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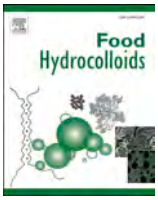

Review

Stimulus-responsive hydrogels in food science: A review

Zhongyu Yang [a,1], Long Chen [a,b,1], David Julian McClements [c], Chao Qiu [a,b], Cuicui Li [a], Zipei Zhang [d], Ming Miao [b], Yaoqi Tian [b], Kunfu Zhu [e], Zhengyu Jin [a,b,*]

[a] School of Food Science and Technology, Jiangnan University, 1800 Lihu Road, Wuxi, 214122, China
[b] State Key Laboratory of Food Science and Technology, Jiangnan University, 1800 Lihu Road, Wuxi, 214122, China
[c] Department of Food Science, University of Massachusetts, Amherst, MA, 01003, USA
[d] Laboratory for Biomaterials and Drug Delivery, Department of Anesthesiology, Division of Critical Care Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, 02115, USA
[e] Shandong Zhushi Pharmaceutical Group Co, LTD, Heze, 274300, China

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ABSTRACT

The unique network structure of hydrogels enables very high levels of hydrophilicity and biocompatibility, while at the same time exhibiting the soft physical properties associated with living tissue, making them ideal biomaterials. Stimulus-responsive hydrogels are particularly effective. Stimulus-responsive hydrogels can respond to the external environment (including light, pH, temperature, electricity, etc.), thus conducting and controlling material properties. In recent years, stimulus-response hydrogel has become a hot-spot. However, there are limited applications of stimulus-responsive hydrogel in food field, which needs to be further explored. This review identified and discussed a variety of response methods that have been developed, including temperature, pH, chemical, optical, electrical and other responsive hydrogels. In addition, the fabrication of stimulus-responsive hydrogels and the current and future applications of these hydrogels in the field of food are reviewed.

1. Introduction

Hydrogels can absorb relatively high quantities of water into their porous polymer networks through hydration and capillary forces (Shen, Shamshina, Berton, Gurau, & Rogers, 2016). In the food industry, hydrogels are usually formulated from natural polymers such as proteins (*e.g.,* gelatin, casein, whey protein, soy protein, and fish) (Zohuriaan-Mehr, Pourjavadi, Salimi, & Kurdtabar, 2009) and polysaccharides (*e.g.,* alginate, carrageenan, pectin, and starch). Numerous fabrication methods are available for hydrogel preparation, including macroscopic gelation, injection-gelation, emulsion-templating-gelation, phase separation-gelation, gel fragmentation, and spray drying methods (Zhang, Zhang, Chen, Tong, & McClements, 2015). Moreover, new methods are being developed such as additive manufacturing (3D printing) of hydrogels (Martinez, Goyanes, Basit, & Gaisford, 2017). There has been strong interest in the development of hydrogels because of their good biocompatibility, simple preparation, and wide application range (Klein & Poverenov, 2020). For instance, they have been utilized as functional materials in drug delivery (Narayanaswamy & Torchilin, 2019), tissue engineering (Naahidi et al., 2017), textiles (Stular, Simoncic, & Tomsic, 2017), food packaging (Batista et al., 2019), and nutrients delivery (Liu, Zhang, Li, McClements, & Liu, 2018; Zhang, Zhang, Chen, Tong, & McClements, 2015). Recently, there has been considerable interest in the design and fabrication of "intelligent" hydrogels that can respond to external stimuli, such as temperature, pressure, light, pH, ionic strength, or enzyme (Chatterjee & Hui, 2021). The introduction of stimulus-responsive effects can enhance the functionality and increase the range of applications of hydrogels. For instance, changes in their swelling or degradation behavior can be used to create novel textural or release characteristics (Koetting, Peters, Steichen, & Peppas, 2015). Previously, the applications of stimulus-responsive hydrogels have mainly focused on drug loading and release in the pharmaceutical industry (Sharma, Jain, & Tiwari, 2020). There have been far fewer studies on the application of these advanced materials in foods. Nevertheless, there may be a number of important applications where they have advantages over existing technologies (Shewan & Stokes, 2013). Indeed, some studies have already shown that stimulus-responsive hydrogels can be used to create intelligent food

* Corresponding author. School of Food Science and Technology, Jiangnan University, 1800 Lihu Road, Wuxi, 214122, China.
E-mail address: fpcenter@jiangnan.edu.cn (Z. Jin).
[1] These authors contributed equally to this work.

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packaging materials (Batista et al., 2019), nutrient delivery systems (Chen et al., 2017; HaqAsif et al., 2021; Zhang, Zhang, Decker, & McClements, 2015), and bacterial detection systems (Vogt, Richard, Dippold, & Laura, 2005). These studies demonstrate the potential of stimulus-responsive hydrogels for certain food applications. In this review, we discuss the classification, preparation, and application of stimulus-responsive hydrogels in foods. Moreover, we discuss potential future developments of this technology in the food industry.

2. Classification of stimulus-responsive hydrogels

Stimulus-responsive hydrogels alter their microstructures and/or physicochemical properties in response to some environmental stimuli, such as pH, ionic strength, temperature, light, enzyme (Koetting et al., 2015). Fig. 1 shows some common stimulus-responsive hydrogels related to the field of food.

2.1. pH- and ion-responsive hydrogels

These kinds of hydrogels respond to changes in the pH or ionic composition of the surrounding solution, which lead to alterations in the electrostatic interactions between the polymer chains that make up the network inside them (Tulain, Ahmad, Rashid, Malik, & Iqbal, 2016). The pH determines the charge state of any ionizable side groups on the polymer chains, such as $COOH \leftrightarrow COO^- + H^+$ or $NH_3^+ \leftrightarrow NH_2 + H^+$. The ionic composition determines the magnitude and range of electrostatic interactions through ion binding and electrostatic screening effects.

The characteristics of pH-responsive hydrogels can be adjusted by changing the composition of the polymer backbone, the cross-linking density of the polymer chains, and the nature of the ionic groups (Yong, Qiu, Kinam, & Park, 2012). This kind of hydrogel has been explored for its potential application as a release system in medical applications because there are appreciable changes in pH within the human body (*e.g.,* mouth, stomach, small intestine, colon, and bloodstream) and in response to injuries or disease (such as tissue/wound inflammation and tumor formation) (Koetting et al., 2015). Thus, controlled release systems designed for targeted drug delivery can be prepared based on the differing pH conditions in different parts of the body.

