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Chemically Responsive Hydrogels, Properties, Pharmaceuticals, and Agricultural Applications: A Review

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REVIEW

Chemically Responsive Hydrogels, Properties, Pharmaceuticals, and Agricultural Applications: A Review

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Abstract

A review of the literature on chemically responsive hydrogels about the selection of selectivity based on classification, properties, and application is presented in this article. Chemically responsive hydrogels are a type of hydrogel that undergo changes in their properties in response to specific stimuli. These hydrogels have attracted significant attention due to their potential applications in various fields, including pharmaceuticals and agriculture. Chemically crosslinked hydrogels are synthesized by covalent crosslinking of end-functionalized macromeres. Currently, a great deal of research is being conducted on hydrogel networks, also known as smart networks or hungry networks. This is owing to their potential use in fields like biomedicine, pharmaceuticals, biotechnology, biosensors, agriculture, oil recovery, and cosmetics. When they sense small changes in their surroundings, smart hydrogels display significant physiochemical changes. Despite this, changes such as these are reversible; therefore, the hydrogels can return to their original state after they have caused a reaction once the trigger has been removed.

Keywords: Hydrogels, Smart hydrogels, Chemical responsive hydrogels, Pharmaceutical

1. Introduction

Hydrogels are three-dimensional polymer networks made from natural or synthetic materials that possess a high amount of water content and possess flexibility [1] as shown in Fig. 1. They are characterized by a rubbery consistency and the ability to absorb a vast amount of water, much like living tissues. As such, they can be used for a wide range of applications. The solid portion of the hydrogel is a network of crosslinked polymer chains, a 3D network usually referred to as a mesh as shown in Fig. 1.

For treating or replacing tissues and organs as effectively as possible, or interacting with live tissues, hydrogels must exhibit properties of reversibility, stability, and biocompatibility [1,3,4]. In nature, hydrogels have existed since the beginning of time. Nature abounds with water-swollen motifs, such as bacterial biofilms, and plant structures, such as the extracellular matrix consists of these components. Throughout human history, hydrogels served a variety of purposes, but they are now being used for biomedical applications. At the beginning of history, hydrogels were used for medical applications. Other materials, such as gelatine and agar, have also been utilized in the past. Researchers studied early versions of the newly synthesized methacrylic polymers [5].

Hydrogel technology has limitations in terms of properties like high crystallinity, insolubility, and biodegradability. In addition, it has unfavorable mechanical and thermal properties, unreacted monomers, and the use of toxic crosslinkers [6–9]. In other words, by using natural or synthetic

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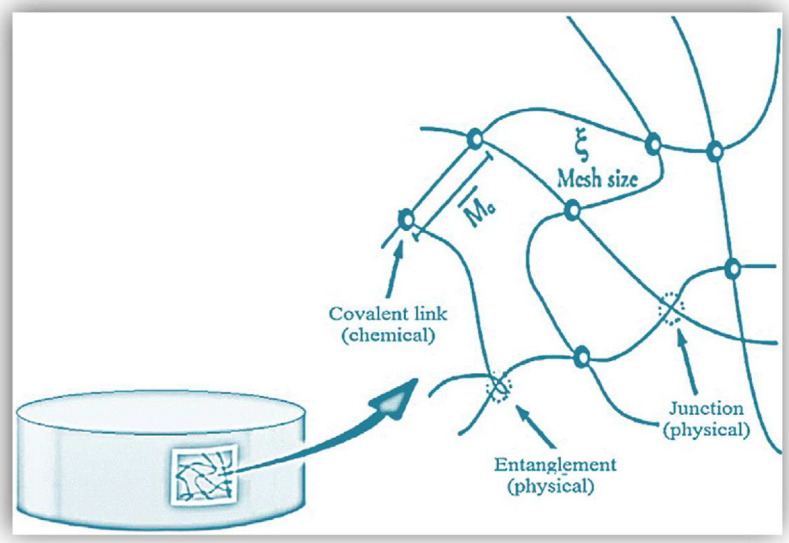

Fig. 1. Structural chemistry of a hydrogel [2].

polymers with specific properties such as biodegradation, solubility, crystallinity, and biological activity, one is less likely to be able to develop these properties by developing novel methods [5,10].

