Review

Recent advances in smart hydrogels for biomedical applications: From self-assembly to functional approaches

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ABSTRACT

This review discusses basic aspects used to control the architecture and functional properties of smart hydrogels. The introduction briefly outlines what has been accomplished regarding smart hydrogels and explores historical aspects and the fundamental understanding of these systems. Then, a short discussion on the chemical interactions and the main variables involved in architectural construction is exhibited. Further analysis provides the basis for optimizing biological responses through system modulation. Finally, we outline perspectives and challenges for building smart hydrogels into functionalized and modulated delivery systems.

1. Introduction

The development of hydrogels as functional biomaterials has revolutionized the field of study concerning responsive materials. Initially, hydrogels were developed for biomedical applications, especially tissue scaffolds and contact lenses [1]. In the late 19th century, hydrogels were first described as colloidal gels from inorganic salt. Around the middle of the 20th century, Wichterle and Lim termed them as water-swollen crosslinked polymeric network(s) [2,3]. Currently, hydrogels can be defined as three-dimensional networks of hydrophilic polymers. These systems have the ability to swell and absorb large amounts of water or biological fluids without losing their structure [4–6]. Their capacity to absorb liquid is due the presence of hydrophilic compounds attached to the polymer chains, such as amid, amino, carboxyl and hydroxyl groups, which are able to ionize in the presence of water. Furthermore, their physical properties, such as swelling, surface characteristics and mechanical strength, can be modulated by physicochemical reactions to improve elasticity and mechanical resistance, which are important features to considered when developing delivery systems [3,7,8].

The most common terms associated with hydrogels are: ocular lens, wound healing [9], super-absorbents [10], tissue engineering, tissue scaffolds, cell immobilization [11] and drug delivery systems [12]. The number of publications reported in the Science Direct database involving hydrogels, containing such keywords, over the last ten years showed exponential growth, including books, journal articles and reference works (Fig. 1). Although this popularity can be observed for all aforementioned subjects, tissue engineering and drug delivery standout since they represent the majority of the publications. Remarkable, nonetheless, is the similar increase of studies regarding tissue scaffolds, tissue engineering, wound healing and drug delivery.

Since 2000, the number of publications involving the term 'hydrogels' expanded notably [13]. In parallel, the wide applicability of hydrogel as functional materials has attracted great interest among researchers and several industry segments [14].

Unlike conventional hydrogels, which exhibit swelling/deswelling properties linked to water availability, smart or stimulus-responsive hydrogels are the most promising materials because of their additional properties. These types of hydrogels are most often related to the physical, chemical and biological fields [13,15,16] and their unique properties can be associated with environmental factors, such as external stimuli that promotes a change in organization.

Although the first studies related to hydrogels appeared in 1894, the word "smart" was introduced in 1948 by Kuhn and co-workers [17]. This most recent nomenclature gained importance because they are capable of exploitation based on specific triggers (stimuli) to induce changes in structure and function [3]. The first publication reported was on poly(acrylic acid) polymer molecules that could undergo structural adjustments according to the media pH [18]. At the same time, publications reported such profiles for different polymeric networks including the pioneering smart hydrogels [18–21]. This drug delivery concept is denominated as "smart" because it can detect prevailing stimuli and respond through structural, morphological or functional changes resulting in the release of entrapped drugs in a controlled manner [22].

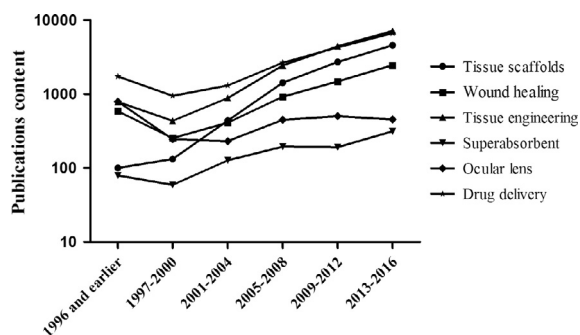A set of criteria has been used to classify these systems, including

Fig. 1. Summary of the content found related to common terms in the Science Direct database. Publications include journal articles, books and reference works. Research conducted in September 2017.

origin (natural or synthetic), degradability and cross-linking mechanisms for self-assembly. Chemically cross-linked hydrogel networks are generated by covalent bounds between polymer chains resulting in permanent junctions [3]. On the other hand, physically cross-linked structures are designed through supramolecular forces (noncovalent) forming rapid and reversible networks, a feature that we are particularly interested in [2]. Smart hydrogels can be classified by several criteria. Publications focused on drug delivery have primarily considered external types of stimuli. Responses can be induced by physical or chemical stimuli. The first type includes: pressure, light, temperature, and magnetic or electric fields. Chemical or biochemical stimuli include ionic strength, pH and ions. Complementing these factors, punctual molecular events, chemical or biological species availability can also be explored [7,8,13]. Moreover, these systems can be designed to respond a multiple stimuli listed above [21].

Many reviews have been reported to introduce the field of stimuli responsive hydrogel systems, although a large portion of these publications focused only on applications. The present review focuses on the basic concepts and responsivity mechanisms guided by dynamic interactions that provide valuable tools for designing smart hydrogels for functional approaches.

2. Self-assembly for designing smart hydrogels

Supramolecular chemistry is defined as the chemistry beyond the molecule. This field has evolved by engaging the fundamental and applied aspects of supramolecular interaction manipulation [23,24]. Although a major focus has been on physical interactions (e.g., hydrophobic, hydrogen bond and electrostatics), the dynamic nature of supramolecular chemistry makes it applicable to the development of smart hydrogels. In this sense, not only non-covalent links but also dynamic covalent bonds can be explored in tailoring stimuli-responsiveness [25–27]. Smart hydrogels might self-assemble by establishing supramolecular interactions such as ionic bonds, weak physical entanglements, and hydrogen bonds. However, covalent chemical links may also be used to obtain the same results [28]. The self-assembly of highly organized macromolecular systems nanostructured by dynamic interactions has been strongly explored in drug delivery systems [2].

Their dynamic nature is an essential feature for the practical design of responsive systems. Therefore, it is mandatory to understand the concept of the dynamics in order to associate its meaning with hydrogels categorized as "smart". The static behavior of conventional hydrogels *versus* the dynamic behavior of smart hydrogels are two extremes of behavior that can significantly affect the performance of drug delivery systems (Fig. 2). This paradigm shift that contrasts the static and dynamic nature of materials has been clearly identified in hydrogel designs. Thus, traditional static hydrogels designed as bioinert materials have been replaced by dynamic systems that incorporate sophisticated functions [29,30].

The physicochemistry behind the supramolecular interactions and

the dynamic covalent bonds are of primary importance to the synthesis steps and performance of biological systems. By manipulating the factors involved in these links, we control the structural properties of the final system. In this context, many supramolecular and dynamic covalent bonds have been explored through the advent of smart hydrogels, as summarized in Table 1.

The development of hydrogels based on supramolecular and dynamic covalent chemistry enables the biological functions that are impossible to achieve by static links. The modulation of drug release from delivery systems, self-healing and tissue adhesiveness are some of the interesting functions that can be tailored by controlling the system properties during the synthesis procedure [39,40]. The dynamics of smart hydrogels can be designed to respond to a physical, chemical or biological stimulus. Upon receiving these external inputs, the hydrogel undergoes a structural/morphological property change, which leads to the desired outcomes. This off-on transition is ultimately responsible for achieving the biological function. Expected responses can be manifold and include degradation, drug release, swelling, changes in shape or surface, conformational modifications or micellization [41].

The final morphology expected for the hydrogel is associated with a series of variables, which primarily includes the synthesis or treatment procedures of the original polymer, monomer composition and their ratios, and the crosslinking method [42].

Polymer science and drug delivery together represent most of the active branches in the development of therapeutics [43]. In drug delivery systems, pharmaceutically active compounds are loaded into a hydrogel, which is then administered to the body where the drugs are released in a sustained manner for periods ranging from several days to several months. Furthermore, introduction or association of the drug to the polymeric pattern can provide a passive function as a drug carrier, alter the degradation process, or minimize immunogenicity and toxicity, in addition to possibly increasing circulation time [41]. Therefore, the frequency of drug administration can be decreased and peak concentrations can be avoided, reducing potentially harmful side effects. Alternatively, hydrogels are used specifically to deliver its content to the target area. Therefore, the hydrogel structure might protect drugs from hostile environments and control drug release by changing the gel structure in response to environmental stimuli.

To further reflect on these systems, the following section will outline different classes of smart hydrogels and their specific features, including functional groups and factors involved in responsiveness. Furthermore, selected comprehensible examples in drug delivery will be given, and, to conclude, a brief outlook of future perspectives will be addressed.

2.1. Thermo-responsive hydrogels

Thermo-responsive hydrogels are one of the most studied classes of stimuli systems in tissue engineering and drug delivery research, as medium temperature may fluctuate in physiological and pathological conditions. These hydrogels, composed mainly of natural and synthetic polymers with balanced hydrophilic and hydrophobic groups in their chains (Table 2) are characterized by their ability to undergo reversible modifications as volume changes. They also swell or de-swell in response to a critical temperature, which causes a sudden change in the solvation of their molecules, conformational state and, consequently, water-solubility [41,44–47].

