influence the degree of swelling of ionic polymers include the properties of the polymer (charge, concentration and pK_a of the ionizable group, degree of ionization, cross-link density and hydrophilicity or hydrophobicity) and properties of the swelling medium (pH, ionic strength and the counterion and its valency) [32].

In addition to the above-mentioned factors, the nature of the buffering species has also been reported to affect the polymer swelling kinetics. Swelling equilibria [47] and swelling rates [48] of poly(methyl methacrylate-co-*N*,*N*-dimethylaminoethyl methacrylate) were found to be markedly affected by the nature of the buffer. Swelling in solutions buffered by weak organic acids was found to reach equilibrium in a few hours, compared with that in unbuffered media, which took weeks or months to reach equilibrium. At fixed pH and ionic strength, it was found that the extent of swelling in buffers with multivalent anions (citrate, phosphate, and so on) was lower than that in buffers with monovalent anions [47].

The effect of concentration of acidic buffering species on swelling rates of cationic hydrogels was studied in buffers of differing pK_a, concentration and pH [49]. Swelling rate was found to increase with an increase in pK_a and concentration of the buffering species, and a decrease in pH of the swelling medium. The study concluded that any change in solution that increases the un-ionized buffer concentration would increase the swelling rate. From this study, two major conditions for pH-sensitive swelling studies of hydrogels were identified. First, the pK_a of buffer should be below the pK_a of polymer amine groups, and second, the delivery of protons to fixed ionizable amines should be a rate-limiting step in hydrogel swelling. Thus, the specific buffer species and its concentrations used in pH-dependent swelling studies of ionic hydrogels need to be reported. Moreover, pH-sensitive swelling studies should be done under conditions mimicking the physiological environment. However, because of variation in buffer components at physiological sites caused by different biological factors, precise pH-sensitive rate control of drug release might limit the use of ionic hydrogels as rate-controlling carriers. However, these hydrogels could be useful as mediators of pH-triggered release at sites where precise rate control is of secondary importance.

A temporally controlled drug delivery system based on pH-oscillators coupled with membrane-diffusion properties has also been proposed [50]. By changing the pH of the solution relative to the drug's pK_a value, a drug could be rendered charged or uncharged. Because only the uncharged form of a drug is able to permeate biological membranes, a temporally modulated delivery profile could be obtained with a pH-oscillator in donor solution. Diffusion of benzoic acid and nicotine across an ethylene-co-vinyl acetate (EVAc) membrane was studied employing mixed Landoldt reaction species as a pH-oscillator.

Besides the properties of the polymer and swelling medium, the physical structure of the polymer network is a major contributor towards hydrogel swelling. While studying the pH-sensitive semi-IPN of chitosan and polyvinylpyrrolidone (PVP) for controlled release of amoxicillin [51], porous freeze-dried semi-IPNs (pore diameter 39.20 ± 2.66 μm) were found to exhibit superior pH-dependent swelling properties compared with non-porous air-dried semi-IPNS.

In an attempt to study the effect of drug solubility on migration through pH-sensitive hydrogels, the release of theophylline (slightly soluble in water) and metoclopramide monohydrochloride (highly soluble in water) was studied from cross-linked copolymers of 2-hydroxyethyl methacrylate and methacrylic acid [52]. Diffusivity of non-ionized drug was controlled by the swelling ratio of the polymer, whereas for ionized drugs a polymer–drug interaction reduced the drug diffusion.

The release of ionic drugs of varying molecular weights from poly(2-hydroxyethyl methacrylate-co-acrylic acid) hydrogels has been extensively studied [53]. Various parameters affecting the transport of drugs and proteins through these hydrogels were taken into consideration. The experimental results were compared with a free-volume-based theory and a deviation was observed because of interaction between the ionized backbone chains and pendant acid groups. According to the free volume approach, a molecule