Depending on their materials, techniques, and applications, hydrogels can be classified in a variety of ways. Chemical and physical polymerization are the standard techniques for inducing crosslinking [11,12]. In Table 1, a few materials, techniques, and applications are listed.

In this review, we discuss the use of chemically responsive hydrogels in a variety of fields, including pharmaceuticals and agriculture. In addition to microfluidic control, biomimetics, biosensors/bio

Table 1. Materials, techniques, and applications used in the preparation of hydrogels.

Material	The technique (s)	Application (s)	Reference (s)
Polyethylene glycol (PEG)	Chemical cross-linking	Drug delivery	[11]
	Photo-polymerization	Implants	[13]
	Free-radical polymerization	Scaffolds	[14]
	Free-radical polymerization	Self-healing	[15]
	Grafting	Bacteriostasis	[16]
Arabic Gum	Photo-induced radical polymerization	Self-healing hydrogel	[17]
Sterculia gum	Radiation-induced	Biomedical	[18]
Hydroxypropyl methylcellulose (HPMC)	Radiation	Scaffolds	[19]
Hydroxyethyl cellulose (HEC)	Chemical cross-linking	Wound dressing	[20]
Chitosan	Photo-polymerization	Biomedical	[21]
	Photo-polymerization	Tissue adhesive	[22]
Carboxymethyl cellulose (CMC)	Freeze-thaw	Enzyme immobilization	[23]
	Chemical cross-linking	Drug carrier agent	[24]
	Chemical cross-linking	Hydrogel beads	[25]
	Copolymerization	Dye removal	[26]
	Chemical cross-linking	Anti-counterfeiting	[27]
	Grafting	Metal ions removal	[28,29]
	Chemical cross-linking	Controlled release	[30]
	Chemical cross-linking	Drug delivery	[31]
Hydroxypropyl cellulose (HPC)	Chemical cross-linking	Thermoresponsive hydrogel	[32]
	Photocrosslinking	Biomedical	[33]
	Freeze-thaw	Biomedical	[34]
Polyacryl amide	Radiation-induced	Agriculture	[35]
Polyvinyl alcohol (PVA)	Freeze-thaw	Drug release	[36]
	Freeze-thaw	Regenerative medicines	[37]
Starch	Radical polymerization	Wound dressing	[38]

actuators, bio separation, and artificial skin, smart hydrogels can be used to create a range of applications. Among its features are reversible swelling and deswelling, high ionic conductivity, high permeability, innovative mechanical properties, and high sorption capability.

2. Classifications of hydrogels

Different types of hydrogels can be categorized into different types according to their physical characteristics, swelling characteristics, preparation method, origin, ionic charge, sources, and rate of degradation. This is in addition to their observed crosslinking nature [39, 40]. Figure 2 illustrates some of the more prominent hydrogels that attract scientists. It is beyond the scope of this article to describe the classification details of each type of hydrogel.

3. Chemically responsive hydrogels

Hydrogels are three-dimensional networks of hydrophilic polymers that can absorb and retain large amounts of water due to physical or chemical crosslinking of individual polymer chains [41]. They are versatile materials with diverse applications in biomedicine, drug delivery, tissue engineering, and environmental engineering. Hydrogels that respond to oxidants are particularly interesting because they can undergo reversible redox reactions in response to changes in the oxidative environment. These hydrogels are designed to contain redox-active groups, such as thiol, disulfide, or selenocysteine, that can undergo reversible oxidation and reduction reactions in response to oxidative stress [42]. The redox-responsive hydrogels can be used to encapsulate and release drugs in response to oxidant stimuli or for targeted delivery of therapeutics to sites of oxidative stress. The development of new synthetic methods has revolutionized the field of biomaterials and expanded the applications of hydrogels, including redox-responsive hydrogels, in various fields of science and engineering [43].

