

REVIEW ARTICLE

SMART HYDROGEL POLYMERS FOR DRUG DELIVERY

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Summary

Smart hydrogels are special type of hydrogels that undergo solution-gelation transition in response to alterations in the environment. Solution-gel transformation is brought about through either physical or chemical cross-linking that occur between the hydrogel chains. Various stimulating factors have been identified to be responsible for the change in the physical state of the intelligent hydrogel. The most important triggering factors are the temperature, pH, ions, electrical signalling, magnetic field, glucose, light and others. Each of these stimulating factors can trigger the swelling of the hydrogel through unique mechanism. Many of these triggering factors are characteristics of the biological systems which make the smart polymers quite beneficial for different biomedical applications. Numerous natural and synthetic polymers have been distinguished to act as smart materials. These polymers impressed the scientists to use them in many biomedical and industrial applications such as drug delivery systems, gene therapy applications, tissue engineering and many other applications.

Key words: hydrogel; solution-gel transformation; smart drug delivery; stimuli-sensitive polymer

Introduction

Hydrogels are defined as three-dimensional networks comprised of hydrophilic polymers that are cross-linked together (1, 2). Hydrogels have the ability to absorb large quantities of water (or physiological fluids) approximating to thousands folds of their initial dry weight with the formation of solid or semi-solid gel structures (2). The cross-linking between polymer chains could involve either physical or chemical interactions. The physical cross-linking usually results in transient intersections, which involves either chain entanglement or weak forces such as hydrogen-bonding, hydrophobic interactions or ionic bonding (3). On the other hand, chemical cross-linking involves covalent bonds and results in permanent junctions (3).

Hydrogels were first utilised as a delivery system for biological application in 1960 by Wichterle and Lim (4). Thereafter, the interest in hydrogels has been increased enormously with thousands of research articles being published on this topic (5). The fame of hydrogels is related to their unique characteristics including biocompatibility with the biological cells and tissues, biodegradability, drug loading capacity, their ability to protect drugs from the surrounding media and capability to produce zero-order controlled drug release (5). These distinctive properties are linked to their rich aqueous content, good miscibility in water and physiological fluids and their soft texture (6).

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In situ gels are intelligent hydrogels, also known as stimuli-responsive hydrogels. they behave, smartly, in response to alterations in the environment (5, 7). They are liquid preparations composed of aqueous polymer solution that undergo solution-gel transmission under the influence of external stimuli (5). The use of these preparation as drug delivery systems would result in dual benefits of being freely flowing during usage which would result in facilitated drug intake with improved patient compliance along with the prolonged contact time with the tissue at the site of application (resulted from the *in situ* formed gel) leading to greater drug bioavailability and improved therapeutic efficacy (7). The type of the triggering stimuli for the *in situ* gelation depends on the type of the polymer used in the formulation whether natural polymers such as chitosan derivatives or synthetic polymers such as poloxamers (8).

Both physical and chemical stimulating factors have recognised and investigated to be responsible of the *in situ* gelation (6).

Since their invention, these systems have gain tremendous focus in experimental studies. Various applications of *in situ* gelling systems have been emerged such as tissue-engineering, gene-therapy and drug delivery system (6). This review focus on different classes of polymers that undergo *in situ* gelation along with examples of these polymers.

Types of triggering factors for stimuli-responsive hydrogels

Smart hydrogels could be classified according to the sort of the external stimuli that triggers the cross-linking between polymer's chains leading to the gelation process (6, 9). Various stimulating factors have recognised including: temperature, pH, ions, electrical signal, light, glucose, enzyme, magnetic field, antigens and others (6).

1. Temperature triggered *in situ* gelation

The thermos-sensitive polymers have both hydrophilic and hydrophobic elements within their structures. The delicate balance between these two portions in the polymer monomers determines the temperature response phenomenon (10). Alteration in temperature causes a change in the interaction between the hydrophilic and hydrophobic sections with aqueous molecules leading to changes in the cross-linked matrix solubility with the resulting phase transition (10, 11). In general, the gelation mechanism involves macroscopic micelles aggregation which could be classified into three distinct types as demonstrated in Figure (1).