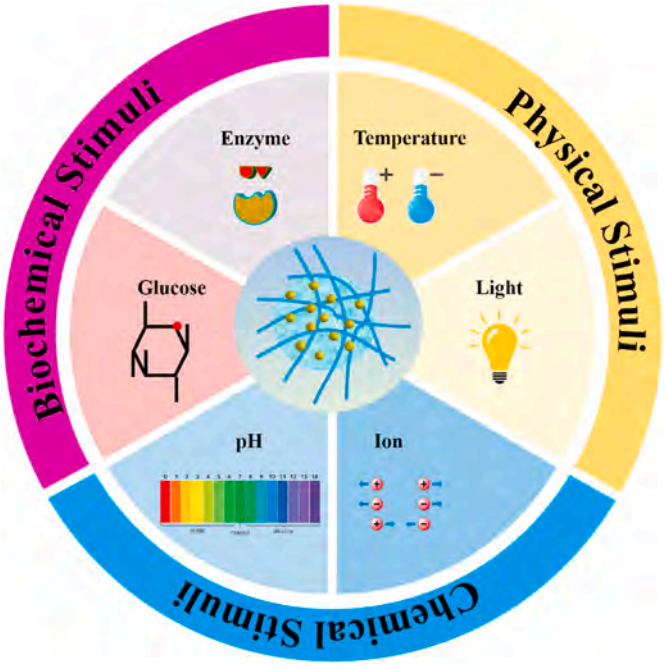

Fig. 1. Classification of stimulus-responsive hydrogels related to the field of food. Adaptation from (Sun, Agate, Salem, Lucia, & Pal, 2021).

pH-responsive hydrogels can be divided into three main types: anionic, cationic, and amphoteric hydrogels. The ionizable groups in anionic pH responsive hydrogels are usually weakly acidic carboxyl groups (such as -COOH and $-SO_3H$) on the polymer chains. When the pH is relatively low ($pH < pK_a$), the carboxyl groups are not fully ionized and so there is only a weak electrostatic repulsion between them so the polymer chains can come close together, thereby leading to a contracted hydrogel. Conversely, as the pH is raised ($pH > pK_a$), the carboxyl groups become more ionized, leading to greater electrostatic repulsion between the polymer chains, thereby causing swelling of the hydrogel. The swelling mechanism of cationic pH-responsive hydrogels is similar to that of anionic ones, but the important functional groups are amines (such as $-NH_2$, -NHR, and $-NR_2$) (Shohraty, Moghadam, Fareghi, Movagharnezhad, & Khalafy, 2015). In this case, when the pH is relatively low, the amines become charged ($-NH_3^+$), which increases the electrostatic repulsion between the polymer chains and leads to swelling of the hydrogel. Conversely, when the pH is relatively high the amines lose their charge, which results in shrinking of the hydrogel. The swelling properties of anionic and cationic hydrogels depend on the number of charged groups on the molecular chain and the degree of ionization. The greater the number and ionization of the ionizable groups, the greater the degree of swelling.

The swelling and shrinking of amphoteric pH-responsive hydrogels is more complex because they contain both amine and carboxyl groups on the polymer chains that can change their charge status (Lu et al., 2014). At higher pH, the carboxyl groups are fully ionized ($-CO_2^-$) and the amine groups are non-ionized ($-NH_2$), leading to strong chain repulsion and swelling (Xie, Yin, Liu, Zhu, & Yang, 2018). At lower pH, the amine groups are fully ionized ($-NH_3^+$) and the carboxyl groups are non-ionized ($-CO_2H$), again leading to chain repulsion and swelling. At intermediate pH, however, both amine and carboxyl groups are charged, which can lead to electrostatic attraction between them, thereby promoting shrinking. In this case, the swelling behavior depends on the type, number, and location of the anionic and cationic groups on the polymer chains.

The swelling/shrinking behavior of hydrogels containing charged polymers can also be modulated by changing the ionic composition around them. For instance, a strongly charged hydrogel may be swollen at low ionic strengths due to the strong electrostatic repulsion between the polymer chains but shrunk at high ionic strengths due to electrostatic screening effects (Dou et al., 2012).

As well as changes in hydrogel pore size (swelling and shrinking), changes in pH or ionic strength may also alter the electrostatic interactions between an encapsulated substance and the polymer network. For instance, under conditions where the encapsulated substance and the polymers have opposite charges, then there will be an electrostatic attraction between them, leading to retention within the hydrogel matrix. Conversely, under conditions where the encapsulated substance and the polymers have same charges (or one of them is non-charged), there will be an electrostatic repulsion (or no electrostatic attraction), leading to release from the hydrogel matrix.

A number of food-grade biopolymers can be used to create pH- or ion-responsive hydrogels, including alginate, carrageenan, pectin, chitosan, chitin and many proteins. For instance, alginate hydrogels have been shown to shrink under acidic conditions (where the carboxyl groups lose their charge) but swell under neutral conditions (where their carboxyl groups are fully charged) (Zhang, Chen, Zhang, Deng, & McClements, 2016). Due to the good biodegradability and biocompatibility of polysaccharides, double-network pH-responsive hydrogels with alginate and κ-carrageenan as the main components have been developed for targeted release of bovine serum albumin in the intestinal tract (Sariyer, Duranoglu, Dogan, & Kucuk, 2020).

2.2. Temperature-responsive hydrogels

Temperature is one of the environmental stimuli that can be easily controlled. Temperature-responsive hydrogels respond to temperature changes with volume changes. Therefore, temperature-responsive hydrogels fall into two primary categories, positively and negatively responsive systems, which are identified by having an upper critical solution temperature (UCST) or a lower critical solution temperature (LCST), respectively (Koetting et al., 2015). Generally, temperature-responsive hydrogels contain both hydrophilic and hydrophobic groups, and the swelling-shrinking transition occurs at either the UCST or LCST (Ullah, Othman, Javed, Ahmad, & Akil, 2015).

The LCST system is the dominant system used in the development of temperature-responsive hydrogels (Schild, 1992). When the ambient temperature is higher than the LCST, the hydrophobic interactions between the non-polar groups in the hydrogel polymer chains increases, leading to the formation of a denser network structure (shrinking). Conversely, when the ambient temperature is lower than LCST, the hydrophobic interaction between the hydrogel polymer chains is weakened, leading to the formation of a more open network structure (swelling) (Belal et al., 2016). The polymers used to form LCST systems are assembled from n-alkyl substituted monomers, polyethylene glycol, and so on. However, the LCST response has also been reported in some natural polymers, such as chitosan (Koetting et al., 2015).

UCST-based hydrogels are much less commonly used than LCST-based ones (Boustta, Colombo, Lenglet, Poujol, & Vert, 2014). The temperature response of these networks can be modified by adding hydrophobic or hydrophilic co-monomers to change the critical temperature.

In the food industry, a variety of biopolymers can be utilized to prepare temperature-responsive hydrogels. For instance, gelatin molecules have regions of helical structure at relatively low temperatures, which leads to the formation of hydrogels through hydrogen bonding between helical regions on different molecules (Djabourov, Nishinari, & Ross-Murphy, 2013). However, they undergo a helix-coil transition upon heating, which results in melting of the hydrogel. Similarly, polysaccharides like agar can undergo a helix-coil transition upon heating, and a coil-helix transition upon cooling, which means that they can also be used to create temperature-responsive hydrogels (Djabourov, Nishinari, & Ross-Murphy, 2013). Conversely, carboxymethyl cellulose (CMC) will form reversible gels upon heating due to an increase in the strength of the hydrophobic attraction between the methyl groups at elevated temperatures.