3.1. Glucose-responsive hydrogels

- Hydrogels with glucose-responsive properties

Diabetes treatment should be facilitated by the development of an insulin delivery hydrogel system that triggers insulin release based on glucose sensing. Insulin and glucose oxidase mixtures that contain glucose-sensitive insulin are attractive materials [44]. Researchers Podual and Brahim et al. [45,46] respectively, developed a kind of material known as "bio-smart". In this class, molecular recognition is combined with actuation, consisting of two types of materials: 2-hydroxyethyl methacrylate (HEMA) and poly methacrylate (PMA). Catalytic hydrogels swell by releasing insulin when

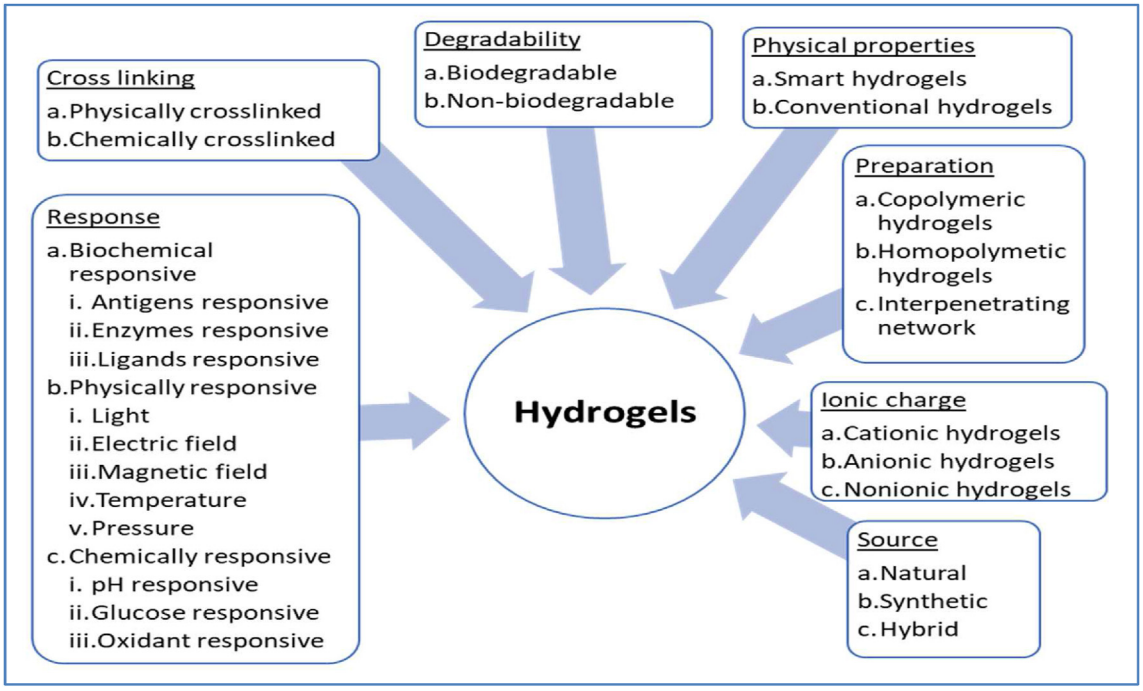

Fig. 2. Physicochemical classification of hydrogels [5].

glucose is converted to gluconic acid by an enzyme called glucose oxidase. This results in a reduction in the pH of the system. By covalently incorporating glucose oxidase into the hydrogel, it can reduce rapid diffusion out of the system and enhance controlled insulin delivery [5,44].

- Concanavalin A based hydrogels

Canavalia ensiform is, a plant that creates glycoproteins in the form of carbohydrates, produces a hydrogel based on concanavalin A (Con-A). In comparison to the presence of glucose-insulin conjugates, free glucose molecules have a stronger binding affinity for Con A [41]. Therefore, when glucose is unbound in the skin, glycosylated insulin is desorbed. Glucose levels determine how quickly glucose-insulin conjugates are released. The free glucose molecules engage in exchange competition with the glucose attached to the polymer as they diffuse into the hydrogel. As a result, the concentrations of Con A and glucose-containing polymers can be changed to alter how hydrogels react to different levels of free glucose. Glucose-responsive hydrogels can also be created without the aid of Con A. It is appropriate to use polymers with phenyl boronic groups, such as poly (3-(acrylamide)-phenyl boronic acid) and its copolymers.