Thermo-responsive hydrogels can be divided into two groups according to their behavior with the surrounding solvent molecules. Extensively studied, lower critical solution temperature (LCST) hydrogels exhibit non-linear responses, where the polymer's solubility decreases as the temperature increases, leading to the formation of a more structures gel. The second type, upper critical solution temperature (UCST) systems, on the other hand, become soluble upon heating.

For the LCTS hydrogels, at lower temperatures, the water molecules are arranged around the polymer, establishing hydrogen-bonds with the
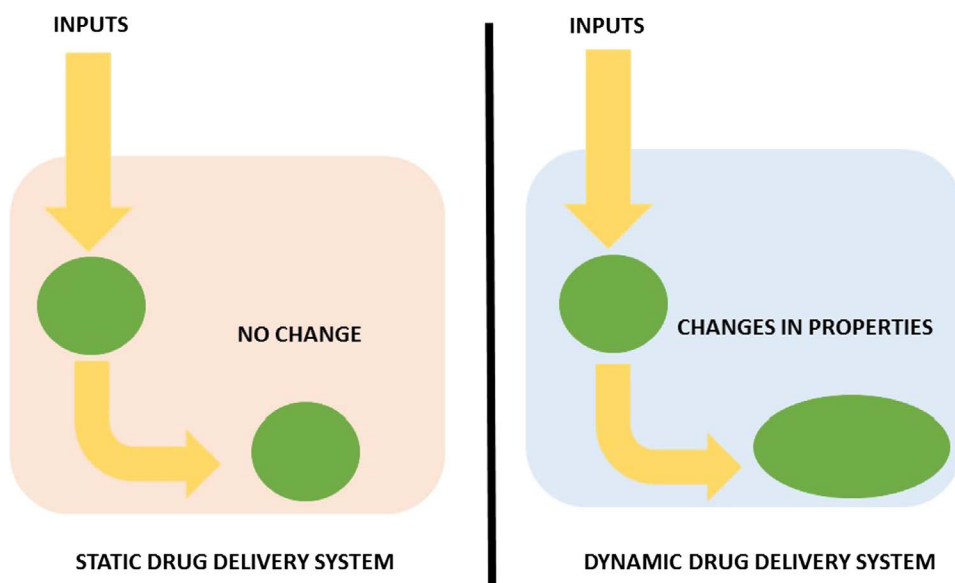
hydrophilic groups of the structure, resulting in a small change in enthalpy and, consequently, low entropy. However, the increase of environmental temperature reduces the energy associated to the water-polymer interaction, allowing an increase in the energy associated to the polymer-polymer interaction. Consequently, the change in enthalpy increases. To maintain the change in Gibbs free energy low and to compensate this increase in the enthalpy term (ΔH), water molecules dissociate from the polymer and the entropy increases. Thus, the polymer dehydrates, transforming itself into a more hydrophobic structure and, lastly, causing phase separation (Fig. 3) [48].

The value of the critical temperature point usually depends on the molecular weight of the polymer, which is lower for longer polymers or for the hydrogen-bonding capabilities of constituent monomer units [49–51].

Typical synthetic polymers used to develop LCST systems are poly(N-isopropylacrylamide) (PNIPAM), poly(N,N-diethyl acrylamide) (PDEAM), poly(methylvinylether) (PMVE), poly(N-vinylcaprolactam) (PVC), copolymer blocks of poly(ethylene oxide), known as Pluronics® and Tetronic®, and poly(pentapeptide) of elastin.

LCST polymers display critical temperature transitions when exposed to a wide range of temperatures, however, biomedicine is more interested in those able to respond at 30–37 °C, close to the body temperature (Table 3). PNIPAM and PDEAM have similar transition temperatures and are the most commonly used polymers in thermo-responsive hydrogel development. For PDEM, the LCST is influenced by polymer tacticity, i.e., the regularity in the arrangement of side groups. On the other hand, for PNIPAM, the transition temperature can be influenced by molecular design with changes in the hydrophilic/hydrophobic balance which is independent of the polymer concentration and molecular weight. The PNIPAM response against increases in temperature (from 32 to 35 °C) was first described by Heskins and Guillet, generating a particular interest in drug delivery systems design, especially due to its biocompatibility compared to PDEAM [52–54].

PMVE is a water soluble LCST polymer which displays temperature transition at exactly 37 °C, making it very interesting for pharmaceutical and biomedical applications. At this temperature, the hydrogen bonds are disfavored and polymer-polymer interactions are favored, promoting the aggregation of PMVE molecules.

Dispersed PMVE can be crosslinked with electrons or γ-rays. This physically produced hydrogel behaves similarly to supramolecular systems, swelling at temperatures below and shrinking at temperatures above the LCST. These systems exhibit a discontinuous temperature-dependent swelling behavior, in which concentration might represent

one of the limitations of the system [52,55].

PVC, another LCST polymer, has interesting properties to be used in medical devices and in implant development, such as water solubility, biocompatibility, high swelling, transition temperature at 33 °C and low cost [52,55,56]. Copolymer blocks of poly(ethylene oxide) and poly(propylene oxide) sequences are a class of commercial polymers marketed as Pluronics®, or Poloxamer, and Tetronics®. These polymers exhibit transition behavior when temperatures are close to the physiological temperature (37 °C), and, because of this, they are extensively used as drug delivery systems and injectable devices for tissue engineering processes. Pluronics® and Tetronics® have an amphiphilic character, and gelation occurs by 3-dimensional packing of the polymer molecules in micelles due to hydrophilic-hydrophobic balance. The LCSTs of hydrogels composed by Poloxamer® and Tetronics® are mainly dependent on their concentration and can be modulated by incorporating different side chains with hydrophilic or hydrophobic segments [44,52]. These synthetic polymers are very useful, but one of their limitations is their non-biodegradability and, for some applications as drug delivery systems, this feature is indispensable.

Despite presenting higher transition temperatures, some natural polymers such as cellulose derivatives, chitosan and gellan gum hold a good biodegradability and can be used to develop thermo-responsive hydrogels. After water dispersion and heating, most of these natural polymers form a gel phase when the temperature is lowered. Cellulose derivatives such as methylcellulose and hydroxypropyl methylcellulose (HPMC) are soluble in water at low temperatures, but after heating at 40 °C and 70 °C, respectively, they form opaque gels (Table 3). The gelation of these polymers is primarily caused by hydrophobic interactions between molecules containing methoxy substitutes. At low temperatures, chains are solvated, and polymer-polymer interactions are disfavored. However, when the temperature is raised, polymer molecules lose their hydrating water, which results in a strong interaction between polymers chains and, consequently, increased viscosity. For physiological applications, these transition temperatures are not applicable, but some strategies can be used to decrease the LCST. Incorporating NaCl decreases the methylcellulose transition temperature to 32–34 °C, and the molar substitution of HPMCP can lower the LCST to 40 °C [49,57–59].

Chitosan (CH), a chitin deacetylated derivative, is a natural cationic biocompatible biodegradable and low-cost polymer composed of D-glucosamine and N-acetyl-D-glucosamine linked by beta (1,4)-glycosidic bonds. CH is soluble in solvents with pH values below 6.0, and because of this, the gelation of CH solutions is pH dependent. However, CH

Table 1
Supramolecular and dynamic covalent bonds explored through the advent of smart hydrogels.

	System	Investigated factors	Remarks	Reference
Supramolecular interactions	Chitosan/tripolyphosphate crosslinked by an electrostatic hydrogel	Chitosan, tripolyphosphate and sodium chloride concentration	Homogeneity and mechanical properties were modulated by concentrations of the components	[31]
	Thermo- and pH-responsive hydroxypropylcellulose-g-acrylic acid and poly(acrylic acid)	Composition ratio	Biodegradability and composition ratio were controlled by changing the composition ratio	[32]
	Thermosensitive chitosan/glycerolphosphate hydrogel	Urea and isobutanol concentration	Gelling and mechanical properties were tuned by manipulating hydrogen bonds and hydrophobic interactions	[33]
Dynamic covalent bond	Disulfide-crosslinked albumin hydrogel	Concentration of serum albumin and pH of the medium	Increased albumin concentration increased hydrogel stability, rheological properties, compressive strength, proteolytic resistance and rate of *in vivo* biodegradation	[34]
	Disulfide-crosslinked hyaluronan hydrogel	Ratio between the polymer and crosslinker	Mechanical and swelling degree were controlled	[35]
	Hydrozone-crosslinked-hyaluronan hydrogel	Type of hydrozone crosslink	Tuning of the charge distribution over hydrazine moieties increased the stability of hydrazine bonds in hydrolysis	[36]
	Phenylboronic acid-modified hydrogel	Type of phenylboronic acid (PBA)	Type of PBA affected the reaction kinetics with glucose	[37]
	Imine-crosslinked hydrogel	Type of hydrazide group	Degradation characteristics were modulated in response to the structure of the hydrazide group	[38]

polymer dispersion can become thermo-responsive by adding a polyol salt to the solution. In this case, at body temperature, CH chains lose their hydrating water and the polyol salt facilitates the interaction between side groups, such as hydrogen bonding, electrostatic interactions and hydrophobic interactions. Thus, CH hydrogels have become valuable tools for cartilage repair [49].