2.3. Light-responsive hydrogels

The properties of light-responsive hydrogels can be adjusted by exposure to light waves of sufficient intensity and appropriate wavelength. The light sources commonly used include near-infrared (NIR) (Matai et al., 2020), visible (Vis) (Hong, Kim, Jeong, Park, & Park, 2020), and ultraviolet light (UV) (Roth-Konforti et al., 2018). Light-responsive hydrogels change their properties by responding to external light stimuli through three mechanisms (Jiang, Wang, Li, Yu, & Chu, 2020). First of all, by grafting photosensitive groups, hydrogels can undergo phase transition after absorbing photons of a certain energy to trigger the response, which is the most common light response mechanism. The second light response mechanism is that the hydrogels containing photoactive molecules generate ions, resulting in the reaction with the hydrogel network or the change of osmotic pressure, and thus the swelling of the hydrogel. Finally, the hydrogel containing photosensitive compounds can change the properties of the hydrogel in response to environmental changes by absorbing photon energy.

Light-responsive hydrogels have been used in food packaging materials to make it have light-activated antibacterial activity to prevent microbial cross-contamination, reduce the risk of foodborne diseases and prolong the shelf life of products (Tosati, de Oliveira, Oliveira, Nitin, & Monteiro, 2018). There have been some examples of researchers using food-grade biopolymers to create light-responsive hydrogels and this could be an important area for future research. Giammanco, Sosnofsky, and Ostrowski (2015) prepared visible light responsive gels using alginate and pectic acid as raw materials and coordinated with Fe (III) ions. Oligomeric proanthocyanidins as a photothermal agent can endow hydrogels with controllable photothermal properties. A hydrogel scaffold with sodium alginate and oligomeric proanthocyanidins as the main components has been prepared, which can respond to near-infrared laser (Ma, Zhou, Chang, & Wu, 2019). The photoresponse and controlled release of the materials can be adjusted by changing the type of polysaccharides and metal coordination environment.

2.4. Glucose-responsive hydrogels

Glucose-responsive hydrogels undergo changes in their structure or properties when exposed to glucose molecules in their environment. There are three main glucose-sensitive substances used to fabricate this kind of hydrogel: glucose oxidase (Jung, Magda, & Han, 2000), concanavalin A (ConA) (Brownlee & Cerami, 1979), and phenylboric acid (PBA) (Kataoka, Miyazaki, Bunya, Okano, & Sakurai, 2012). Glucose-responsive hydrogels can be used as glucose sensors and insulin delivery systems for those suffering from diabetes (Cai et al.,; Chen et al., 2019).

In biomedicine, there have been a large number of studies on the construction of controlled release systems for insulin delivery using glucose responsive hydrogels to improve the therapeutic effect of diabetes and the quality of life of patients (Lee et al., 2018). For instance, glucose-responsive chitosan microgels have been developed for the treatment of type 1 diabetes (Gu et al., 2013). In this case, insulin was encapsulated within a hydrogel matrix to maintain its stability and biological activity. The microgel is designed to release insulin at a fixed rate under normal blood glucose conditions, but when the blood glucose concentration increases, it releases insulin at a faster rate, thus acting as a self-regulating system (Gu et al., 2013). Similar kinds of systems may also be useful for some applications within the food industry. By smearing the hydrogel which can combine with glucose on the electronic tongue, the juice containing different concentrations of glucose can be detected to distinguish different commercial brands of apple juice (Daikuzono et al., 2019).

2.5. Enzyme-responsive hydrogels

Enzyme-responsive hydrogels undergo changes in their structure or properties in response to the presence of specific enzymes in their environment. These kinds of systems may be useful for the controlled release of bioactive components in specific regions of the human gut, where particular enzymes are most concentrated (such as proteases or amylases). They may also be useful for controlling fermentation processes in the food industry since microbes release different enzymes in different growth stages. Enzyme-responsive hydrogels are usually based on the ability of specific enzymes to hydrolyze specific polymers in the hydrogel matrix, *e.g.*, proteases will digest proteins while amylases will digest starches (Zhang, Zhang, Chen et al., 2015). Alternatively, the hydrogel matrix may contain an encapsulated substrate that undergoes a change when it comes into contact with a specific enzyme in the environment or vice versa (Cheng, Jin, Qi, Fan, & Li, 2015). Phosphatase (Shigemitsu et al., 2018), trypsin (Panayiotis et al., 2018), matrix metalloproteinases (Joshi et al., 2018) are all common enzymes used to prepare enzyme-responsive hydrogels. Compared with physically and chemically stimulus-responsive hydrogels, enzyme-responsive hydrogels have many advantages, such as high catalytic efficiency, good substrate specific selection and so on.

2.6. Multiple stimulus-responsive hydrogel

At present, there have been many studies on single stimulus-responsive hydrogels, but usually the conditions for the application of stimulus-responsive hydrogels are not only single environmental stimuli, therefore, the development of dual or even triple stimulus-responsive hydrogels has attracted wide attention. Zhao & Li. (2019) used Tremella polysaccharides, carboxymethyl cellulose and Nonionic surfactants as main raw materials to prepare pH/temperature-responsive hydrogels for controlled release of hydrophobic drugs by free radical polymerization. Liao et al. (2020) synthesized Fe_3O_4, *in situ* in carboxymethyl chitin hydrogel matrix using hericium Erinaceus residue as raw material, and synthesized a kind of pH/magnetic double sensitive intelligent hydrogel. The pH/magnetic sensitivity and swelling degree of hydrogels can be regulated by changing the content of Fe_3O_4, and the release behavior of 5-fluorouracil in vitro is controlled by pH. The digestive system of the human body is a complex environment, and the environmental conditions such as pH, temperature and enzymes are different in the gastrointestinal tract (Mcclements, Decker, Park, & Weiss, 2009). Researchers often need to consider these factors when designing drug delivery systems using stimulus-response hydrogels, which provides a reference for food scientists to design stimulus-response hydrogels to deliver nutrients. The delivery system undergoes a series of complex physical and chemical changes as it passes through the mouth, stomach, small intestine and large intestine. As the particles pass through the digestive tract, the pH of the aqueous phase around the particles in the release system will undergo considerable changes, which will lead to changes in the charge on the various components of the particles (such as surfactants, proteins and polysaccharides), thus changing their composition, structure and interaction (McClements & Li, 2010). In addition, there may be a change in temperature from the initial food to the human body, which may cause changes in the physical state, interactions of specific components that impact digestibility (McClements & Li, 2010). Secondly, there are various enzymes in the mouth, stomach and small intestine that can digest food components, such as lipids (lipase), phospholipids (phospholipase), protein (protease) and starch (amylase) (Esmon, Debault, Carroll, Comp, & Esmon, 1984). Ma et al. (2017) developed the ion strength/pH/enzyme three-response site delivery hydrogel of L-glutamic acid and L-lysine mixed peptides according to the conditions of gastrointestinal tract. According to these environmental conditions, food scientists can design hydrogels with multiple responses to achieve targeted release of nutrients in various parts of the gastrointestinal tract of the human body, which will have a good application prospect. Table 1 briefly lists the synthesis methods, response modes and mechanisms of some common stimulus-responsive hydrogels.