- Hydrogels based on glucose oxidase

Concanavalin-A has been tested as a crosslinker for the formulation of glucose-responsive hydrogels; phenylboronic acid and glucose dehydrogenase have been tested as biosensors [47]. As glucose oxidase oxidizes glucose into gluconic acid, it is the enzyme most used to detect glucose levels, since it changes the pH of the system, one that can be used to control insulin delivery with pH-sensitive hydrogels. When the pH of poly (diethylaminoethylmethacrylate) PDEAEM-based hydrogels is lowered, ionization takes place, causing swelling and the release of insulin. By using grafted porous membrane filters and immobilized glucose oxidase, glucose-sensitive hydraulic flow controllers may be developed based on polyanions such as (methacrylic acid-co-butyl methacrylate) [48]. Consequently, the chain expands at normal pH. In turn, as the glucose oxidase converts it into gluconic acid, the pH decreases, and the carboxyl groups are protonated, which gives rise to chain collapse [47,48].

- A hydrogel based on PVA

The formation of complexes in PVA hydrogels occurs through the formation of phenyl borate and hydroxyl groups, whereas polyol polymers compete for their crosslinking owing to their glycolytic mono functionality (one binding site) [49]. This causes the hydrogel to swell and insulin release to increase as glucose concentration increases and crosslinking decreases as shown in Fig. 3.

3.2. Hydrogels with pH-responsive properties

A polymeric hydrogel with ionic pendant groups is capable of accepting or donating hydrogels [50], which have dramatic changes in ionization degree, also called pK_a or pK_b. Electrostatic repellence

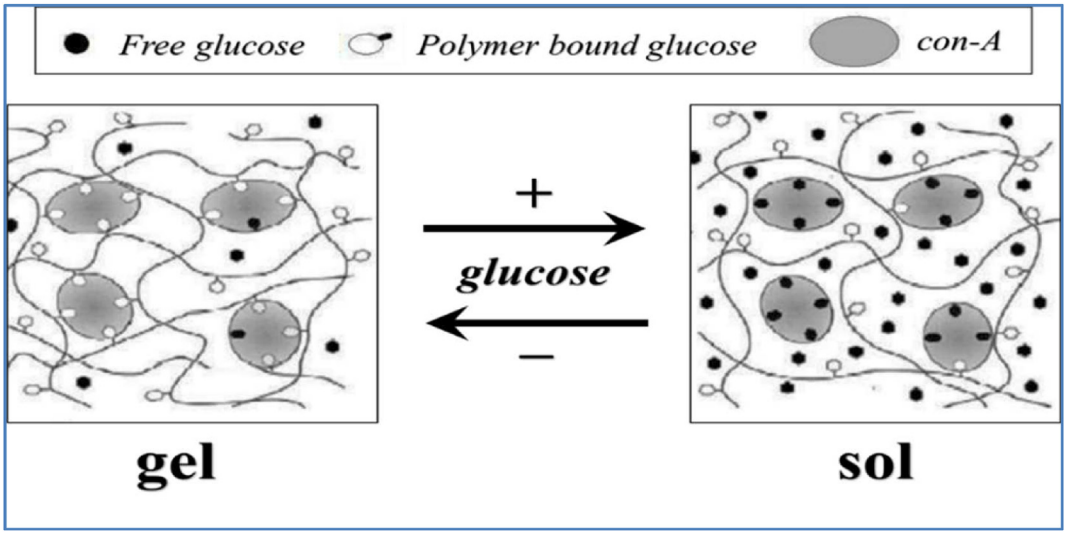

Fig. 3. The sol–gel transition of glucose-sensitive hydrogel [5].

between ionized groups produces a sudden volume transition at a junction that is caused by ionized pendants that rapidly change their net charges. This results in an increase in force during osmotic swelling [51]. Hydrogels with different pH responses can be either anionic or cationic. As a result of the deprotonation of pendant molecules such as carboxylic acid or sulfonic acid in an environment with an elevated pH, the pendant molecules begin to ionize. This causes swelling of the hydrogel [52–54]. As an alternative, cationic hydrogels contain pendant groups, like amine groups, at which ionization occurs below the base of pK_b. Due to the enhanced electrostatic repulsion, causes swelling occurs [52,55].