Gellan gum (GG) is a hydrophilic and anionic exopolysaccharide composed of repeated units of glucose, glucuronic acid, rhamnose (at a 2:1:1 molecular ratio) and two acetyl substituents, acetate and glycerate, which are linked to glucose residue adjacent to the glucuronic acid. GG is biocompatible, biodegradable and can originate hydrogels at low concentrations. Upon heating, these polymer solutions adopt a random coil conformation. Then, when temperature decreases, the chains adopt a double-helical conformation with ordered junction zones, resulting in a three-dimensional network. These characteristics make GG an interesting material for pharmaceutical applications [49,60–64].

Hydrogels composed only of natural polymers have limited responses at physiological temperature. On the other hand, synthetic polymers show very fast responses, forming structured hydrogels. However, it is necessary to be aware that biocompatibility and good biodegradability are often essential for biological use. Therefore, the association of natural and synthetic polymers can contribute to forming material with the desired properties for specific biological application.

From 2005 to 2010, 330 publications per year included LCST, while only 44 per year were addressed UCST. The main reason for this disparity is based on the fact that most UCST polymers have a transition temperature below 25 °C, which makes them infeasible for pharmaceutical and medical product development. Moreover, the biodegradability of this polymer class has not yet been proven. The UCST group is composed of acrylamide (AAm) and acrylic acid (AAc) derivatives, such as poly-3-dimethyl(methacryloyloxyethyl) ammonium propane sulfonate (PDMAPS) and poly(3-[*N*-(3-methacrylamidopropyl)-*N*,*N*-dimethyl]ammoniopropane sulfonate (PSPP), and zwitterionic polymers. Their use as UCST is dependent on their concentration in solution and ranges from 32 °C at 0.1% (w/v) to 15 °C at 8% (w/v).

Several polymers can be included in both UCST and LCST classes, e.g., poly(ethylene oxide) (PEO), which shows a loop-shaped miscibility gap with UCST > LCST. The temperature transition of PEO is influenced by ionic strength and chemical crosslinking by radiation. PEO is non-biodegradable, thus its toxicity is a concerning point [65,66].

Thermo-responsive hydrogels usually exhibit a pressure sensitivity response, in which the degree of swelling is influenced by hydrostatic pressure near the LCST. PNIPAM, discussed earlier, has an increased degree of swelling under increased pressure [47]. The behaviors described for LCST and UCST systems are not restricted to aqueous environments, but only aqueous systems are of biomedical interest.

Among the many applications of thermo-responsive hydrogels, their use in tissue engineering stands out most. Tan and co-authors (2009) synthesized a PNIPAM conjugated with hyaluronic acid using a thermoradical polymerization method. They observed an LCST for this hydrogel near to 30 °C, which formed a structured and porous hydrogel able to encapsulate adipocytes and resist enzymatic activity. Based on a preliminary *in vivo* study, the authors demonstrated the usefulness of *in situ* PNIPAM-hyaluronic acid hydrogel as an injectable system for adipose tissue engineering [67]. Several applications are also highlighted by the authors, including the development of drug delivery systems. Gao and contributors (2005) developed PNIPAM nanocapsules with temperature-tunable diameters and permeability by precipitation polymerization. In this work, they were able to effectively control the release of a fluorescent compound. At the LCST (32 °C), the nanocapsules shrunk, and the release of the compound, from its internal cavity, was inhibited [68].

PMVE, as previously described, can be used in the development of drug delivery systems that respond to body temperature. Arndt and co-authors (2001) synthetized a thermo-responsive micro-hydrogel by

Table 2
Molecular structure of thermo-responsive polymers.

Polymer	Molecular structure
Poly(N-isopropylacrylamide) - PNIPAM	
Poly(N,N-diethylacrylamide) - PDEAM	
Poly(methyl vinyl ether) - PMVE	
Polyvinyl Chloride - PVC	
Pluronic®	
Tetronic®	
Gelan Gum	
Methylcellulose	
Hydroxypropyl methylcellulose	
Chitosan	
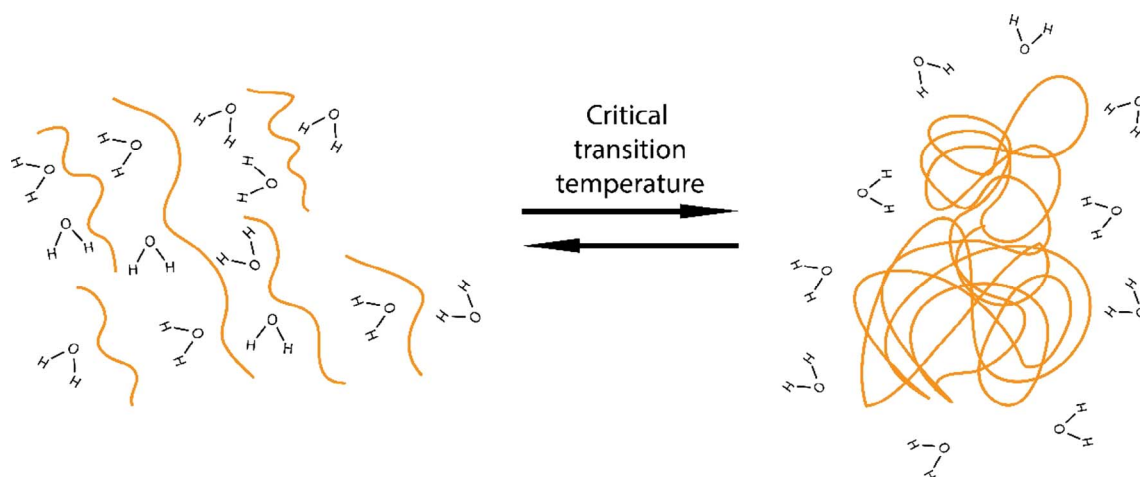
Fig. 3. Schematic illustration of LCST hydrogel behavior.

Table 3
Phase transition temperatures for polymers with LCST and UCST behavior.

Polymer	Transition temperature (in water)
PNIPAM	30–34 °C
PDEAM	32–34 °C
PMVE	37 °C
PVC	30–50 °C
Pluronic® and Tetronic®	30–40 °C
Gellan gum	50–60 °C
Methylcellulose	40 °C
HPMC	70 °C
AAm and AAc	15–25 °C

using radiation. Their system consisted of microparticles that stayed in a swollen state under the LCST and rapidly shrunk near 37 °C, forming compact spheres with pores for liquid diffusion and drug release [69].

Poloxamer® is very useful synthetic polymer with LCST, used in skin devices for drug release, for example. Pillai (2003) studied a gel formulation using poloxamer 407 for transdermal insulin delivery. The properties of this hydrogel were evaluated by *ex vivo* and *in vivo* skin permeation studies in rats with a chemical enhancer and/or iontophoresis. They demonstrated that the Poloxamer® hydrogel was physically and chemically stable during the storage period and that modulate insulin release and permeation through the skin is possible, reaching an effective plasma concentration when applying an electric current [70].

Regarding natural polymers, injectable CH and glycerophosphate hydrogels were described by Chenite and co-workers (2000). These authors found that, below room temperature, these formulations are liquid which permits encapsulation of living cells and therapeutic proteins. At body temperature, however, they are able to form monolithic gels. *In vivo* tests showed that liquid formulations were converted into gel implants *in situ*. Thus, this system could be successfully used to deliver biologically active growth factors as well as an encapsulating matrix for living chondrocytes applicable in tissue engineering [71].

2.2. Light-, electric- and magnetic- responsive hydrogels

Electric, magnetic fields, and light exposure are the main external physical stimuli used to tune drug release kinetics from smart hydrogels. Once these exogenous stimuli can be controlled, they have the advantage of modulating drug release spatially and temporally [72–80].

Among the given classes of light-responsive systems, the stimulus source used can be derived from visible, near infrared (NIR) or ultraviolet (UV) light. There are two types of UV light responsivity: photopolymerization and photocleavage systems.

Photopolymerization consists of the gelification process of a liquid polymeric formulation to obtain a hydrogel system. Although it has been used as one stage in hydrogel synthesis, photopolymerization can also be used to induce *in situ* gelation [81–85]. In order to occur photopolymerization, photoinitiators, such as benzoin derivatives, benziketals acetophenone, and hydroxyalkylphenones, must interact with visible or UV light to form free radicals [86,87]. Another approach is the functionalization of hydrophilic polymers with photosensitive molecules, such as cinnamate, coumarin, or benzyl diethyldithiocarbamate, which are able to undergo intermolecular photodimerization after UV light exposure [88–90].

Nitrocinnamate-derived polyethylene glycol (PEG-NC) *in situ* hydrogels were developed for fibroblast growth factor (bFGF) incorporation. UV light (365 nm) was used to promote photo-crosslinking of PEG-NC. The cross-link density and the degree of swelling were influenced by the UV exposure time, modulating the drug release profile [82].