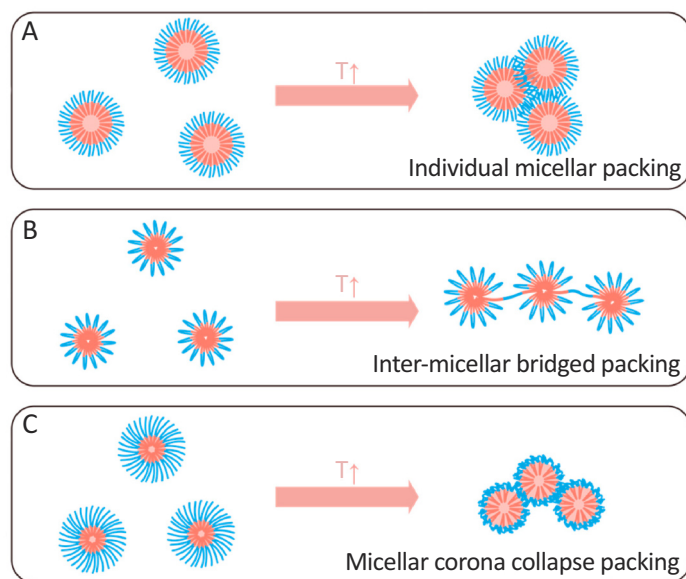


Figure 1. The different micellar-aggregation mechanisms. (A) represent the individual micellar packing, (B) represents the inter-micellar bridged packing and (C) represents the micellar corona collapse packing (11).

Thermal responsive hydrogels could be sub-classified into three different classes, depending on the critical gelation temperature, including: negative-temperature systems, positive-temperature systems and thermo-reversible systems (10, 12). The negative-temperature systems are those that possess low critical temperature, so they undergo gelation as the surrounding temperature falls below this critical temperature (12, 13). In contrast, the positive-temperature systems have high critical temperature and they swell when the temperature of the environment exceeds the critical point (12)(13). Swelling-shrinking mechanism, which is brought about through covalent crosslinking between polymer chains, is responsible for gelation in both negative and positive temperature systems (10, 13). On the other hand, thermo-reversible systems are systems that exhibit gelation mediated by temperature-sensitive solution-gel phase transition mechanism rather than through shrinking-swelling approach. Different molecular interactions are involved in the volume changes of thermo-reversible systems including hydrogen-bonding and hydrophobic interactions (13).

To be optimum temperature-sensitive hydrogel system, the polymer solution should be freely flowing at room temperature (~23 °C) while converting into non-flowing gel at physiological temperature (32-37 °C) after application or administration (8). The ideal critical temperature for solution-gel transition is the physiological temperature, since this would facilitate the clinical manipulation and no additional heat source (in addition to the body temperature) is required for gelation to happen (14).

There are many polymers that exhibit the temperature-sensitive behaviour such as poloxamers (Pluronics), chitosan derivatives, cellulose derivatives, N-isopropylacrylamide derived systems, PEG/PLGA derived systems and gelatine (15).

1.1 Poloxamers (Pluronics)

Poloxamers are triblock co-polymers composed of poly (ethylene oxide)-b-poly (propylene oxide)-b-poly (ethylene oxide) (PEO-PPO-PEO) (8, 10).

The thermo-sensitive characteristic of poloxamer is linked to the presence of hydrophilic (ethylene oxide) and hydrophobic (propylene oxide) portions within their structure (10). The critical gelation temperature can be adjusted by changing concentration, composition and molecular weight (10). Gelation occurs due to variations in the physicochemical properties of the poly ethylene oxide and poly propylene oxide portions that form the structure of the poloxamer triblock (10). As the temperature increases, the poloxamer blocks will gather forming micelles in which the hydrophobic (PPO) chains are folded forming the core of the micelles while the hydrophilic (PEO) chains are joined with water forming a shell that cover the micelle core (15)(10). Further increase in temperature will cause the micelles to gather up forming larger micelles and at this time, gelation take place (10). The general structural formula of poloxamer is illustrated in Figure (2).

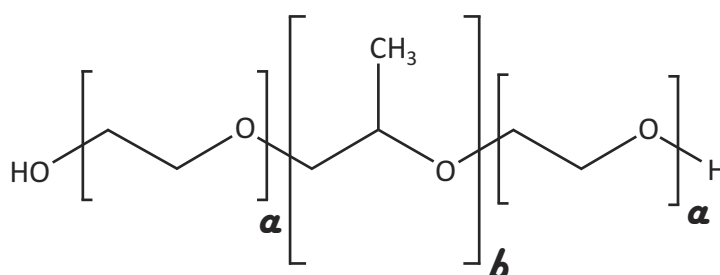


Figure 2. The general structural formula of poloxamer (16).