- Properties of pH-responsive hydrogels

Anionic hydrogel swelling is influenced by a few major factors, according to a study by Gupta et al. [52], published in 2002. The degree of ionization of a polymer will be determined first by the concentration of the groups, their crosslink density, their ionic charge, their pKa and pKb, their hydrophilicity, and their hydrophobicity. Two other factors to consider are the properties of the swelling medium, such as its pH, ionic strength, counterions, and its poly (vinylsulfonic acid) (PVSA) value [56–58]. Based on a pH variation, researchers observed the ionization of polydiethylamino ethyl methacrylate (PDEAEMA) and its copolymer in Fig. 4.

An article published recently by Abbasi et al. [59] discussed the porous silica as drug carrier for controlled delivery of sulfasalazine to studied the effect of alginate-N, O-Carboxymethyl chitosan gel coating into the drug release rate in a simulated intestinal media. The media was kept at 37 °C and pH 6.8 and 7.4 and subjected to continuous ultrasonic waves to simulate body fluid flow. The released results were studied in simulated gastric and intestinal media and show that no burst release occurred in both coated and functionalized samples and the swelling degree of coats at basic and neutral media decreased by the presence of alginate in the network. Moreover, concluded that the coat with a 50:50 ratio can release the colon drugs in 24 h at a suitable rate. It is also envisioned that functionalization was a factor boosting drug uptake, however, the release rate was lower in the functionalized samples.

Any factor that affects electrostatic repulsion, such as pH, ionic strength, or counterions, will affect swelling. This phenomenon is illustrated in Fig. 5. Two phases of hydrogel can be seen in this figure: a gel-like phase formed by polymer–polymer interactions and a polymer–polymer phase that is gel-like. In this condition, the hydrogel shrinks due to its hydrophobicity. Polymer and aqueous solution are well mixed in the second phase due to interactions between the solvent and polymer. In the second phase, hydrophilicity and swelling are at their maximum levels [41].

4. Applications of chemical responsive hydrogels

There was an astounding variety of hydrogels available for engineering, biology, and pharmaceuticals [60–63]. Among the many uses of polyelectrolytes are hydrogels that can transfer chemical

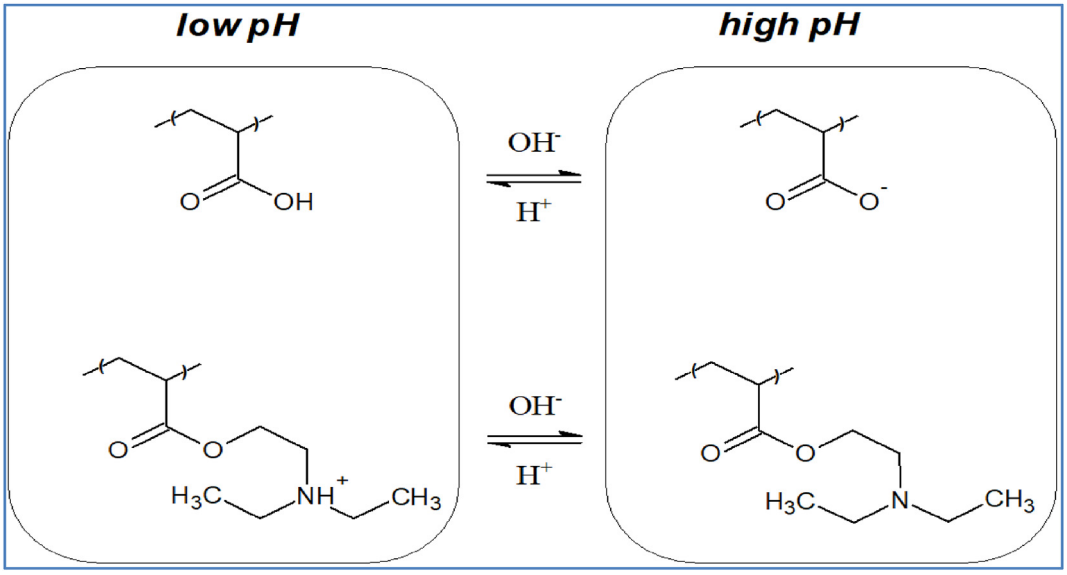

Fig. 4. Induced ionization of polyelectrolytes under pH-dependent conditions [4].