On the other hand, the main principle of the photocleavage for light-responsive hydrogels is based on the use of cross-linkers that exhibit photosensitivity (e.g., *o*-nitrobenzyl derivatives and azobenzene). These molecules, after exposure to light, undergo either photoisomerization or photooxidation, which lead to changes in the hydrogel matrix structure and, consequently, in drug or biomolecule release [74,91–94]. Irradiation with UV light at long wavelengths (365 nm) or visible light (400–500 nm) leads to irreversible photoisomerization of the *o*-nitrobenzyl ether group. However, some differences in the absorbance and quantum yield of this photosensitive crosslinking agent at different wavelengths, result in different degradation rates. Therefore, the choice of wavelength can be very important to control the release of drugs from this responsive system [74].

It is important to note that UV light holds some disadvantages when used as a physical stimulus for smart hydrogel drug delivery. UV has poor penetration into some body parts, and it can be potentially carcinogenic, especially under long-term exposure [80,95,96]. One of the strategies used to overcome these problems is adopting smart hydrogels containing up-converting nanoparticles (UCNPs) as the UV light source. This is an alternative because UCNPs are able to convert photon energy, absorbed from NIR light, into UV light [97,98]. Thus, the cross-linked photosensitive molecules absorb the UV light to initiate the *gel-sol* process, triggering the release of drugs [72,91,95]. An important parameter to be considered about these systems is the distribution of the photocleavable cross-linker molecules and the UCNPs. Yan and co-workers (2012) have incorporated UCNPs into a polymeric bulk hydrogel, while Jalani and co-workers (2015) coated UCNP particles with hydrogel. Based on the structural arrangements and reflected in laser power densities and laser time exposures, these disparities trigger

different drug release profiles from the hydrogel matrix [91,95].

Electric fields are also used as external physical stimuli to modulate drug release from smart hydrogels. These systems, termed electro-conductive hydrogels (ECHs), are developed from either polyelectrolytes [99,100] or from an intrinsically conducting polymer (ICP) within a tridimensional cross-linked polymer network [79,101]. When an electric field is applied, driven charges are moved. Thus, ICPs can undergo electrochemical oxidation/reduction, leading to structural changes in the hydrogel and, subsequently, polymeric network erosion to release the incorporated drug [79,101,102]. Drug release from electro-responsive hydrogels can be related to drug charge, as shown by Choi and co-workers (2015). In their study, tetracycline was incorporated into carbon nanotube (CNT)-incorporated polyvinyl alcohol (PVA)-based hydrogels. At pH 8.0, tetracycline becomes negatively charged, and therefore, faster release was observed when a negative electric current was applied. This effect is due to repulsion between the drug and the negative bias. However, when a positive electric current was used, release was slower [101].

Several published studies have reported high-frequency magnetic fields (HFMFs) as external stimuli for drug delivery; a strategy which aims to accumulate these systems in an affected area. HFMFs are less invasive than electric fields or light exposure methods because they are able to highly permeate tissues with low energy absorption.

Magnetically responsive hydrogels are developed by incorporating magnetic iron oxide nanoparticles (MIONs), also known as super magnetic iron oxide nanoparticles (SPIONs), into the polymer matrices. They are widely explored, especially in association with thermo-responsive hydrogels.

The use of MIONs, incorporated to responsive polymers, is based on their capacity to transform electromagnetic energy, from an external high-frequency field, into heat. This event is related to the hysteresis that occurs, which can activate specific responses, such as drug release in a controlled manner [103,104]. As an example, ferrogel systems containing MIONs were developed by Hu and co-workers (2007), under HFMFs. They were activated kinetically and thermally (for large nanoparticles) promoting microstructural and molecular modifications, such as shrinking of the gelatin matrix, a thermosensitive polymer, which can control the drug release from the network with desirable precision [105]. An important parameter to be considered in these systems is the polymer/MIONs ratio. Sometimes, increased polymer/MIONs ratio reduces the saturation magnetization value, and consequently, the drug release decreases under a magnetic field [106].

2.3. pH-responsive hydrogels

The human body exhibits substantial pH changes in different body parts when functioning normally (Fig. 4). Within women's bodies, while healthy vaginal mucosa is an acidic environment (pH 4.0–5.0) the colon exhibits a pH value ranging from 7.0 to 7.5. In addition to the significantly different pH values exhibited in different tissues, some disease states can also cause pH changes in the human body [41]. The pH spectrum among different sites represent attractive targets for biomedical and pharmaceutical fields by which pH-responsive hydrogels could respond to a dynamic environment [42]. Moreover, pH changes might be easily manipulated and are applicable for *in vitro* and *in vivo* conditions [107].

Chemical stimuli, such as pH change, directly affect the interactions between polymer chains and between polymer chains and solvent molecules [108]. Similar to macromolecules, such as protein and nucleic acids, a polymer network contains ionizable groups that can donate or accept protons in response to pH, which primarily results in solubility and structural changes and, consequently, swelling or deswelling. Brønsted acids and bases are mostly used as respective pendants since their protonation/deprotonation occur at pH values between 4.0 and 8.0. Charged polymers in aqueous solution are polyelectrolytes, which might adopt expanded conformation as a result of electrostatic repulsion, enabling the hydration process. The transition point is governed by the pK_a value, and when the pH of the medium approaches the pK_a, the ionization degree of the polymer suffers a dramatic change [108]. Furthermore, charge exposition in aqueous medium is guided by the presence of carboxylic and amine groups that designate anionic and cationic behavior, respectively, two different classes of pH responsive hydrogels [22,42].

The cross-linking process between responsive polymeric chains results in the self-assembly of smart hydrogels, changing its hydrodynamic volume according to the pH value. The swelling of polyelectrolyte hydrogels occurs most often as a result of electrostatic repulsion between charges on the polymer backbone, which is directly related to pH alterations [21]. Mechanical properties and turbidity can also be changed by pH modifications [108]. Despite the system alterations promoted by pH, it is important to highlight that a dynamic response is essential for their applicability [21]. The critical pH value that determines their responsiveness can be modified by the incorporation of hydrophobic moieties, generally by copolymerization with hydrophobic monomers [108]. Amino acid residues can also be introduced on synthetic polymer chains to induce responsiveness through carboxyl groups.

pH-responsive polyacids almost always carry carboxylic groups and exhibit pK_a values in the range of 5.0–6.0. At higher pH values, the carboxylic group is deprotonated, yielding polyelectrolytes and electrostatic repulsion between molecular chains. On the other hand, at low pH, they are maintained as non-ionized macromolecules [108]. The most common examples are described in Table 4. Fig. 5 illustrates a hydrogel consisting of acid polymer chains that are responsive to pH variations in the surrounding medium.

Studies have frequently reported that synthetic polyacid monomers include acrylic acid, methacrylic acid, maleic anhydride, N,N-dimethylaminoethyl methacrylate and sulfonamide-containing polymers [109–112]. The pH-sensitive polyacids containing sulfonamide groups exhibit pK_a values ranging from 3.0 to 11.0, which enables the ionization of the hydrogen atom from the amide nitrogen [112].

Amine groups from polybases release protons under basic conditions, but accept them at low pH values yielding polyelectrolytes (Table 4). Examples of weak polybases are poly(N,N-dimethyl aminoethyl methacrylate), poly(N,N-diethyl aminoethyl methacrylate), aromatics 4-vinylpyridine, 2-vinylpyridine, poly (vinyl imidazole), and poly(L-lysine) [108,112–114].

pH-responsive behavior can also be found among natural polymers such as alginate, albumin, chitosan, pectin and gelatin [115–118]. When comparing synthetic homologues to natural patterns, it is necessary to highlight the high capacity of natural polymers to degrade in the body, an ideal feature for drug delivery platforms [119].

Chitosan and alginate are representative natural polybase and polyacid polysaccharides, respectively, that suffer physical crosslinking through hydrophobic or charge interactions. Swelling or liquid expulsion occurs based on the availability of the ionized group along the polymer chain. Ionized groups at high densities promote charge accumulation and, subsequently, electrostatic repulsion, and swelling. For chitosan, protonation of amino groups under low pH promotes electrostatic repulsion between cationic segments [120,121]. Pectin and alginate are anionic polysaccharides found in polyacid biodegradable hydrogels; alginate being composed of both guluronic acid (G) and mannuronic acid (M); whereas pectin contains galacturonic acid, which provides abundant carboxylate and hydroxyl groups. This feature yields high hydrophilicity and polymer chain extension by charge repulsion according to the pH [119]. While homopolymers based on weak polyelectrolytes appear to be pH responsive, the majority of these smart systems are developed by the combination of functional domains to achieve ideal responsiveness. Thus, the association between biopolymer and synthetic chains should be taken into account [112].