Poloxamers are available commercially under the name of Pluronics®. They consist of a wide diverse of materials that vary in their surface active and physical properties depending on the values of (a), the PEO, and (b), the PPO, parameters. These two parameters represent the relative quantities of ethylene oxide and propylene oxide groups used during their synthesis (16). The typical poloxamer grades are represented in Table (1).

Table 1. The typical grades of poloxamer (16).

| poloxamer | Physical form | A (quantities of ethylene oxide) | B (quantities of propylene oxide) | Average molecular weight |
|-----------|---------------|----------------------------------|-----------------------------------|--------------------------|
| 124 | Liquid | 12 | 20 | 2090-2360 |
| 188 | Solid | 80 | 27 | 7680-9510 |
| 237 | Solid | 64 | 37 | 6840-8830 |
| 338 | Solid | 141 | 44 | 12700-17400 |
| 407 | Solid | 101 | 56 | 9840-14600 |

Poloxamer 407 (P407) is solid at room temperature. It is composed of 73% of ethylene oxide (16, 17). Poloxamer 407 is a non-toxic and non-ionic surface-active agent with reversible thermo-sensitive gelation characteristic. It is well-recognised by the FDA as an “inactive ingredient” with many applications in pharmaceutical industry including intravenous preparation, ophthalmic formulations, topical dosage forms and oral formulations (solution and suspension) (17).

1.2 Chitosan

Chitosan is a natural cationic polysaccharide derived from chitin which is insoluble polymer naturally occurs in the crustacean exoskeleton, insect exoskeleton, fungi, algae cell-wall and others (18, 19). Chitin is one of the most popular natural-occurring polymers (only second to cellulose) (19, 20). The hydrolysis of chitin under alkaline conditions gives chitosan with improved solubility profile (10, 18).

Chitosan is non-toxic, biocompatible, biodegradable and suitable for incorporating both hydrophilic and lipophilic medications which make it superior to many natural polymers (8, 10). In addition, chitosan has mucoadhesive properties which increase the contact time at the site of application and improve the efficiency of drug delivery (8). However, the thermo-sensitive gelation property of chitosan is weak and results in hydrogels that suffer from poor thermal and acidic stability and poor mechanical strength (19). In order to overcome this obstacle, physical and chemical cross-linking approaches have been used through the addition of various cross linkers to chitosan (10, 19). The amine and hydroxyl groups of chitosan are the active groups that react with the cross linker leading to gelation (10). Physical cross linking mechanisms usually mediated by ionic bonds while chemical ones are brought about by covalent bonds leading to much stronger gel strength (19). Most of the chemical cross-linkers are biologically incompatible such as glutaraldehyde, formaldehyde and others. This is in contrast to the physical cross-linkers such as sodium tripolyphosphate and oxalic acid as they are non-toxic and biocompatible (19).

1.3 Cellulose derivatives

Cellulose is the most copious naturally produced polymer (18, 21). Cellulose is composed of polysaccharide chain made of glucose unite that are linked together through beta-1,4 chemical bonds (18, 21). Cellulose is insoluble in aqueous solutions, however, the esterification of the hydroxyl group of cellulose using hydroxypropyl or methyl entities would impart water solubility feature to the originally insoluble cellulose (10, 22). Methylcellulose is the most frequently investigated cellulose derivatives for incorporation as *in situ* gelling agent (21).

Methylcellulose is thermo-sensitive polymer, which undergoes multi-step gelation process starting from hydrophobic association followed by phase-separation which ultimately leads to gelation (18). Methylcellulose has numerous beneficial characteristics including film-forming tendency, fat insulation activity and low moisture and oxygen permeation rate (18). On the other hand, methylcellulose suffered from many drawbacks. First of all, it possesses relatively high critical gelation temperature (about 60-80 °C). This makes it inappropriate to be used alone as *in situ* gelling agent (10). Different approaches were applied to address this limitation and adjust the critical temperature to be closer to the physiological temperature. The most important one is through modifying the chemical structure of methylcellulose and combining it with another materials (such as hyaluronic acid) (18, 21). Furthermore, methylcellulose exhibited relatively low muco-adhesion properties which would negatively influence the efficiency of its use as a drug delivery system (18).

1.4 Poly N-isopropyl acrylamide derived systems

Poly N-isopropyl acrylamide (pNIPPA) is one of the most common synthetic polymer to be utilized in the fabrication of smart thermos-sensitive hydrogels in biomedical practice (23). The chemical structure of pNIPPA is characterized by the presence of both hydrophilic functional group (amide) and hydrophobic side chain (isopropyl) (24).