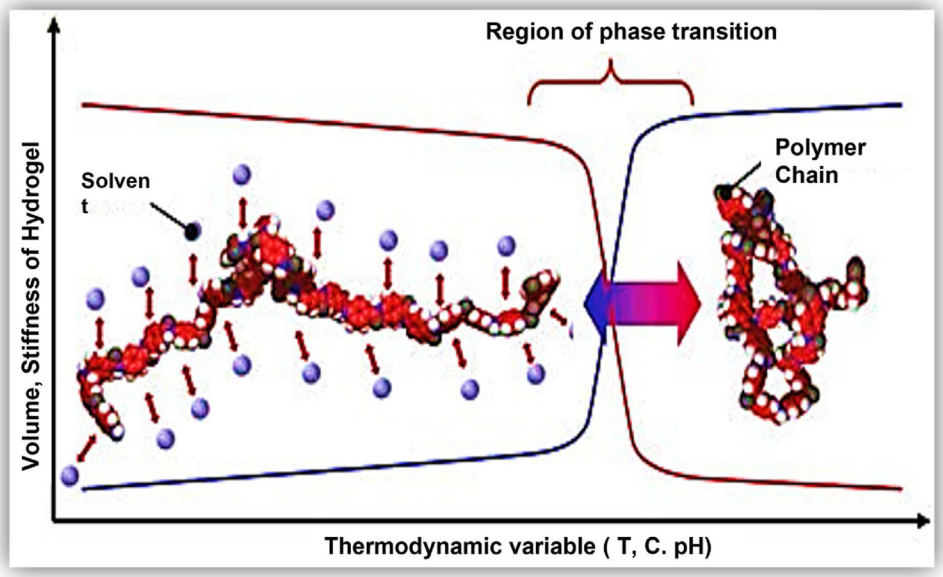

Fig. 5. Hydrogels with stimuli-responsive phase transitions.

charges along the chain and bind to oppositely charged proteins and peptides to form complexes. This includes delivering drugs, proteins, peptides, nutrients, hormones, and cells, as well as in agriculture and biotechnology [64]. Several synthetic carriers have been developed that use catalytic polymers to break up large particles into smaller ones and to cover DNA with negative charges. In addition to being widely applicable for delivering DNA and oligonucleotides from viral or non-viral sources, these characteristics make them ideal for transfecting most types of cells, genes, antisense therapies, and bile acids [65]. As a result of small changes in their surroundings, such as electrical fields, magnetic fields, solvents, pH, ionic strengths, and temperatures, hydrogels often experience large volume changes [66].

4.1. Pharmaceutical applications

Hydrogels are increasingly being used as a versatile platform in the field of pharmaceuticals due to their excellent biocompatibility, high water absorption, and retention properties [41]. These unique characteristics of hydrogels make them suitable for various pharmaceutical applications such as drug delivery, wound healing, and tissue engineering. In drug delivery, hydrogels are used as carriers that can interact with mucosal linings in different parts of the body such as the gastrointestinal tract, colon, vagina, and nose, allowing for a prolonged residence time at the delivery location [67]. Additionally, the specific properties of hydrogels can be tailored by means of modification and compounding to achieve a wide range of functionalities. For instance, the controlled release of drugs can be achieved by incorporating stimuli-responsive hydrogels, which respond to external stimuli such as pH, temperature, and light [68,69]. The use of hydrogels in pharmaceuticals is therefore a promising avenue for the development of novel drug delivery systems and biomedical applications.

4.1.1. PVA-based based hydrogels

Diabetes, liver, intestine, colon, blood, brain, nerves, and thyroid cancer are among many applications of this technology [66]. The pharmaceutical delivery system is effective for delivering drugs under control [61,63]. According to Sanchez et al., 2019, a drug delivery system with crosslinked composite PVA beads is achieved by increasing the PVA content and crosslinking the level of the beads [70].