3. Fabrication of stimulus-responsive hydrogels

Stimulus-responsive hydrogels are mainly fabricated using three main methods: chemical, physical, and enzymatic cross-linking methods. Chemical cross-linking methods include free radical-, grafting-, and radiation-polymerization approaches (Ahmed, 2015; Akhtar, Hanif, & Ranjha, 2016). Many food materials have been used to prepare stimulus-responsive hydrogels by chemical cross-linking. Quercetin was grafted onto chitosan to form chitosan-quercetin conjugate, which can be used as a multi-functional component of multi-responsive hydrogel (Cirillo et al., 2019). Zhu, Ma, Wang, Zhang, and Zhang (2016) prepared multi-responsive hydrogels from lotus root starch by free radical polymerization. Physical cross-linking methods mainly utilize hydrogen bonding, hydrophobic attraction, and electrostatic attraction to hold the polymer network together (Jones & McClements, 2010). Enzymatic cross-linking methods utilize specific enzymes to create bonds between the polymers in the network. Various types of stimulus-responsive were prepared with natural/synthetic polymers (Table 2).

3.1. Chemical cross-linking

The chemical cross-linking method involves the formation of covalent bonds between functional groups on different polymer chains. The hydrogels prepared using this approach typically have good structural stability because the bonds formed between the polymers that make up the network are relatively strong.

3.1.1. Radical polymerization

Free radical polymerization is the most common method for chemical preparation of hydrogels based on synthetic polymers. These hydrogels are typically prepared by free radical polycondensation or copolymerization of monomers in the presence of appropriate cross-linking agents (Fig. 2A). The common free radical polymerization methods include bulk, solution, suspension, and emulsion polymerization (Li, Jia, & Yin, 2021). Monomers, initiators, and cross-linking

Table 1
Synthetic methods, response modes, mechanisms of stimulus-responsive hydrogels (Muhammad et al., 2017; Su, Xia, Li., & Xiao, 2019).

Nature of Stimulus	Stimulus	Synthesis method	Response	Mechanism
Physical stimuli	Temperature	Free radical polymerization; ATRP; RAFT; Freeze drying; Ultrasonic radiation	Volume; Transmittance; Change the shape	Shift in temperature changes polymer-polymer and polymer-water interaction responsible for swelling and drug release.
	Light	Free radical polymerization; ATRP; RAFT	Volume; Transmittance; Change the shape	Exposure to light (UV and visible light) reversibly changes the hydrogel from its flowable form to non-flowable form and vice versa.
	Electric field	Copolymerization; Blend	Volume; Osmotic pressure	Changes in electrical charge distribution within the hydrogels matrix on theapplication of electric field cause swelling–deswelling and is consequently responsible for the on demand drug release.
	Magnetic Field	Encapsulation	Volume	When a magnetic field is applied, it causes pores in the gel to swell leading to drug release.
	Pressure	Free radical polymerization	Volume; Change the shape	Swelling under increased pressure and vice versa. This fact is due to an increase in lower critical solution temperature (LCST) value of hydrogels with pressure. LCST is the temperature below which negative thermo responsive hydrogels swell.
Chemical stimuli	pH	Free radical polymerization; ATRP; RAFT	Volume; Dissociate	Shift in pH causes change in the charge on the polymer chains leading to swelling and drug release
	Glucose	Free radical polymerization; ATRP; RAFT	Volume; Change the shape	Hydrogels show swelling in response to increased glucose concentration. The complex formed between glucose and phenylboronic acid drives the swelling of the hydrogels and consequently insulin release.
Biological stimuli	Enzyme	Free radical polymerization; Enzymatic cross-linking; ATRP; RAFT	Volume; Change the shape	Enzymes cause hydrogel degradation and consequently the drug release. This is called a chemically controlled drug release mechanism
	DNA	Free radical polymerization; Enzymatic cross-linking; ATRP; RAFT	Volume; Change the shape	Single stranded (ss) DNA grafted hydrogel probes show swelling in the presence of ssDNA

Table 2
Fabrication of stimulus-responsive hydrogels.

Fabrication	Category	Polymers	Reference
Chemical cross-linking	Radical polymerization	Poly (ethylene glycol)methyl ether methacrylate	Wang and Wei (2016)
	Chemical cross-linking	Whey protein	Abaee, Madadlou, and Saboury (2017)
	Grafting	Chitosan-cellulose, carboxymethyl cellulose, styrene sulfonate	Chaykar, Goharpey, and Yeganeh (2016)
	Radiation	Gelatin, carrageenan	(Aliste & Del Mastro, 2016)
	Condensation reaction	Cellulose nanofiber	Kobe, Yoshitani, and Teramoto (2016)
Physical Crosslinking	Freeze-thawing	Locust bean gum, beta-glucan	(Tanaka, Hatakeyama, & Hatakeyama, 1998; El Hosary et al., 2020)
	Hydrogen bonds	Cyclodextrin, polypseudorotaxane	Feng, Zhou, Dai, Yasin, and Yang (2016)
	Hydrophobic interactions	Methyl cellulose, carboxymethyl cellulose	(Fredrick, Podder, Viswanathan, & Bhuniya, 2019; Pan, Zhuang, Zhang, Wang, & Wang, 2018)
	Electrostatic interactions	Cellulose microfibrils	Masruchin, Park, and Causin (2015)
Enzymatic crosslinking		Poly (ethylene glycol) methacrylate	Wei et al. (2016)

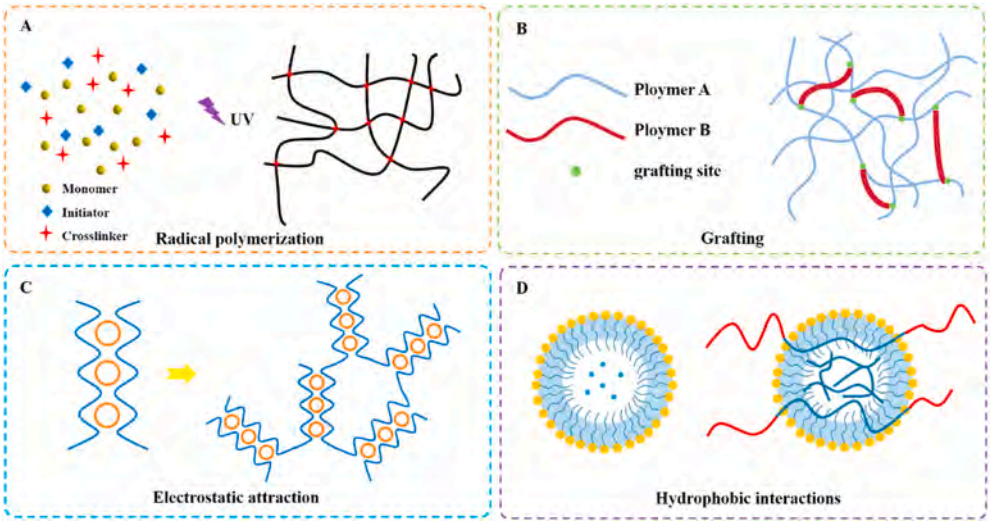

Fig. 2. Fabrication of stimulus-responsive hydrogels. A. Radical polymerization; B. Grafting; C. Electrostatic attraction; D. Hydrophobic attraction.