Many approaches have been applied in the synthesis of pNIPPA. The most frequently used methods are free-radical polymerization, graft co-polymerization and atom-transfer radical polymerization (23, 25). pNIPPA derived hydrogels have low critical solution temperature of around 32 °C which is a bit below the physiological temperature (about 37 °C). Unlike natural products, synthetic polymers have many drawbacks including inadequate mechanical strength, limited capacity of drug loading and inferior biodegradability (24). Therefore, the efficiency for using pNIPPA derived hydrogels can be maximised by either co-polymerization with other polymers (either natural or synthetic) or through combination with self-assembled organic systems or inorganic based nanoparticles in order to improve the critical solution temperature, drug loading efficiency, biocompatibility and physical strength of the formed gel (23, 24). These properties enable pNIPPA derived hydrogels to be very useful for various applications and functionalities in biomedical scale as smart materials (23, 24). For instance, they are suitable candidates for incorporation as drug delivery carriers with controlled drug release profile, wound dressings, enzyme immobilization, cell cultures and tissue engineering platforms (24, 25).

1.5 PEG/PLGA derived systems

These are produced through copolymerization between two synthetic polymers, namely, the polyethylene glycol (PEG) and poly ((lactic acid) co-(glycolic acid)) (PLGA) (10). Both of these synthetic polymers are FDA approved for biomedical applications (26, 27). PEG is hydrophilic substance which imparts biocompatible property to the prepared copolymer, while PLGA is hydrophobic polymer with biodegradable characteristic that is resulted from its ester foundation (27). The rate of biodegradation can be adjusted by controlling the proportion of lactide to glycolide within the PLGA blocks as well as the proportion of PEG to PLGA within the copolymer (26). On the other hand, the ratio of PEG to PLGA, also, influence the critical gelation temperature of the copolymer-based hydrogel (27). It had been estimated that a ratio of greater than one is required to fabricate thermos-sensitive hydrogel having critical gelation temperature close to the physiological temperature (27).

The diblock systems are unable to produce hydrogel due to their high aqueous solubility, while the triblock systems are excellent thermos-sensitive polymers that can form hydrogels with adjustable properties (27). PEG/PLGA triblock hydrogels are extremely useful for the preparation of controlled drug delivery systems of hydrophobic medications with the intentions to give extended release profile (up to several months) (28).

1.6 Gelatine

Gelatine is a natural occurring polymer (29). It can be produced by enzymatic, acidic or basic hydrolysis of collagen which can be obtained from bovine or porcine (29). Its chemical structure is based on peptide with a high proportion of the amino acids, namely, proline, hydroxyproline and glycine (29, 30). Gelatine is one of the components of the extracellular matrix, which imparts many benefits to its use as biomedical substance (29, 31). For instance, it is considered safe, non-immunogenic, biocompatible and biodegradable (29, 31). In addition, it is very rich in factors that can stimulate cellular adhesion, multiplication and differentiation (29).

Gelatine based hydrogels are unique among other thermo-sensitive hydrogels of being negative-temperature systems (29)(31). They have low critical gelation temperature of about 35 °C above which gelatine solution is liquid and upon cooling below this temperature a gel is formed by physical cross-linking (29, 31).

Untreated gelatine hydrogels have numerous disadvantages including poor gel strength and fast degradation (29). Modification of gelatine can be brought about through the numerous functional groups located on the side chains leading to enhanced cross-linking. This modification could be achieved through either enzymatic reactions

(mediated by tyrosinase or transglutaminase enzymes) or through covalent bonding using glutaraldehyde (29). These modified gelatine hydrogels have improved properties.

2. pH triggered *in situ* gelation

pH-sensitive polymers (known as polyelectrolytes) are defined as those that contain either acidic or basic groups within their chemical structures (14, 32). These groups are capable of accepting or releasing a proton in response to alteration in the environmental pH in the same way as monobases or monoacids (14, 32). However, the dissociation constants (pKa) of these groups are very unique resulting from the fact that they are unable to become completely ionized due to the influence of the electrostatic repulsive forces that are scattered along the neighbouring polymer chains (33). The physical characteristics of these polymers, particularly, volume, chain entanglement and solubility are greatly influenced by the surrounding factors especially pH and ionic strength (33). Therefore, their aqueous solutions can undergo transition between two different states. The first state is the highly condensed (packed) state in which the polymer chains are extremely coiled and this state exist when the pH of the solvent interfere with the ionization of the polyelectrolytes (34, 33). While the second one occurs when the basic or acidic groups of the polymer become ionized this will create great repulsive forces between the ionised groups that present along the polymer basal structures leading to polymer expansion (swelling) with great increase in hydrodynamic volume (34, 33).