Table 3. Hydrogel-based products on the market

Product	Manufactured by/ marketed by	Hydrogel composition	Indication	Remarks	Reference
SQZ Gel™ oral controlled release system	Macromed (Sandy, UT, USA)	Chitosan and polyethylene glycol	Hypertension	pH-Sensitive, once-a-day tablet of diltiazem hydrochloride	http://www.macromed.com
Hycore-V™ and Hycore-R™	CeNeS Drug Delivery (Irvine, UK)	–	Vaginal and rectal infections, respectively	Localized delivery of metronidazole	http://www.cenes.com
Cervidil® vaginal insert	Controlled Therapeutics, UK; marketed by Forest Pharmaceuticals (St Louis, MO, USA)	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening at or near term	Product contains 10 mg dinoprostone (PGE2) abd exhibits *in vivo* release rate of ~0.3 mg h^{-1}	htt://www.btgplc.com
Moraxen™	CeNeS Pharmaceuticals; marketed by Schwartz Pharma (Monheim, Germany) and Amarin Corporation (London, UK) in UK and Eire, and Bioglan Pharma (Hitchin, UK) in the rest of Europe	–	End-stage cancer pain	Once-daily rectal slow-release product of morphine sulfate	http://www.cenes.com
Smart Hydrogel™	MedLogic Global (Plymouth, UK)	Poly(acrylic acid) and poly (oxypropylene-co-oxyethylene) glycol	Used for development of ophthalmic, buccal, nasal, vaginal, transdermal, injectable, implantable, and non-aerosol pulmonary drug delivery systems	Mucoadhesive liquid composition that undergoes sol–gel transformation at body temperature, can be tailored for stimuli-responsive drug delivery	http://www.medlogic.com
Aquamere™	Hydromer (Somerville, NJ, USA)	Interpolymers of PVPand PVP--grafted copolymers with urethane	Skincare, topical and oral drug delivery	–	http://www.hydromer.com
Aquatrix™ II	Hydromer	Chitosan–PVP	Skin adhesive gels, wound and burn dressings, implants, and drug delivery matrices	–	http://www.hydromer.com
Hypan®	Hymedix International (Dayton, NJ, USA)	Hydrophilic acrylate derivatives with a unique multiblock structure	Used in the manufacture of soft contact lenses, and moisturizing wound gels and dressings	–	http://www.hymedix.com

is supposed to pass across the available mesh area during swelling of the hydrogel. The solute radius to pore radius ratio was not applicable in the case of polymeric networks in which chain fluctuations alter the pore or mesh size. Peppas and Barr-Howell measured free volume for transport in terms of equilibrium volume, degree of swelling, the molecular weight between cross-links or the mesh size [54].

Drug release pattern

The pH-responsive drug release can be designed in a monophasic or pulsatile pattern. Peroral controlled delivery requires uniform drug release with an increase in pH gradient in different segments of gastrointestinal lumen. Albumin cross-linked 1-vinyl-2-pyrrolidinone hydrogels were studied for their swelling behaviour at different pH values [55]. Swelling of the hydrogel was found to increase markedly above pH 7.0, thus correlating with the maximal transit time of the drug delivery system through the intestines. In another study, the PAA–poly(ethylene oxide) (PEO) IPN was found to exhibit variations in its swelling behaviour with a gradient increase in the pH of the swelling medium (pH 1.2 for two hours, pH 6.8 for the next two hours, followed by pH 7.4 for further time intervals) [19].

A pulsatile pattern of drug release is required in disease states exhibiting a rhythmic pattern. Pulsatile systems for localized delivery of heparin and streptokinase, based on a poly(*N*-isopropyl acrylamide-co-methacrylic acid) hydrogel, were assessed for their swelling behaviour in response to pulses in temperature and pH [21]. The weight:swelling ratio was found to respond quickly for variations in temperature from 33°C to 36°C and in pH from 5.7 to 5.3.

Hydrogels are not homogeneous in their structure. The presence of more than two phases (swollen and collapsed) has been reported in hydrogels consisting of copolymers of randomly distributed positively and negatively charged groups [56]. In these hydrogels, polymer segments interact with each other through attractive or repulsive electrostatic forces and hydrogen bonding. Combination of these forces seems to result in the existence of several phases, each characterized by a distinct degree of swelling, with abrupt changes. Hence, such a system can be used for multi-phased drug delivery.

Marketed hydrogels

Attempts are being made in several laboratories to facilitate the entry of hydrogel-based products into the market. Application of hydrogels is not restricted to just drug delivery, but various biomedical applications of hydrogels include their usage in soft contact lenses, surgical implants, breast implants, surgical catheters, suture coatings, wound dressings, absorbents, hybrid organs, biosensors, and so on [3,12,30]. Even after so much research on hydrogels for drug delivery, there have been few commercially successful hydrogel-based drug delivery systems. Most of them are over-the-counter dressings and surgical aids. The majority of hydrogels that has met with commercial success have trademarks, are registered products or are patent protected. A brief review of some of the hydrogels that have gained commercial value with time is shown in Table 3. The information might not be exhaustive, but is an indication of the market success of hydrogels.

Conclusion

Drug delivery has undergone a revolutionary advancement in the past few years. With the advent of novel delivery systems, various drug molecules have been revived of their therapeutic and commercial benefits. The introduction of stimuli-responsive systems has further strengthened the link between therapeutic need and drug delivery. A lot of research is ongoing in various laboratories to explore stimuli-responsive hydrogels as drug delivery systems for better patient care. The success of hydrogels as delivery systems can be judged by several marketed preparations. In the present scenario, the major considerations during the formulation of hydrogel-based drug products are their mechanical strength and response-time in a physiological environment. Fast-responding hydrogels releasing maximal drug in less time while maintaining the structural integrity in a biological system will be the more appreciated delivery systems. Moreover, a high level of *in vitro–in vivo* correlation in their performance will determine their future success. The exploitation of these polymeric networks for improved therapeutic efficacy will open newer arenas in drug delivery.

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