4.1.2. A hydrogel-based on PEG-PCL

According to Saidi and colleagues. 2019, to determine the effects of structural parameters on diclofenac sodium release and swelling ability kinetics from pure PEG and PEG–PCL hydrogels, they synthesized two kinds of hydrogels using the ROP and click chemistry methods. According to the study, the molecular weight and the relative hydrophobic/hydrophilic composition of PEG must be considered when evaluating the enlargement process and release mechanism. The Korsmeyer-Peppa

model provided the most satisfactory fit for the swelling and release data. The degree of expansion and flexibility of networks will decrease with greater cross-link density and PCL concentration [71].

The negative thermosensitive swelling behavior is caused by the presence of hydrophilic and hydrophobic block copolymers in diacrylates derived from PEG for drug delivery and Poly-ϵ-caprolactone (PCL) for tissue regeneration. As a result of in vitro degradation, degradation occurred after 3–8 months. Pharmaceutical applications are suitable for these hydrogels due to their degradability, biocompatibility, functionality, and elasticity [1,10,71,72].

4.1.3. PHEMA-co-DMAEMA-based hydrogels

The hydrogel can fulfill the release drift which is required for many drugs because zero-order drug kinetics is crucial for their delivery. Glucose-intensity hydrogels are capable of releasing additional insulin [73]. Some of these polymers are pH-sensitive, such as poly (DIDEEMA), and glucose oxidase, which exchanges glucose for gluconic acid, which regulates insulin release [71,73]. In their study, Traitel et al., 2000, modeled in vivo insulin release by encapsulating glucose oxidase, catalase, and insulin in poly (2-hydroxyethyl methacrylate-co-N, N-dimethylamino ethyl methacrylate). Consequently, these hydrogels are not pH-sensitive and contain glucose that diffuses into them when they are exposed to physiological fluids, where glycogen oxidase acts as a catalyst for converting glucose to gluconic acid causing swelling and insulin release. Furthermore, chemically crosslinked hydrogels are unstable in water and swell more when exposed to glucose than those that are not crosslinked [74]. For an explanation of the chemistry behind oxidation and catalysis, consider the following equation:

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{GluOx}} \text{Gluconic Acid} + H_2O_2$$

$$H_2O_2 \xrightarrow{\text{Catalase}} 1/2O_2 + H_2$$

According to Fig. 6, the above is a summary of how swelling and tissue release occurs.

4.2. Agriculture industry

One promising approach to nutrient release into plants has been investigated more recently by incorporating hydrogels containing fertilizer [75]. Leaching, chemical processes, excessive rainfall, and other factors contribute to the loss of nutrients applied to the soil [76,77]. To encourage soil fertility, several polysaccharides have been utilized as fertilizer release systems, such as chitosan, pectin, and carboxymethyl cellulose [78]. Hydrogel demonstrated as a soil conditioner by several researchers. For instance, according to Agaba et al., the moisture retention of a particular soil affects plant growth. This is because water affects the properties of the