The pH sensitive behaviour depends mainly on the pKa of the polyelectrolytes (35). The pKa is defined as the pH of the environment at which equilibrium is established between the concentrations of the ionised and the unionised forms (35). pKa provides a reflection about the behaviour of the pH-sensitive polymer at different pH values (35). Accordingly, polyelectrolytes can occur in two distinct classes (34-35). The first one is the cationic pH-sensitive polymers, such as chitosan, which undergoes swelling at relatively low pH range, while the second class (the anionic pH-sensitive polymers) exhibits swelling at relatively high pH scale (35). There is a great variation in the pH of the physiological fluids, therefore there is a great opportunity to enhance the drug delivery through the use of smart polymers that specifically undergo swelling/shrinkage transition at physiological pH (14, 32, 36). The gelation pH of the smart polymer could be precisely tailored. This can be achieved by either altering the ionisable groups or modifying the polymeric backbone structure (33).

Many of the natural polymers that have thermo-sensitive behaviour also exhibit pH-sensitive characteristics. They are said to have dual thermo-pH sensitivity. Examples of such polymers include chitosan, cellulose and gelatine (34). Chitosan is the only cationic natural polymer with a pKa of about 6.5. Therefore, when the pH of the solution drops below 6.5, chitosan undergoes swelling (34). On the other hand, certain modifications in cellulose structure would impart pH sensitivity character (34). For instance, the addition of cystamine to the aqueous solution of cellulose acetoacetate would results in smart hydrogel with pH sensitivity character (34). Finally, various techniques have been utilised to produce gelatine based hydrogel with pH-responsiveness including nanogel fabrication using polymerization of emulsion in the absence of solvent, copolymerization with acrylic acid and methacrylate and beta-cyclodextrin grafting technology (34, 37, 38).

Synthetic polymers that demonstrate pH-triggered *in situ* gelation are acrylic acid derivatives (such as carbopol and poly (N,N -dimethylaminoethyl methacrylate)) and polyethylene glycol (PEG) (15, 33).

2.1 Hyaluronic acid based systems

Hyaluronic acid (HA) is a natural negatively charged polymer that contains carboxylic acid moiety within its structure (39, 40). The chemical structure of HA belongs to linear polysaccharide group that is composed of repeating disaccharide blocks (39, 40). Each disaccharide is made of N-acetyl glucosamine and D-glucuronic acid monomers that are linked together through $\beta(1,3)$ and $\beta(1,4)$ glucosidic linkages (39, 40).

HA is widely distributed in-vivo as a major component of the extracellular matrix and synovial fluid (40). It performs several functions such as lubrication and supporting the general shape of matrix between cells (33). in addition, HA play a significant part in the signalling process between cells that influence cellular growth, multiplication and differentiation as well as in the inflammatory responses (41). Hence, HA is highly biocompatible

with the living tissues which makes it very promising to be used as biomaterial in various applications. Also, HA is safe, biodegradable, biologically-reactive with exceptional rheological characteristics (40). However, it is highly viscous and susceptible to numerous enzymatic activities leading to rapid degradation. Both of these disadvantages limit the effective biomedical utilisation of HA (40).

2.2 Acrylic acid and methacrylic acid derived systems

Poly (acrylic acid), known as carbopol, is composed of acrylic acid monomers that are cross-linked forming a polymer with high molecular weight (14). Carbopol has the advantage of being mucoadhesive polymer which further improves the drug delivery (16). This mucoadhesive character results from hydrophobic interactions, hydrogen bonding or electrostatic interactions (16). There are many derivatives of carbopol that are commercially available such as carbopol 934 and carbopol 940 (15).

Carbopol (acrylic acid polymer) undergoes solution-gel transition as the pH of the aqueous solution exceeds its pKa, which is equal to 6 (14, 42). Carbopol has an anionic carboxyl group that experiences a partial dissociation in aqueous solution which begins to straighten forming elastic coil structures (15). The degree of dissociation and ionization highly depends on the pH of the surrounding environment. In acidic environment, only small portion of the polymer's carboxyl group become dissociated and their solution maintain flowability (no gelation occurs) (15). As the pH increases and exceeds the pKa of the polymer, a great proportion of the carboxyl groups will be ionized and accompanied with subsequent production of anionic charges that cover the backbone of the polymer (15). These negatively charged groups will generate electrostatic repulsive forces between them causing uncoiling and expansion of the polymer (up to 1000 folds of its initial volume) with the resulting gel formation (15).