agents are the main three components used to prepare hydrogels by free radical polymerization. Generally, monomers are water-soluble molecules containing a double bond that can be cross-linked. The cross-linking agent is usually a molecule containing at least two double bonds that can be polymerized. The initiator is a substance that is capable of producing a sufficient quantity of free radicals under appropriate conditions, such as heating, irradiation, or electrolysis. As an example, hydrogels with dual response to pH and temperature have been produced by co-polymerization of acrylic acid and acrylamide using free radical polymerization (Zhou, Weng, Qiang, Zhang, & Jian, 2003). In addition, Shabir et al. (2017) prepared pH-responsive hydrogels by grafting acrylic acid and methacrylic acid as monomers onto these polysaccharides from flaxseed by free radical polymerization.

3.1.2. *Interpenetrating polymer networks*

Interpenetrating polymer networks (IPNs) are a unique polymer blend formed by the interpenetration and entanglement of two polymers through the network (Dashtebayaz & Nourbakhsh, 2019). In this case, however, there are covalent bonds between the polymers within each separate network but not between the polymers in different networks. There are three main types of interpenetrating polymer networks: (i) IPNs, which are formed by two polymer networks interacting and entangled with each other; (ii) homo-IPNs, which are IPNs comprised of two polymers with the same structure that each forms a separate polymer network; and (iii) semi-IPNs, one component is a cross-linked polymer network, while the other polymer consists of linear chains interspersed within the polymer network (Dragan, 2014; Gupta & Srivastava, 1994). It should be noted that a similar kind of structure can be formed by polymer chains that form cross-links through physical interactions (rather than covalent bonds). A new method of fully-interpenetrating polymer network using chitosan as raw material has been studied. Abandansari et al. (2018) developed an injectable fully-interpenetrated polymer network by integration of Diels-Alder (DA) crosslinked network and thermosensitive injectable hydrogel.

3.1.3. *Radiation polymerization*

Radiation polymerization has several advantages, including high controllability of reaction conditions, wide range of monomer selection, and simple processing operations. Therefore, the preparation of hydrogels by radiation polymerization has become a major research focus in recent years (Han et al., 2018). In this case, polymerization is initiated by the generation of free radicals in monomer solutions when they are exposed to high energy radiation. Water-soluble polymers without double bonds can also be cross-linked to form hydrogels under radiation due to the generation of free radicals that promote bond formation between functional groups on different polymer chains. For instance, Ghobashy et al. (2020) prepared a new type of self-healing hydrogel with good mechanical strength by radiation polymerization using acrylic acid monomers as raw material. In another study, a pH-responsive hydrogel based on polysaccharides was prepared (Ghobashy, Elbarbary, & Hegazy, 2021). The pH-responsive hydrogel prepared by crosslinking chitosan with two kinds of anionic polymers by

γ-irradiation can release the drug effectively.

3.1.4. Grafting

According to the type of activated initiator, grafting is mainly divided into chemical and radiation grafting (Fig. 2B). Chemical grafting is initiated by chemical reagents that react with functional groups on the polymer chains, whereas radiation grafting is initiated by high energy radiation (Varaprasad, Raghavendra, Jayaramudu, Yallapu, & Sadiku, 2017). These types of hydrogels have been produced from food-grade polymers. For instance, chitosan-based hydrogel beads with high porosity, good pH responsiveness and biocompatibility have been produced by γ-irradiation graft co-polymerization using L-glutamic acid as a source of monomers (Nisar et al., 2021). These hydrogels have potential for the controlled delivery of anticancer drugs for localized cancer therapy (Nisar et al., 2021). Starch, as a common polysaccharide in food, has also been used to study the preparation of stimulus-responsive hydrogels. A temperature and pH dual-responsive starch was prepared by grafting soluble starch with butyl glycidyl ether and introducing 2-chloro-4, 6-diglycino-[1,3,5]-triazine (CDT) groups (Zhang et al., 2018).

3.2. Physical crosslinking

Hydrogel networks can also be formed by physical (rather than covalent) cross-linking of the polymer chains. These hydrogels are often much more sensitive to changes in environmental conditions, such as temperature, pH, and ionic composition, than hydrogels formed by covalent cross-linking (Jones & McClements, 2010). A variety of different kinds of physical interactions may play an important role in the formation of cross-links between polymer chains.

3.2.1. Hydrogen bonds

Hydrogen bonds play a crucial role in stabilizing the internal structure of some biopolymer molecules, as well as in the formation of cross-links between different biopolymers (McClements, 2015). In polymer solutions, intramolecular and intermolecular hydrogen bonds can act as cross-linking points. These bonds are usually a result of relatively strong dipole-dipole interactions between opposite partial charges on hydrogen atoms (*e.g.*, $-H^{\delta+}$) and other atoms (*e.g.*, $-O^{\delta-}$). Although individual hydrogen bonds are relatively weak, they can act in concert to form relatively strongly cross-links. Hydrogen bond formation typically increases with decreasing temperature, which is linked to the formation of helical regions in polymer chains where multiple interactions can occur. Hydrogen bonds have also been reported to exhibit self-repairing properties (Dai et al., 2015). Examples of food polymers where hydrogen bonding is important are gelatin and agar (Pandey et al., 2017). These polymers undergo a coil-helix transition when cooled, which is linked to a sol-gel transition.

3.2.2. Electrostatic interactions

Electrostatic interactions are also a common type of physical force responsible for cross-linking between polymers. Polyelectrolytes can be cross-linked with polyvalent ions with opposite charge by electrostatic interaction or by electrostatic interaction between two opposite-charged polyelectrolytes (Fig. 2C) (Hoffman, 2002). Alginate is a polysaccharide that is often crosslinked by electrostatic interactions to form hydrogels. Typically, cationic calcium ions (Ca^{2+}) act as salt bridges between anionic carboxyl groups ($-COO^-$) on the alginate chains. pH-responsive core-shell hydrogel microspheres have been prepared that consist of an alginate core surrounded by a carboxymethyl cellulose shell using an *in situ* gelation method, which may be suitable for drug delivery purposes (Yan, Chen, Zhang, Lu, & Sun, 2021).