Due to its rigid crystalline structure, chitosan exhibits low solubility in water and in biologic fluids (pH 7.4), which might limit its use in
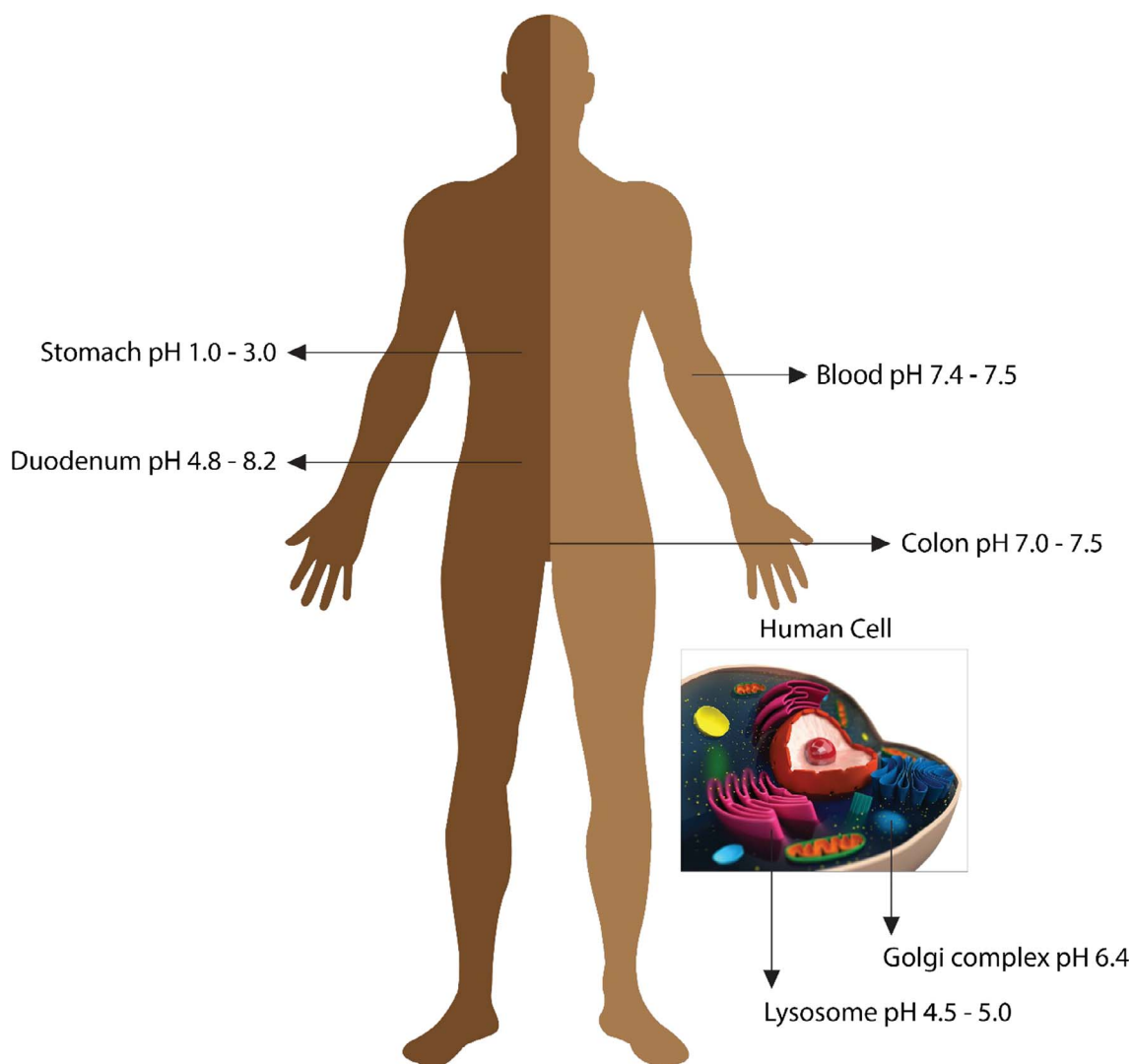
Fig. 4. pH values in several healthy tissues and cell compartments.

hydrogel development. However, a variety of chitosan copolymers can overcome this limitation, allowing the design of pH-responsive systems [122]. Given its excellent biocompatibility and biological properties, carboxymethyl chitosan (CM-CS) demonstrated good solubility in a wide range of pH. This was due to the additional presence of COOH groups, provided by substitution, which also governs their swelling behavior. Thus, the CM-CS have great potential as an oral drug delivery system that allows drugs to reach the colon [107]. CM-CS crosslinking with glutaraldehyde was used to design a pH-responsive delivery system, which enables higher pH-dependent swelling and drug release in a controlled manner at intestinal pH [115].

One of the most exploited applications of pH-responsive systems is the development of oral platforms since oral delivery requires drug resistance to enzymatic attacks and to the pH gradient along the gastrointestinal tract [107]. The use of copolymers consisting of methacrylic acid (MAA) and grafted poly(ethylene glycol) (PEG) chains, known as P(MAA-g-EG), was widely explored by Peppas and co-workers to develop an oral delivery platform for therapeutic proteins. The developed network showed pH-responsive behavior linked to the MAA polymer, which exhibited a pK_a of 4.8. Watkins and Chen synthesized lysine-based hydrogels from poly(L–lysine isophthalamide) (PLP) crosslinked with L–lysine methyl ester to create a pH-responsive platform for oral administration of pharmaceutical drugs (ranging from 0.3 to 2000 kDa) to target the colon. In acidic environments, PLP carboxylic

groups are protonated, promoting network collapse and drug retention. In the small intestine, these groups become negatively charged, and the three-dimensional structure absorbs a large amount of water, allowing for drug release [123]. Biodegradable and pH-sensitive hydrogels composed of polyacrylic acid derivatives (PAAD) and poly(L-glutamic acid) (PGA), synthesized by Gao and co-workers, showed interesting properties for their use as insulin drug delivery by oral administration [124].
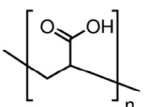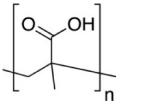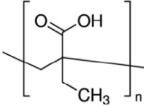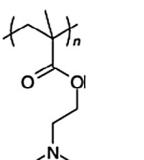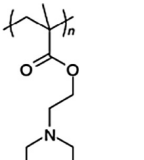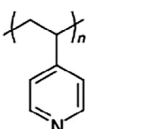
2.4. Salt- or ionic strength-responsive hydrogels

Based on different salt concentrations, some polymers undergo structural changes, which make them ionic strength- or salt-responsive systems [125]. Some studies have demonstrated that some polymer conformational transitions can be induced by different salt species and concentrations in the surrounding medium [126]. Similar to the previously described classes of pH-responsive polymers, this proposed mechanism of responsiveness is based on increased hydrophobic interactions promoted by salt concentrations which results in a reduction of electrostatic repulsion between the copolymers, enabling network precipitation [112]. Although sodium phosphate or sodium sulfate buffers promote a gradual reduction of hydrogel swelling, this behavior is not associated with phase transition [125].

This feature can be extremely important because some biological

Table 4
Molecular structure of common pH-responsive polyacids and polybases.

Polyacids polymer	Molecular structure
Poly(acrylic acid) **PAAc**	*(molecular structure)*
Poly(methacrylic acid) **PMAAc**	*(molecular structure)*
Poly(2-ethyl acrylic acid) **PEAAc**	*(molecular structure)*

Polybasis polymer	Molecular structure
Poly(N,N-dimethylaminoethyl methacrylate) **PDMAEMA**	*(molecular structure)*
Poly(N,N-diethyl aminoethyl methacrylate) **PDEAEMA**	*(molecular structure)*
Poly(4-vinylpyridine) **P4VP**	*(molecular structure)*

processes, such as nerve excitation, muscle contraction, and cell loco-motion, involve ionic strength modifications [127]. However, these polymers are less abundant than pH- and temperature-responsive polymers and, consequently, have not been widely explored as smart drug delivery systems [7,128].

Some weak polyacids such as poly(acrylic acid) and methacrylic acid show an increased degree of ionization upon the addition of li-thium methoxide salt, which promotes viscosity changes. The shrinkage of coils is explained by the attraction between the mobile osmotically ion pairs. Neutralized polyacrylate hydrogels exhibit reversible volume changes by the addition of both monovalent and divalent cations in a concentration similar to physiological conditions [127].

Hydrogels composed of N-isopropylacrylamide (NIPAAm), a non-ionic polymer, exhibit a known lower critical solution temperature. Park and co-workers demonstrated that the NIPAAm polymer also showed a sharp volume phase transition depending on the sodium chloride concentration in the surrounding medium [126].

Polyaspartic acid has been used in hydrogels that have the capacity of high swelling. However, ionic hydrogels commonly have reduced swelling capacities in saline solutions, especially because of electro-static repulsion and decreased osmotic pressure. Zhao and co-workers studied the swelling profile of these hydrogels in various chloride and sulfate salt concentrations. The results demonstrated that swelling ca-pacity is related to the cation charge and that it sharply drops in the presence of multivalent cations. They also reported that this reduction can be related to the greater number of univalent cation atoms [129].

A poly(N-isopropylacrylamide) (PNIPAM) hydrogel with specific sensitivity was synthetized by Liu and co-workers by introducing di-benzo-18-crown-6 comonomers into the network. The developed system exhibited thermal responsivity and a swelling ratio sensitive to the presence of K^+ [130].