Other acrylic acid based polymers belong to the group known as poly (alkylacrylic acid). In this group, the most important polymers that possess pH responsive nature include poly (propyl acrylic acid), poly (ethacrylic acid) and poly (methacrylic acid) (43, 44). All of these polymers have been investigated as a carrier for gene delivery (43, 44). They demonstrate pH-dependent membrane adhesion property as confirmed by their haemolytic ability. This property further increase their gene carrier efficacy (43, 44).

Methacrylic acid, on the other hand, is synthetic monomer industrially produced by oxidative reaction of alkenes obtained from petroleum (45). Esterification of methacrylic acid with various chemicals results in the formation of compounds with specific biomedical importance (46). These esters have been used as the building blocks of many functional polymers such as hydroxyethyl methacrylate, methoxyethyl methacrylate and N,N-dialkylaminoethyl methacrylate (12).

Poly (N,N-dimethylaminoethyl methacrylate) (PDMAEMA) is methacrylate derived synthetic polymer with pH responsive character (47). It is positively charged polyelectrolyte that includes a tertiary amine group within its chemical structure (47). It is soluble in aqueous solutions with a pKa of about 7.3, which is very close to the pH of the physiological fluids and this property makes it ideal smart polymer for the application in hydrogel formulations for the delivery of anionic drug molecule, as well as, genes and enzymes (47). Swelling of the polymer occurs in acidic environment as a result of the protonation of tertiary amine group when the pH is lower than the pKa which leads to electrostatic repulsion of the positively charged polymer chains (47). In addition, PDMAEMA have temperature sensitivity nature with lower critical gelation temperature ranging between 32 °C and 53 °C (48). Accordingly, PDMAEMA is considered one of the dual pH-thermal responsive polymers which further increase its usefulness as a smart polymer in biomedical fields (47, 48).

3. Ion triggered *in situ* gelation

Ion-triggered polymers are negatively charged polysaccharides that are able to interact with the positively charged ions that present in the physiological fluids (like Ca^{2+} , Na^{1+} , K^{+1} , Mg^{2+} and others). The overall solution-gel transmission is best described by "egg-box" model which was introduced by *Fraeye et al.* (49)(50). According to this model, the first step in the gelation involves the dimerization between two identical parallel chains of the polymer that occur through interaction with Ca^{2+} ions (or other cations) (15, 51, 52). This step is facilitated by electrostatic forces and hydrogen bonding. Thereafter, Ca^{2+} ions promote the aggregation of the formed dimers (known

as the egg-box) through electrostatic interactions with the generation of tetramer, hexamer and so on (51). The ion-triggered gelation is demonstrated in Figure (3).

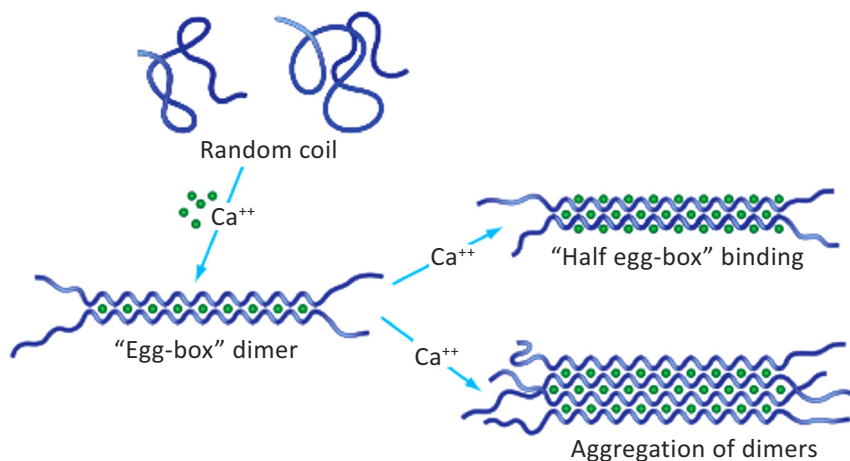


Figure 3. The egg-box model for ion-triggered gelation (50).

Biological fluids are very rich in cations (particularly Ca^{2+}) so the use of these systems is very useful to achieve prolonged residence time and controlled release behaviour of the formulation (51).