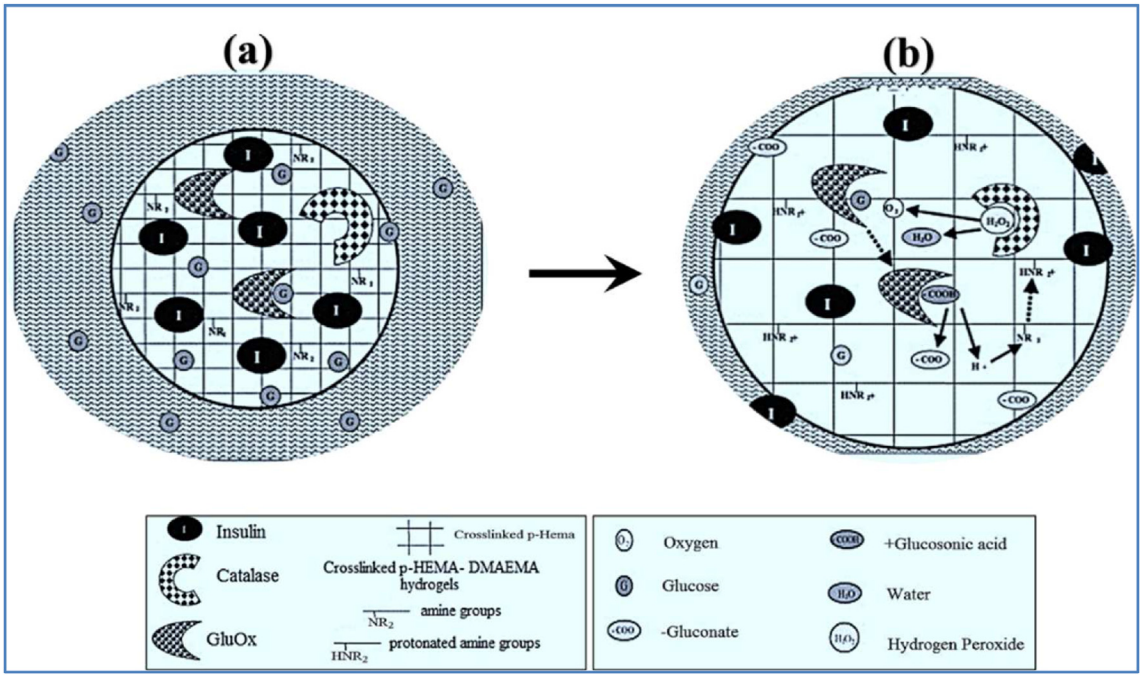

Fig. 6. Schematic of Unswollen/swollen hydrogels as presented on p (HEMA-DMAEMA) [74].

soil, such as aeration, temperature, fertilizer transportation, water uptake, and transformation [79].

According to Demitri et al., the development of a carbodiimide-crosslinked hydrogel formulation can be applied to arid and desert environments to deliver water and nutrients. In the authors' opinion, the principal advantage of hydrogels is that they can control the release of water displaced by drying soil. Consequently, soil humidity will remain high for some time. Hydrogel also increases the porosity of the soil, allowing root roots to receive more oxygen [80].

According to Parvathy et al., hydrogels affected the physical-chemical and biological characteristics of soil, when g-poly (acrylamide) was saponified cassava starch. Additionally, the same hydrogels were used to investigate the effects of chili (Capsicum annum L.) growth parameters in various irrigation periods. Using superabsorbent matrices, which can control the release of adsorbed water, we found that the amount of moisture retained in the soil is directly related to the concentration. Furthermore, researchers noted that hydrogels may also serve as alternative options for combating global climate change as they can improve soil characteristics, particularly when moisture availability is low. Several of these matrices were demonstrated to have excellent slow-release properties and very effective water retention capabilities, which indicates that they are suitable for agricultural use since they minimize fertilizer loss and improve water efficiency [81].

Various types of poly (2-acrylamido-2-methyl-1-propanesulfonic acid) (PAMPS) hydrogel were tested under various conditions by Radwan et al. To optimize the process, several variables were changed. A potential application for this hydrogel in agriculture was also tested. In the study, several factors were optimized, including water temperatures, cross-linking agents, and pH [82]. Several polysaccharides-based controlled-release formulations including hydrogels are presented in an article by Campos et al. Polysaccharides, in the authors' opinion, offer the following advantages over synthetic polymers: they are eco-friendly, have a high holding capacity, are relatively inexpensive, and are biodegradable [83].

Hydrogel irrigation technology can only be used to apply fertilizer, herbicides, and germicides to plants with minor drawbacks, according to Neethu et al. [84]. Hydrogel agriculture can be practiced without reducing crop yield or nutritional value without drastically reducing the use of synthetic fertilizers. Sustainable agriculture in arid and semi-arid regions and areas with similar ecological constraints would benefit from this practice. Agro-ecosystems are prevented from pollution due to potassium polyacrylate, which is non-toxic and safe for use [84].

5. Conclusions

This review provides an overview of the literature concerning hydrogels in the last twenty years. It describes how hydrogels are classified based on their chemical and physical properties with a special focus on chemically responsive hydrogels for pharmaceutical, agrochemical, and industrial applications. The research direction for this review suggests identifying polymers that behave in different ways depending on stimuli (physical, chemical, and biochemical) in addition to studying future generations of hydrogels that swell spontaneously when contacted with cancer cells and lungs. As the materials absorb a lot of aqueous fluids within a short period, they can be used in applications such as the desalination of water and eco-sustainable agriculture.

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