2.5. Bioresponsive hydrogels

Bioresponsive hydrogels, also called biologically stimulated or bio-molecule responsive hydrogels, are biomaterials able to undergo structural modifications (swelling or deswelling, degradation or erosion and mechanical deformation) mediated by biological reactions. Changes might occur in response to increased concentrations of specific biomolecule availability (proteins, peptides, enzymes, antibodies) in physiological environments or under pathological conditions [131].

Living organisms utilize an arsenal of molecular mechanisms to maintain homeostasis, including tissue development and repair, im-mune responses and blood coagulation processes [132].

Antibodies and T cells are important biomolecules responsible for maintaining normal body functions by controlling immune responses and autoimmunity, extremely affected in diseases such as cancer. Enzymes, which are highly selective in their reactivity, are vital cata-lysts and highly efficient in a series of biological pathways [133] and can be used as important signals for disease diagnosis [134]. All of these
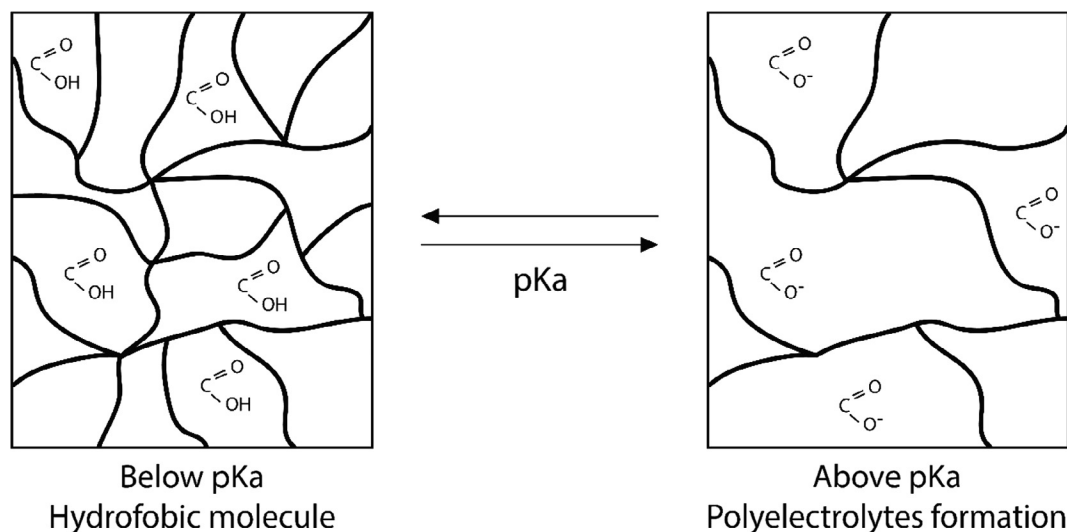

Fig. 5. A polyacid hydrogel response to surrounding medium pH variations.

biomolecules may provide important signals to monitor biological functions or detect physiological changes.

The use of bioresponsive hydrogels can provide material platforms that recognize target biomolecules, such as biomarkers, promoting drug release or signaling transduction [15,135,136]. Many research groups have recently focused in the development of bioresponsive hydrogels as smart self-regulated biomaterial systems, useful not only for drug delivery [133,137–142] but also for diagnosis, cell cultures [15,135,136], biosensors, or matrices for tissue engineering and regenerative medicine [135].

Bioresponsive hydrogels can be classified according to their behavior and most of them exhibit three types of responsiveness. The first, is related to glucose-responsive hydrogels designed with entrapped insulin, which selectively bind glucose molecules, triggering a response according to blood glucose levels [37,143–145]. The second type, enzyme-responsive hydrogels, contain enzyme-sensitive substrates, such as short peptides, which can be programmed to respond to a specific enzyme [146]. This concept is especially attractive since enzyme distribution occurs differently in different body parts and, primarily, in healthy and in diseased environments. The third class is represented by antigen-responsive hydrogels, which exhibit antigens incorporated into their structural networks to recognize specific antibodies [133,147–150].

Glucose-responsive hydrogels are widely used in diabetes treatments [42], compensating for the inability of the pancreas to control glucose levels in the blood [135]. Furthermore, these systems can exhibit different strategies for insulin self-regulation: those that use glucose oxidase, lectin (concanavalin A) and phenylboronic acid [131,132,151].

Glucose-responsive hydrogels designed with the glucose oxidase enzyme (GOX), entrapped along the polymer chain, show a mechanism of responsiveness to pH changes in the environment. This occurs due the cleavage of glucose molecules, followed by swelling/shrinking according to glucose levels. Essentially, when glucose concentration increases in the blood, GOX converts glucose to gluconic acid and H_2O_2, which lowers the pH inside the hydrogel. This reduction induces the ionization of functional groups and polymer chain repulsion inside the network, leading to hydrogel swelling and insulin permeation throughout the network reaching the blood [42,47,135,136,152].

Hydrogels designed with entrapped GOX have been reported since 1963, when Bernfeld and Wan successfully immobilized these enzymes into acrylamide hydrogels. Later, in 1985, Albin and co-workers immobilized GOX into hydrogels based on N,N-dimethylaminoethyl methacrylate, hydroxyethyl methacrylate, and tetraethylene glycol dimethacrylate, obtaining a glucose-sensitive insulin delivery device. Since then, many studies have been performed with hydrogels using the same GOX pathway [42,143,153]. Recently, Traitel and co-workers showed that a glucose-responsive hydrogel based on the pH-responsive poly(2-hydroxyethyl methacrylate-co-N,N-dimethylaminoethyl methacrylate) polymer, also known as poly(HEMA-co-DMAEMA), reached high swelling and insulin release rates when exposed to high levels of glucose concentration in the medium [145].

The second main pathway for glucose responsiveness consists of incorporating lectins, such as concanavalin A (Con A), into hydrogels [42]. Lectins are carbohydrate-binding proteins able to form complexes with glycoproteins and glycolipids present on the cell surface. Glucose-responsive systems designed with entrapped Con A are able to control the release of glycosylated insulin by lectin-binding in response to free glucose [135,152]. These systems exploit the competitive binding behavior of Con A with glucose and glycosylated insulin, since Con A has a higher affinity for glucose than the glycosylated moieties. Therefore, expansion of the polymer chains leads to swelling and, consequently, insulin release by diffusion [152].

A hydrogel system composed of glucosyl-terminal PEG and insulin conjugates was covalently bound to Con A and then attached to a poly(vinylpyrrolidine-co-acrylic acid) backbone. Published work demonstrated that this system promoted controlled insulin release without greatly modifying the hydrodynamic hydrogel volume. Furthermore, the surface-modified hydrogel was able to load a large amount of drugs into the network [154].

The last main mechanism of glucose-responsive hydrogels is based on phenylboronic acid (PBA). The ability of PBA to sense glucose and to release insulin in a controlled manner is due to their affinity for polyol molecules (sugar alcohols). After recognizing glucose molecules, PBA is reversibly complexed with polyol compounds. The interaction between immobilized PBA and glucose leads to volumetric changes, which allows insulin release [37,42,135]. In aqueous environments, phenylborate groups exhibit an equilibrium between uncharged and charged forms. The reaction between PBA and glucose occurs through the cationic charged forms and, therefore, the reaction shifts the overall gel charge density toward cationic charged species as a consequence of the dissociation equilibrium. The increased charge into the hydrogel promotes polymers chain repulsion and increased hydrophilicity, leading to swelling [42,135]. In 1959, Lorand and Edwards were the pioneers to describe, in a quantitative study, the complexation of boronic acids and polyols. Since then, a series of studies has been performed to investigate the binding affinity of boronic acids with different diols, including fructose and glucose [144,155]. A novel glucose-responsive hydrogel system based on covalent dynamic bonds and inclusion complexation was developed using the poly(ethylene oxide)-*b*-poly vinyl alcohol (PEO-*b*-PVA) diblock polymer, α-cyclodextrin (α-CD) and phenylboronic acid (PBA)-terminated PEO crosslinker. While dynamic covalent bonds between PVA and PBA provide sugar-responsive crosslinks, the inclusion complexation between PEO and α-CD, can provide hydrogel formation and hydrogel stability. PBA is an organoboronic acid capable of forming a dynamic complex with a polyol, such as PVA, however, in the presence of glucose, these complexes are dissociated once the biding constant of glucose-PVA is higher than PBA-PVA. Thus, the developed system provided drug release in response to glucose levels under physiological pH [39].

In cellular environments, most stimuli-responsive mechanisms are under the control of enzymes [156,157]. Thus, enzyme-responsive hydrogels can be a promising approach to respond directly to the target molecule. These systems can be designed based on peptidic building blocks; i.e., short sequences of amino acids, specifically degraded or digested by certain enzymes; which results in hydrogel degradation [42]. Since enzymes are highly selective in their reactivity, responsiveness is specific [135]. The enzyme access to self-assembled gels promote supramolecular architecture modifications based on the degradation process, which might result in swelling/shrinking or transformation of surface properties [135,146]. The first reported application related to tissue engineering was a metalloproteinase (MMP)-sensitive PEG-based hydrogel developed for cartilage repair and chondrocyte culture. MMP-sensitive peptides were used as hydrogel crosslinkers, yielding a material that was specifically degraded by gelatinase and collagenase. Thus, this bioresponsive hydrogel exhibited a release rate that could be modulated by cellular enzyme secretion [158].