Pectin, alginate and Gellan Gum are the most frequently ion-responsive polymers used for drug delivery (51).

3.1 Pectin

Pectin is ion-sensitive polysaccharide that is consisted of galactourinic acid (52). It is obtained from natural sources, particularly, from cell-wall of plants (52). It is a hydrophilic polymer characterized by two distinct structural areas (52). The first area is the flat backbone area which is composed of D- α -galacturonate units that are joined together through (1,4) glycosidic linkage (15, 51, 52). The second area is the hairy area or the branched area which is made of simple sugars such as D-glucose, D-galactose, D-xylose, L-arabinose or L-rahmnose (52). The extent of galactourinic acid esterification/methoxylation determines the gelling character of the polymer (52). Pectin with high extent of methoxylation lacks the ion responsive behaviour while pectin with lower extent of methoxylation rapidly responds to the alteration in the ionic conditions (15, 51). In addition, pectin has mucoadhesive and penetration enhancer properties, both of which are very beneficial for development of drug delivery systems (51).

3.2 Alginates

Alginates are negatively charged natural polysaccharides extracted from the cell wall of certain seaweed (marine algae) (53, 54). Chemically, they are long molecular chains in which two types of monomers are exist (53, 54). Firstly, (1,4)- α -L-glurunic acid entities, which provide the polymer with linearity and elasticity, while the second monomer type is composed of (1,4)- β -D-mannuronic acid, which is responsible for the rigidity of the polymer (53, 54). The relative proportion of these two building blocks within the molecular chain determine the overall physicochemical nature of alginate (whether elastic or rigid) (53, 54).

Alginates have many advantages that make them very promising materials for various biomedical functionalities (such as drug delivery, implant and tissue engineering and wound dressing) (53). Some of these advantages include alginate is biocompatible, soluble, having concentration dependent viscosity, pseudoplastic rheological property and good porosity (53). However, these polymers are not free from limitations and challenges such as rapid biodegradatin and the instability in living organisms (caused by cellular adhesion character). Also, they resulted in hydrogels that possess insufficient mechanical strength (53).

3.3 Gellan Gum

Gellan Gum is a natural occurring linear polysaccharide produced by bacteria named *Sphingomonas elodea* (51). It is formed as exocellular negatively charged polymer that require complete de-esterification by alkali treatment prior to commercial utilization (15). This de-acylated Gellan Gum (DGG) is a polymer composed of tetra saccharide monomers which are (1, 3)-b-D-glucose, (1, 4)-b-D-glucose, (1, 4)-a-L- rhamnose and b-D-glucuronic acid in a molar ratio of 1:1:1:1 (51). DGG results in the formation of non-flexible hard gel. In contrast, the acylated Gellan Gum would produce elastic transparent gel (51). The gelation process involves two steps (51). The first one is the double helical formation step followed by cationic complexation step. Both of these steps are triggered by cations (51).

4. Electrical signal activated *in situ* gelation

Electrical current is one of the environmental stimuli that can trigger hydrogel response (55, 56). Polyelectrolytes (pH sensitive polymers) are usually used in the manufacture of electro sensitive hydrogels (55, 57). Polyelectrolytes undergo conformational changes in response to the applied electrical signal which appear in the form of swelling, shrinking or bending (which occurs when the hydrogel undergoes swelling on one side and shrinking on the other side) (55, 57). The exact response type is determined by the position of the electrical electrode with respect to the hydrogel surface whether there is a direct contact between the electrodes and the hydrogel surface or if the hydrogel is settled in aqueous medium into which the electrodes are introduced. Also, the presence of electrolyte within the system has a major impact on the hydrogel's response to the electrical field. These effects become apparent upon comparing the electrical triggered response of poly acrylamide based hydrogel with that of sodium acrylic acid-acrylamide copolymer based hydrogel (55, 57). In the former case, the direct application of electrical impulse to the surface of the hydrogel would result in shrinkage of the hydrogel mostly at the anode site. This volume collapse at the anode is attributed to the simultaneous migration of aqueous hydrogen ion to the cathode (with the subsequent loss of water at the anode) and the attraction of the anionic acrylic acid groups toward the anode (55, 57). While in the latter case, the electrical field is delivered into aqueous solution in which the hydrogel is placed in such a way that the electrodes are not in direct contact with the hydrogel surface. The hydrogel response is influenced by the quantity of electrolyte (sodium ions) that present in the aqueous solution. If too little or even no electrolytes are present in the system, then the hydrogel tends to shrink due to the migration of sodium ions to the cathode so that the sodium carboxylate group of the polymer would be converted into carboxylic acid group. While in the presence of high sodium concentration in the aqueous solution, the application of electrical current would cause the hydrogel to swell as a result of the greater inward movement of the sodium ions as compared to the outward movement. This swelling is more dominant at the anode leading to hydrogel bending (55, 57).