3.2.3. Hydrophobic interactions

The conformation, interactions, and functional performance of some biopolymer molecules are affected by hydrophobic interactions (Djabourov, Nishinari, & Ross-Murphy, 2013). In particular, these interactions play a critical role in protein folding and lipid bilayer formation (Fig. 2D) (Donald, M., & Engelman, 2005; Tanford, 1978). In stimulus-responsive hydrogels, hydrophobic interactions can be used to reversibly adsorb/desorb target particles. The strength of hydrophobic interactions typically increases with temperature, which can be useful for creating temperature-responsive hydrogels. For instance, temperature-responsive hydrogels have been formed from polymers based on the lowest critical solution temperature (LCST). Below the LCST, the hydrogen bonds between the hydrophilic parts of the polymer chain and water molecules play a dominant role, but above this temperature the hydrophobic interactions become dominant and the hydrogen bonds become weaker (Kim, Jung, Jang, & Huh, 2014). This kind of interaction is important in hydrogels formed from carboxymethyl cellulose, which tends to gel at high temperatures due to an increase in hydrophobic attraction between the methyl groups on the polymer chains.

3.2.4. Crystallization

Some polymers adopt a random coil structure in aqueous solutions under one set of conditions (*e.g.*, high temperatures) but become arranged into ordered structures and form microcrystals under another set of conditions (*e.g.*, low temperatures). These microcrystals can act as physical cross-linking points between the polymer molecules, leading to the formation of a hydrogel network. Crystallization is less common than other physical cross-linking methods but it is often used to prepare PVA hydrogels, where it is usually accompanied by hydrogen bond formation (Nugent, Hanley, Tomkins, & Higginbotham, 2005; Yokoyama, Masada, Shimamura, Ikawa, & Monobe, 1986). A number of food-grade polymers may form hydrogels through this mechanism. For instance, polysaccharides such as agarose, starch and cellulose derivatives usually exist as random coils when dispersed in hot aqueous solutions, but form helical structures when cooled that lead to the formation of microcrystal regions that act as cross-links (Jeong, Kim, & Bae, 2012). Physically cross-linked chitosan grafted poly (vinylalcohol) hydrogels have been formed using this approach by controlled freezing and thawing cycles (Xiao, Feng, & Gao, 2010).

3.3. Enzymatic crosslinking

Compared with other cross-linking methods, enzymatic crosslinking has the advantages of strong specificity, high efficiency, and the use of no toxic residues. Enzymatic crosslinking can produce strong covalent bonds between polymer chains using relatively mild conditions. Moreover, the enzyme molecules themselves do not become part of the cross-linked hydrogel formed. Some of the most common cross-linking enzymes used for this purpose include horseradish peroxidase (HRP) (Wang et al., 2019), transglutaminase (TG) (Tsai, Hong, Lee, Cheng, & Yu, 2019), and tyrosinase (Kim et al., 2018). These enzymes can be used to cross-link food grade polymers, such as many proteins and some polysaccharides. Ruzengwe, Amonsou, and Kudanga (2020) crosslinked Bambara peanut protein with glutamine transaminase. Glutamine transaminase can promote the formation of higher strength hydrogel network and improve the properties of hydrogel. New hyaluronic acid hydrogels based on horseradish peroxidase and choline oxidase double enzyme crosslinking were also developed and found to have good stability and biocompatibility (Gao et al., 2020).

4. Application of stimulus-responsive hydrogels in foods

There are many examples of the application of stimulus-responsive hydrogels in foods. Stimulus-responsive hydrogels can be used to create smart packaging materials to convey food quality and safety information to consumers, to control the delivery of nutrients in the human body, and to detect microbial contaminants in food to ensure food safety (Fig. 3). It can be seen that the application of stimulus-