Enzyme-responsive hydrogels are also widely exploited to release drugs specifically in the colon. The use of pH-sensitive monomers (acrylamide derivatives and acrylic acid) cross-linked with azo-aromatic bonds allows the degradability of the system to be restricted to the colon environment. Its responsiveness, in this case, is based on its ability of shrinking in the upper portions of the gastrointestinal tract, but when the system reaches the small intestine, where the pH increases, the swelling process begins. When the system arrives in the colon, the hydrogels reach their highest swelling degree. The cross-linked bonds are degraded by the action of azo-reductase enzymes or mediators. Subsequently, the hydrogel network can be degraded by cross-link cleavage, and the drug can be released at the desired site [159].

Hydrogels based on dextran polymers can also compose enzyme-responsive systems, since dextranases are present in colonic microbiota.

These systems cross-linked with diisocyanate degraded both in a human colonic fermentation *in vitro* model and in an animal *in vivo* model. In addition, data showed that drug release from the hydrogel was dependent on the presence of dextranases in the release medium [160].

Biodegradable polymers include naturally derived polymers such as pectin, amylose, gellan gum, chitosan, chondroitin sulfate, alginate, and dextran; [161] and artificial non-biodegradable polymers such as PEG/poly(ethylene oxide) (PEO), poly(2-hydroxyethyl methacrylate) and poly(N-isopropylacrylamide), which are enzyme-cleavable networks that are promising materials for developing site-specific drug release systems by enzymatic decomposition [134,136,161].

Antibodies are biomolecules able to recognize specific antigens and to establish contact through supramolecular interactions [133]. Thus, antigen-responsive hydrogels are able to undergo volume or structural changes in the presence of antibodies [133,135]. Miyata and co-workers produced the first antigen-responsive hydrogel by coupling rabbit immunoglobulin G (rabbit IgG) to N-succinimidyl acrylate (NSA) [147]. When the antigen-responsive hydrogel was placed in a buffer solution containing antibodies cross-link density decreased due to the dissociation of the antigen-antibody binding in the presence of free antigen. Therefore, the authors observed that system swelling was dependent on the antigen concentration [145]. Lu and co-workers developed an antigen-responsive hydrogel by using a polymerizable antibody Fab′ fragment, obtained from the monoclonal anti-fluorescein BDC1 antibody (IgG2a). This antibody was copolymerized with N-isopropylacrylamide (NIPAAm) and N,N′-methylenebis (acrylamide) (MBAAm; cross-linker) using redox initiators. The hydrogel showed reversible volume changes, and the antigen responsiveness was dependent on the Fab′ content, pH, and temperature [148]. This field of research continues to grow as new compositions of responsive polymer are developed in the next generation of smart materials.

3. Smart hydrogels as functional delivery systems

Smart hydrogels by nature can represent a model system for studying dynamic interactions between cells, between cells and extracellular matrixes, and between drug delivery and biological systems, as all these interactions can be of dynamic nature. However, the application of these bioactuating systems requires a sophisticated molecular design, which increases their potential applications [162]. Once it is a complex process in its entirety, only a deep knowledge of target pathology, science of the polymeric materials and therapeutic strategies provide the systemic reasoning required to design these systems.

Regarding material science and biological systems, new science is concerned with the design of smart materials for biological applications. To evolve in this field, we should gather multidisciplinary knowledge for this specific purpose [163,164].

Some diseases are known for significant changes on the homeostasis state. The evaluation of changes that characterize a pathological condition enables the exploitation of timely responsiveness to a particular biological event, as intrinsic properties constitute the basis for designing smart delivery systems [164]. In this sense, a smart system can be initially designed from target pathology characteristics. Here, we highlight some pathological aspects that can be explored toward this objective.

3.1. Smart systems designed for inflammatory processes

An inflammatory process is an organism's response to tissue injury or infection and involves the coordinated action of immune system cells and the release or activation of mediators such as growth factors, cytokines, chemokines, eicosanoids, biogenic amines and neuropeptides. A series of successive events promotes increased vasodilation and capillary permeability at the inflammation site, resulting typical inflammatory signs, such as pain, heat, redness and swelling [165,166].

This process is divided into two response patterns: acute and chronic. Acute events are typically of short duration (minutes, hours or days) and are triggered by the activation of local and migratory cells, such as mast cells, macrophages, neutrophils, and monocytes with, local stimuli that lead to the expression of interleukins and tumor necrosis factors. On the other hand, chronic responses have last longer and involve marked cell migration, such as lymphocytes and macrophages, and the proliferation of vessels, fibrosis and tissue necrosis [167,168].

Maintenance of the inflammatory process for an extended period can result in the development of several chronic diseases [168]. Rheumatoid arthritis, for example, is an autoimmune disease with a worldwide prevalence of 1%, particularly affecting people from 30 to 55 years old. Its pathology is characterized by an intense inflammatory response in the synovial cavity of joints, which occurs due to the recruitment of inflammatory cells, such as T and B lymphocytes, dendritic cells, macrophages, neutrophils and fibroblasts [169]. Activated T cells proliferate and stimulate the production of inflammatory cytokines, which work as a stimulus for macrophage and fibroblast activation. In addition, secrete tumor necrosis factor (TNF–α) and interleukins (IL–1, IL–6, IL–15 and IL–18) are mediators that trigger the migration of neutrophils to the inflammatory area.

As a consequence, inflammatory processes trigger hypertrophy of the synovial membrane, angiogenesis, and drastically increase synovial fluid volume, intracapsular pressure and temperature. Another feature concern the alterations of the synovial liquid: in physiological conditions, the synovial liquid is clear, light yellow and viscous with a pH ranging from 7 to 7.8. In pathologic states, the synovial liquid becomes turbid and acidic [170]. The enzyme production and lower pH contribute to accelerated tissue degradation, as well as cartilage and bone erosion [171].

Taking into account the aforementioned inflammatory particularities, the development of responsive drug delivery systems as hydrogels for intra–articular administration represents an advantageous strategy for treating chronic inflammation directly at the affected joint. These systems enable high drug concentrations at the desired site with limited systemic toxicity. Especially for rheumatoid arthritis, smart features might explore the following aspects: pH changes (in synovial liquids) and temperature (explored through the differences between ambient and body and also between regions of healthy and inflamed tissues). Furthermore, the presence of many enzymes at the inflammation site can be taken into account.

Thermo-responsive hydrogels might represent an interesting alternative because they are liquid at room temperature, which facilitates administration by site injections, and form a compact mesh when in contact with intra–articular temperatures equal to or higher than 37 °C due to the inflammatory process. This ability allows local retention for extended periods of time in addition to controlled drug release [172]. Other important approaches include using the presence of many enzymes at the inflammation site to control drug release and hydrogel degradation [173]. Some catalytic enzymes present at the inflammation site are uniquely chemo–, region–, and enantioselective and function under inflammatory conditions (pH 5–8, > 37 °C) [174]. Hyaluronic acid, dextran, poly(ethylene glycol), PEO and PLA polymers are examples that can be used to develop this kind of responsiveness [167,175].

Smart hydrogels may be a promising strategy for treating inflammatory bowel disease (IBD), which consists of Crohn's disease and ulcerative colitis [176]. Mucus depletion, *in situ* accumulation of positively charged proteins, and the presence of esterases and matrix metalloproteinases are characteristics of IBD that have been exploited as targets in the development of smart systems [177–179]. As an example, a smart hydrogel was developed to provide a system able to interact with mucus oligosaccharides by electrostatic forces, and promote drug release through the hydrolysis process, induced by esterases. Therefore, the developed hydrogel was able to adhere to the inflamed mucosa and act as a reservoir to promote sustained drug release [179].

Zhou and co-workers developed supramolecular smart nanofibers/hydrogels to repair the colonic mucosa and reduce the inflammatory process. The main strategies used were: (1) specific drug release from hydrogels after azoreductase activity occurred in the colonic microflora; (2) D–peptides to increase the resistance to proteases, so the hydrogel system could reach the colon intact following oral administration; and (3) dynamic interactions from self-assembly providing flexibility and system adaptation to a series of mucosal surfaces [180]. The association of these strategies highlights the importance of understanding the microenvironment of the disease to engineer effective delivery systems.

3.2. Smart systems designed for cancer therapy

Cancer is one of the most aggressive diseases responsible for death around the world. For decades, chemotherapy has been the main treatment used. However, most of the chemotherapeutic agents are non-specific and exert several toxic side effects, which limits the dose that can be used and jeopardizes the patients' quality of life [181]. Based on the absence of consistent disparities between pathological and normal tissue, designing effective therapies for malignant diseases, such as cancer, has faced great difficulties [182]. However, some differences in metabolic and nutritional events, among a series of solid tumors and the surrounding normal tissue, can be observed. The accelerated increase in the population of expanding tumor cells is not supported by normal vasculature, leading to oxygen and nutrient deficiencies. Thus, tumors exhibit increased proliferation and angiogenesis [183,184].