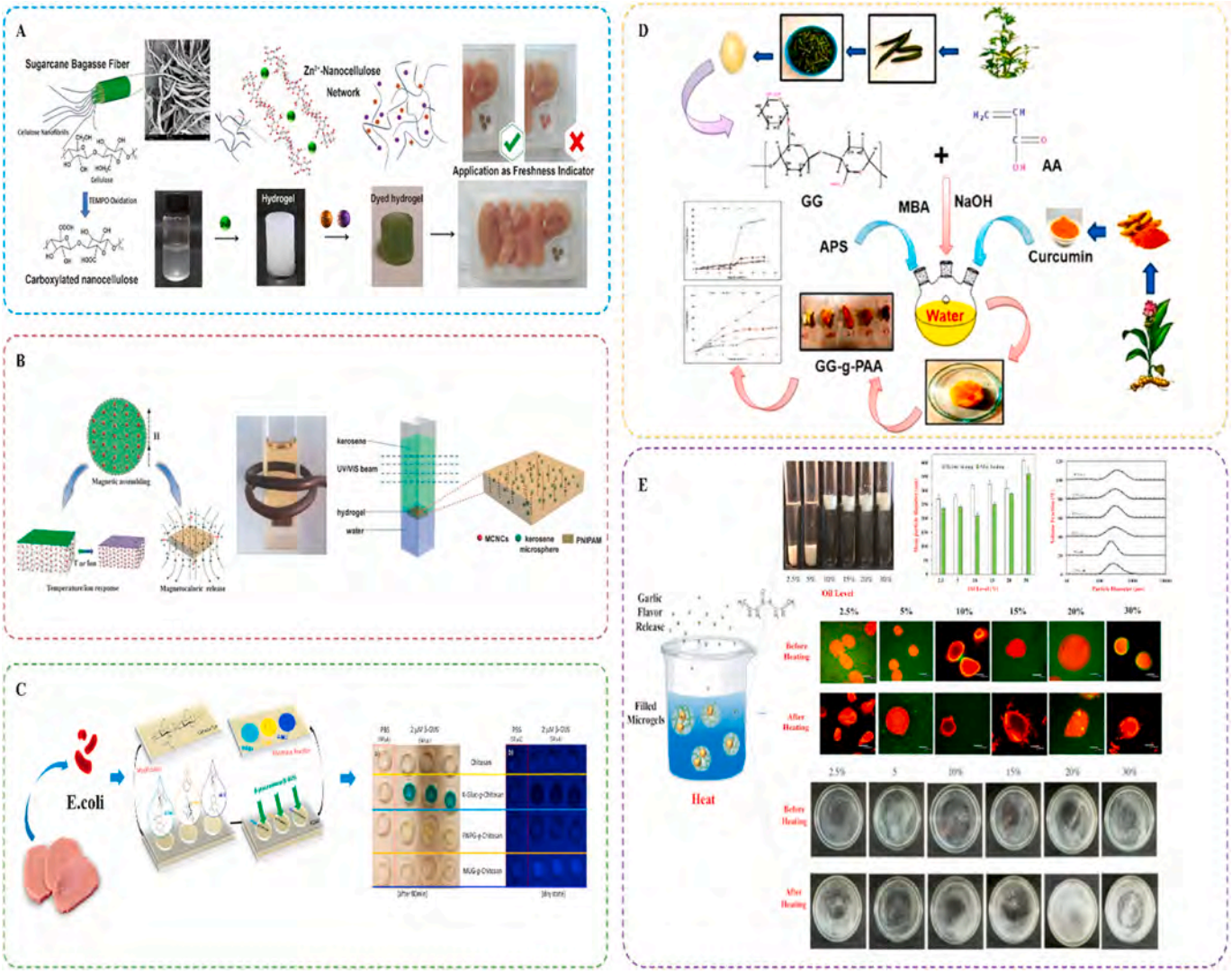

Fig. 3. Application of stimulus-responsive hydrogels in the food field. A. Preparation of stimulus-responsive hydrogel as a colourimetric freshness indicator for intelligent food packaging; B. Application of stimulus-responsive hydrogel for controlled release of dyeing oil; C. Enzyme-responsive hydrogel for detection of multiplexed bacteria; D. pH-responsive hydrogel based on guar gum as a renewable material for delivery of curcumin; E. Application of stimulus-responsive hydrogels in the encapsulation and release of flavors. Source: Fig. 3A is adopted from (Lu et al., 2020); Fig. 3B is adopted from (Wang et al., 2016); Fig. 3C is adopted from (Jia, Mareike, & Holger, 2018); Fig. 3D is adopted from (HaqAsif et al., 2021); Fig. 3E is adopted from (Wang, Doi, & McClements, 2019).

responsive hydrogels in food is very broad and promising.

4.1. Food packaging materials

Food packaging materials can be described as traditional, active, or intelligent according to their intended functions (Batista et al., 2019). Traditional packaging materials are mainly used to create a physical barrier that protects the foods, which depends on their optical, mechanical, and barrier properties. Active packaging materials contain additional functional components that are designed to protect the foods during storage and increase their shelf life, such as antimicrobials or antioxidants. Intelligent packaging materials are designed to monitor the quality and safety of foods during storage and provide information to consumers about their properties (Kalpana, Priyadarshini, Maria Leena, Moses, & Anandharamakrishnan, 2019). For instance, intelligent packaging may contain a colorimetric indicator that changes color in response to a change in pH in the food, which is related to alterations in the maturity, quality attributes or safety of the food (Barska & Wyrwa, 2017). Stimulus-responsive hydrogels can be utilized to create active and intelligent packaging materials. These are often formulated from natural materials (such as food-grade proteins, polysaccharides, and lipids) to as to ensure they have good sustainability, low environmental impact, and low toxicity (Azeredo, 2013).

Some pH-sensitive dyes have been incorporated into stimulus-responsive hydrogels as indicators of food freshness in intelligent packaging. For instance, Lu et al. (2020) prepared nanocellulose hydrogels containing a pH-responsive dye, which gave a color change in response to changes in the quality of chicken breasts during storage (Fig. 3A). Other researchers have also developed pH-responsive chitosan hydrogels from chitosan, polyethylene glycol, and acetic acid, which could be used to assess the quality, freshness, and safety of foods during storage (Athauda, Banerjee, & Karmakar, 2020). Alpaslan, Dudu, Sahiner, and Aktasa (2020) used multi-functional hydrogel as food packaging material and add anthocyanin to hydrogel as a natural plant colorant. The hydrogel can respond to pH and change color, indicating the change of food during storage. In addition, pH-responsive hydrogels for monitoring minced pork spoilage have also been developed (Suthasupa, Padungkit, & Suriyong, 2021).

4.2. Flavor encapsulation and release

Some flavor substances are lost during food processing and storage due to their volatility and chemical instability. Stimulus-responsive hydrogels can also be used to encapsulate and control the release of flavor compounds in foods, thereby improving their quality attributes. The overall sensory perception of foods depends on the type, amount, and rate of volatile flavor compounds released before, during, and after mastication. In this case, it is useful to have strategies to control the release of flavor molecules from foods so that they can reach the appropriate flavor receptors (Cayot, Dury-Brun, Karbowiak, Savary, & Voilley, 2008). Hydrogels can be used to encapsulate flavors and to control their release characteristics (Madene, Jacquot, Scher, & Desobry, 2010). Their effectiveness depends on their microstructure, rheology, and interactions with the flavor molecules (Naknean & Meenune, 2010). For instance, a flavor molecule may be retained within a hydrogel if it is attracted to the molecules in the polymer network but released if it is not (Zeeb, Fischer, & Weiss, 2014). Researchers have developed pH-responsive hydrogels that are dissociated in the presence of saliva, which leads to the release and perception of the encapsulated flavors (Amiryousefi, Mohebbi, Golmohammadzadeh, & Koocheki, 2016). In another study, it has been shown that pH changes can lead to disintegration of gel structures and the release of flavor substances, which can therefore be used as a triggered release system (Kwan & Davidov-Pardo, 2018). In a recent study, it was shown that hydrogels could be used to control the release of volatile garlic flavors during cooking (Fig. 3E) (Doi, Wang, & McClements, 2019; Wang, Doi, & McClements, 2019). These hydrogels broke down in the presence of high salt concentrations, which might be useful for developing ion-induced delivery systems.

4.3. Nutrients delivery

Stimulus-responsive hydrogels may also be used to encapsulate and control the release of nutrients. Nutrients are substances that promote the growth and development of the human body and maintain good health (such as proteins, lipids, carbohydrates, vitamins and minerals), whereas nutrients are minor bioactive substances that may be able to prevent or cure certain kinds of chronic diseases, or enhance human wellbeing or performance (such as polyphenols and carotenoids). The efficacy of these bioactive nutrients is often hampered by their poor solubility, chemical stability, and bioavailability characteristics (Ezhilarasi, Karthik, Chhanwal, & Anandharamakrishnan, 2013; McClements, 2015). Hydrogels, especially microgels, can be designed to encapsulate these bioactive substances and overcome these problems (Liu, Zhang, Li, McClements, & Liu, 2018).

Hydrogels have been utilized by a number of researchers to encapsulate nutrients intended for oral delivery in the food industry. For instance, pH-responsive hydrogels have been developed to increase the chemical stability of β-carotene (Chen, Li, Li, McClements, & Xiao, 2017) and curcumin (Kharat & McClements, 2019) by protecting them from stressors in their environment. They have also been utilized to mask the off flavors associated with some bioactive substances, but then release them in the human gut (Rocha, Coimbra, & Nunes, 2017). Chitosan has been used to fabricate pH-responsive hydrogels that can slowly release nutrients under strongly acidic gastric conditions but then rapidly release them under neutral conditions in the small intestines, thereby enhancing their overall bioaccessibility (Qu & Luo, 2020). Oxidized gelatin and resistant starch have been used to prepare hydrogel microspheres to encapsulate resveratrol and control its release in the gastrointestinal tract (Wang, Luo, & Xiao, 2021). A guar gum hydrogel with pH- and ion-responsiveness has been used to encapsulate and deliver curcumin under gastrointestinal conditions (Fig. 3D) (HaqAsif et al., 2021).