First described by Otto Warburg, selective and active processes occur to provide adjustments on energy metabolism during uncontrolled cell proliferation and cancer progression. One of these events consists of shifting from oxidative phosphorylation to aerobic glycolysis for ATP production, even in the presence of oxygen [185,186]. As a result of high glycolytic metabolism rates, high levels of lactate/H^+ (lactic acid) are produced. Furthermore, the preservation of enhanced glycolytic flux and intracellular physiological pH is performed by the efflux of lactic acid to the extracellular microenvironment, preventing intracellular acidosis, which might result in cell death [182,187]. This condition results in acidic pH at the tumor microenvironment. Although, sometimes this characteristic is seen as a disadvantage due to drug permeation difficulties and to facilitating tumor invasion, it can also represent a target for developing smart hydrogels [188]. Therefore, pH-responsive systems that effectively deliver anticancer drugs might carry and stabilize the therapeutic agent at physiological pH, in addition to releasing the drug at this condition [189]. Numerous hydrogel systems have been proposed in this sense, particularly for local administration, where antitumor drugs can be directly transported to the cancer microenvironment [122,190–192].

The first aspect to be taken into consideration before designing a pH-responsive hydrogel is the target pH. Thereafter, the pK_a value of the polymer chain should determine its applicability. The utilization of weak polyacids, such as the alginate polymer, to design pH responsive systems may be interesting for this approach [193]. In acidic environments, according to the polymer pKa, alginate chains represent a matrix surrounded by negative charges, which are able to interact with positively charged drugs through supramolecular interactions. The acid environment makes these polyelectrolyte complexes stronger and more stable, which results in different drug release profiles, according to the pH changes at the tumor environment [190,194].

Such pH-responsive systems might also be beneficial in intracellular microenvironments. It is well known that cell internalization occurs primarily through the endocytic mechanism. This event results in system confinement inside an acidic endosomal and lysosomal lumen. Exploring this mechanism, nanogels exhibit interesting results as smart systems [195,196].

An additional striking feature that should also be explored in cancer therapy is based on the fact that an association between inflammation and cancer has been proposed [197]. Therefore, all previously described events considered regarding inflammatory processes may also be useful for developing smart systems for cancer therapy. Changes in tumor vasculature permeability and cell membranes, lower hydrostatic pressure and increase of localized temperature are conditions to be taken into account.

Considering the spontaneous hyperthermia in tumoral tissues, a temperature-responsive system based on chitosan–poly(N-isopropylacrylamide-co-acrylamide) polymer was developed by Wang and co-workers to explore tumor microenvironments. Their results demonstrated the release of the drug in a temperature-dependent manner that favored cellular uptake against the tumor hyperthermia condition [198]. Furthermore, differences between the internal and external body temperatures have been extensively explored for localized therapy [199–202].

Another factor to consider is that the presence of some enzymes, such as esterases, can be explored to project responsiveness [192]. MMPs are zinc-dependent endopeptidases and are responsible for cleaving a series of extra-cellular matrix components. It is known that, in normal tissues, MMPs are expressed in minute amounts, whereas in tumoral tissues, especially in advanced stages of cancer, they are overexpressed [203]. In particular, MPP2 is associated with tumor progression, angiogenesis and metastasis. Thus, MPPs can therefore be used to promote responsiveness alone or in combination with other strategies [204–206].

Among all the tumor characteristics that can be explored to develop smart hydrogels for cancer therapy, pH differences are most explored to target tumor cells [188]. However, systems specifically oriented by pH changes are still limited compared to receptor targeting or endosomal pH targeting. This reality is justifiable due to the narrow pH window between normal and pathologic tissue. To complement this approach, more data on the changes of system kinetics are needed, which would allow the necessary adjustments for this purpose.

3.3. Smart systems designed for diabetes mellitus

Diabetes mellitus is a worldwide public health problem, which consists of a group of metabolic diseases characterized by hyperglycemia resulting from insulin secretion defects, insulin action, or both. In 2012, approximately 1.5 million deaths were directly related to diabetes, of which 43% occurred to individuals below the age of 70. In 2014, statistics showed that approximately 422 million people were diabetic, representing approximately 8.5% of the adult population. Recently, the World Health Organization (WHO) estimated that the worldwide number of deaths related to diabetes is approximately 2.9 million/year, and this number is expected to increase by approximately 50% in the next 10 years [207,208].

Under physiological conditions, increased glucose levels in the blood trigger a cascade of events that result in the synthesis and secretion of insulin by β-cells. Thus, insulin promotes decreased glucose levels by increasing glycogenesis and glucose uptake. When the blood glucose level returns to normal, the amount of insulin in the blood decreases [208].

The WHO recognizes two main forms of diabetes mellitus: type 1 and type 2 [208,209]. Type 1 diabetes is most common among children and is characterized by the lack of insulin production as a consequence of autoimmune destruction [208,210]. Type 2 diabetes generally occurs in middle-aged people, and insulin resistance is its main defect, which is characterized by low responses of target tissues to insulin [208,211,212].

Traditionally, diabetic patients, especially type 1 patients, have been treated by regularly applying subcutaneous insulin injections. This procedure is quite inconvenient, painful, can trigger hyperinsulinemia and allergic reactions and it is known low patient compliance. In addition, conventional medicines administered through alternative routes, such as dermal, rectal, ocular, oral, nasal, and pulmonary

methods, are usually accompanied by low bioavailability. Therefore, innovative drug delivery systems have been intensively researched. Today, it is already possible to predict the production of responsive systems that are able to release insulin in response to blood glucose levels. In this context, the design of new drug delivery systems, such as smart bio-hydrogels, represent a promising strategy [208].

Based on glucose sensing and recognition strategies, some hydrogels show properties that can facilitate insulin diffusion. The described materials undergo a variety of changes, such as swelling, shrinking or degradation, in response to glucose, and each approach may offer a possible benefit [213].

Diabetes pathology and its particularity allows for the exploration of adjoining features to produce smart systems. For instance, although we know insulin peptides are heavily damaged at the acidic stomach, orally administered smart hydrogel systems might mitigate this problem, providing the necessary drug protection in the acidic environment and allowing drug release in lowers parts of gastrointestinal tract. Biocompatible and biodegradable natural polysaccharides are interesting materials to be used for these purposes. Blends of different polysaccharides enable the modulation of physical-chemical properties for the desired drug release profiles. Therefore, the understanding of system dynamics along with pathological particularities might provide a realizable self-assembly system that is able to exert the desired therapeutic effects.

4. Future perspectives

Science is constantly in expansion and fundamentally, the introduction of new technologies creates challenges for those responsible for regulating aspects applied on these new products, particularly if they may cause risks to health and environment. The absence of a homogeneous and clear regulatory guidelines involving technology-based smart systems creates an unstable scenario where benefits can be confused with risks, hindering their clinical outcome.

We can reflect on how our standard of living has been improved by significant progress in many fields related to science and engineering. However, it is important to note that our lives have been changing very quickly, and scientific progress along with regulatory aspects must accompany these changes. In this context, the design of smart systems offers important advances and novel solutions to a series of diseases and life threatening health conditions. In this literature review, a series of smart hydrogels developed for various applications by scientists and technologists all over the world were discussed. However, while many scientific reports have been published, a low number of hydrogel products are currently being used in clinical trials. This time lapse reflects the need for optimized designs of advanced smart systems, that focus on important aspects of human diseases and therapy efficacy along with toxicity predictions and regulatory improvements.

Misleadingly, hydrogels are commonly prepared or synthetized first, and suitable applications are later investigated for that system. In current research practice, preparations have not yet been designed considering any particular application or biological condition. Therefore, this current approach promotes unavoidable gaps between properties and applications. Thus, stimuli-responsive systems should be projected at the molecular level before considering the desired biological application. However, it is very likely that synthetically produced materials will approach the complexity of biologically spontaneous events soon through the use of non-linear chemical reaction networks [214].

Foreseen to be highly promising, the nanoarchitectonics of smart hydrogels must be based on basic research and researchers should adapt the properties of the drug delivery systems to obtain the desired biological effects. Additionally, to accomplish material self-assembly and the stimulation of spontaneous processes, professionals must bear in mind all legal guidelines established by local authorities.

Researchers believe that the use of dynamic hydrogels as drug delivery systems is still in its initial stage. However, the importance of these systems remains incontestable and highly promising.

Currently, the association of stimulus responsiveness and other design strategies can provide synergistic effects for targeted drug delivery. Furthermore, the development of a successful smart hydrogel delivery system requires exquisite material engineering and should, now more than ever, also include a multidisciplinary approach to gather expertise from polymer scientists, medical doctors, chemists and pharmacists.

Further rational studies of function-based systems can lead to the development of innovative and promising drug delivery systems.

Acknowledgements

Conflict of interest

The authors declare no competing financial interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eurpolymj.2017.12.004.

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