Probiotics are living microorganisms that provide health benefits to humans by altering the composition of the gut microbiota. They have been reported to enhance the development of the immune system and to promote the digestion and absorption of some nutrients. They are often added to yogurt or beverages to promote human intestinal health (Sylvia, Edward, & Jones, 2006). However, it is important to ensure that a sufficiently high level of active probiotics reach the colon to have beneficial effects on the human body. pH-responsive hydrogels have been developed as delivery systems for probiotics. For instance, hydrogels assembled from pineapple pulp cellulose have been used to protect probiotics from the highly acidic environment in the stomach and then release them in the neutral environment of the small intestine (Xing & Huang, 2021). pH-responsive hydrogels have also been assembled from peach gum polysaccharide (PGP) and *Auricularia auricula* polysaccharide (APP) using an inverse emulsion cross-linking method (Zhu, Yu, Chen, & Song, 2018). These hydrogels contained a PGP-APP semi-interpenetrating network that was relatively stable and dense, which helped to protect the probiotics within a gastrointestinal tract model.

4.4. Food risk monitoring

Contamination of foods with microbes can lead to a reduction in shelf life, increased food waste, and food safety concerns (Kumar et al., 2017). Therefore, the ability to rapidly detect microbial contamination of foods is important. Traditional plate counting methods for detecting bacteria are accurate but time consuming, and so there is a need for alternative rapid methods. A number of researchers have examined the potential of using stimulus-responsive hydrogels for this purpose (Su, Ge, Chen, & Xu, 2020). The adhesion of bacteria to hydrogel sensing interfaces is affected by many factors, including moisture, chemical composition, polarity, and charge. Electrostatic, hydrophobic, and hydrogen bonding interactions often play an important role in determining the adhesion of bacteria to hydrogel surfaces, but these interactions are often not targeted and specific. Therefore, components such as enzymes, antibodies, and polysaccharides are often added to the hydrogel matrix to enhance their selectivity and sensitivity (Su et al., 2020).

Enzyme-responsive hydrogels have also been explored for their potential to detect bacterial contamination (Fig. 3C). These hydrogel-based sensors can be used to detect bacterial metabolites in an environment suitable for bacterial growth, which allows one to identify the presence of specific bacteria (Su et al., 2020). This method is accurate, but it takes a relatively long time. *Escherichia coli* is an important form of bacteria that contaminates foods. Eating food contaminated by *E. coli* may cause intestinal diseases such as dysentery and pose a serious threat to human health. Therefore, there is a need to rapidly detect *E. coli* to improve food safety (Vogt et al., 2005). A sensing hydrogel has been developed for the rapid and selective detection of the enzymes secreted by the O157:H7 strain of pathogenic enterohemorrhagic *Escherichia coli* (EHEC) (Ebrahimi, Dohm, Mueller, Jansen, & Schoenherr, 2016). This sensor was able to discriminate the pathogenic O157:H7 strain of *E. Coli* from a non-virulent K12 strain. These chitosan-based hydrogels were formed by attaching a series of fluorescence sensors to the chitosan molecules in the gel network, which enabled different enzymes and bacteria to be determined. The further development of composite hydrogels that combine highly sensitive fluorescence/chromogenic reagents, bioactive enzymes, and hydrogels will lead to a wider range of enzyme-responsive hydrogels for bacterial detection and identification.

4.5. Miscellaneous applications

Stimulus-responsive hydrogels can also be used for the separation of proteins and lipids in the food industry. For instance, stimulus-responsive hydrogels have been developed that are hydrophobic under one set of conditions and so can selectively adsorb a hydrophobic target. However, when the conditions are altered, the stimulus-responsive hydrogels become hydrophilic and the affinity to the hydrophobic target is weakened, thereby leading to its release. Temperature-responsive polymer composite hydrogels have been assembled from

acrylic acid, polyoxyethylene ether, and N-isopropylacrylamide monomers (Liu et al., 2015). These hydrogels were able to adsorb a model protein (bovine serum albumin) from aqueous solutions over certain temperature ranges. PNIPAM clay nanocomposite hydrogels have been fabricated using an *in situ* free radical polymerization for application as filtration membranes (Teng, Xie, Wang, Zhu, & Jiang, 2016). The membrane material developed was shown to be suitable for performing oil/water separations because of its strong hydrophobicity, anti-adhesion, and self-cleaning attributes. Hydrogels with temperature-, ion- and magnetic-responses have also been developed that have potential for application in foods. These hydrogels changed color, contracted, or swelled under the external stimulation, which could be utilized to control the retention and release of a model lipophilic dye (Fig. 3B) (Wang, Yang, Wang, Chen, & Chen, 2016). In addition, stimulus-responsive hydrogels have been developed for visual detection of substances in food. A *o*-phenanthroline composite hydrogel was formed by free radical polymerization that was successfully used for high-throughput visual detection of free Fe^{3+} in milk (Victoria Martinez, Rivarola, Cristina Miras, & Barbero, 2017).

5. Summary and future outlook

The microstructure or physicochemical properties of stimulus-responsive hydrogels respond to changes in environmental conditions, such as pH, ionic composition, temperature, light exposure, or enzyme activity. For instance, there may be a change in pore size (swelling/shrinking), interactions (attraction/repulsion) or integrity (gel-sol transition). Stimulus-responsive hydrogels can therefore be considered to be "intelligent" or "smart" materials that have a number of potential applications in foods. Previously, they have been mainly been used for non-food applications, such as tissue engineering (Jiang et al., 2019), drug delivery (Li & Mooney, 2016), biosensor development (Culver, Clegg, & Peppas, 2017), textiles (Stular et al., 2017), and sewage treatment (Sharshir, Algazzar, Elmaadawy, Kandeal, & Yang, 2020). Despite their great potential, there have only been a relatively few studies on the application of stimulus-responsive hydrogels in foods. For instance, they have been used for the development of intelligent food packaging materials (Athauda et al., 2020), the triggered release of nutrients, and the detection of harmful microorganisms (Zhao et al., 2018). There is therefore considerable scope for further research in a broad range of application areas in the food industry. In particular, there is a need to identify suitable food-grade materials that can be used to assemble hydrogels that will respond in a controlled way to specific external stimuli. Moreover, there is a need to identify suitable fabrication methods that can economically produce these hydrogels at a scale that is suitable for commercial applications. Finally, there is a need to explore a wider range of applications within the food industry. For instance, hydrogels whose appearance or texture changes in response to a specific change in environmental conditions could be used to create foods with novel quality attributes and that produce novel sensory sensations. Moreover, further research is required to create delivery systems that will retain and protect bioactive molecules within foods but then release them in specific locations of the human gastrointestinal tract (such as mouth, stomach, small intestine, or colon).

Author statement

Zhongyu Yang: data curation, writing draft and funding acquisition. Long Chen: data curation, writing draft and funding acquisition. David Julian McClements: supervision, conceptualization, review and editing. Chao Qiu:supervision and project administration. Cuicui Li:visualization and editing. Zipei Zhang: visualization and editing. Ming Miao:supervision and project administration. Yaoqi Tian: supervision and project administration. Kunfu Zhu:visualization and data curation. Zhengyu Jin: supervision, review, and funding acquisition.

Declaration of competing interest

No conflicts of interest are declared for any of the authors.

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