These stimuli responsive hydrogels are particularly important in the design of biosensors, drug delivery devices that provide pulsatile release. In addition, it is useful for the development of synthetic muscles and many other beneficial biomedical applications (55, 56).

5. Photo-sensitive *in situ* gelation

Photo-sensitive hydrogels are specific type of smart hydrogels that respond to alteration in the intensity of UV or visible light within the environment leading to conformational changes in the molecular structure of the polymer (58). Among other stimuli, light is easily controlled, highly effective, non-invasive, safe and available. Therefore, photo-sensitive hydrogels have extensively explored as means that aid in laparoscopy, surgery, wound healing, tissue engineering and for the subcutaneous depot injection with the objective of controlled drug release (59, 60).

These hydrogels are composed of polymer backbone to which a photo-reactive entity (chromophore) is attached (58). Poly (lactic acid), polyethylene glycol (PEG) and poly peptide based polymers are examples of the most commonly used polymers as a foundation for the synthesis of photo-sensitive hydrogels. Trisodium salt of copper chlorophyllin (visible light sensitive chromophore), leuco derivative (UV light sensitive), azobenzene, *O*-nitrobenzyl, coumarin derivatives, anthracene derivatives and cinnamic acid derivatives are among the most promising photo-reactive moieties (55, 58, 59, 60). There are four locations for the attachment of the photo-sensitive functional group to the polymeric network, namely, across the polymer backbone, across the polymer side chains, at the crosslinking

spots or distributed within the aqueous phase of the hydrogel (58, 60). The location of incorporation as well as the type of the chromophore greatly influence the photo triggered response of the polymer (58). The two most significant drawbacks of these systems are the fact that the response to light is relatively slow and there is a the diffusion of the photo reactive molecules out of the hydrogel network as the hydrogel polymer swells (55).

6. Glucose activated *in situ* gelation

These smart hydrogels are particularly useful for the development of insulin delivery systems. These systems are capable of releasing insulin in accordance to the fluctuation in the plasma glucose level (13, 61). The release of insulin from such systems is very challenging since the quantity should be precise and the timing of release should be accurate (on need) (57). Hence, two fundamental requirements in the design of such delivery system in order to achieve these goals: having glucose sensitive capacity and the self-controlled turn-off tendency (57). Glucose triggered hydrogels could be sub-classified into three main classes: the glucose-oxidase loaded hydrogels, the lectin (concanavalin A, Con A) loaded hydrogels and the phenylboronic acid loaded hydrogels (55, 57, 61). Among these, the most frequently utilised approach for glucose sensing is through glucose oxidase enzyme loaded onto pH-sensitive polymer (57). Glucose oxidase mediates glucose oxidation with the generation of gluconic acid and subsequent drop in the pH of the surrounding media. This change in pH triggers the release of insulin from the polymer following a mechanism that vary depending on the type of the polymer used, whether poly cation or poly anion (62). In case of poly cation, the polymer swell by the reduction in pH with the release of insulin (57, 62). In contrast, poly anion usually used to graft a porous membrane in which the pores are closed by the expanded polymer chains when the pH is around 7. The drop in pH (caused by the conversion of glucose into gluconic acid through the activity of glucose oxidase) would trigger polymer chain collapse with the subsequent opening of the pores and hydraulic flow of insulin from the hydrogel to the surrounding. In both of these cases the release of insulin is enhanced by the increase in glucose levels (57).

Lectins are specific type of proteins that have the ability to bind and form complexes with glucose and various carbohydrate-containing compounds (such as glycolipids and glycoproteins) (61). This special glucose-binding nature of lectins has been exploited by researchers to develop insulin delivery systems (61). Concanavalin A, is a lectin derivative with four glucose-binding sites that possess higher affinity for binding glucose compared to other glycosylated compounds (such as glycosylated insulin) (57, 61). One of the strategies to fabricate glucose-sensitive insulin delivery system is through the synthesis of glycosylated insulin derivative, which is both pharmacologically active and stable, and binding this compound with concanavalin A to form complex (57, 61). The release of glycosylated insulin from this complex is determined by the concentration of glucose. Glucose molecules compete with the glycosylated insulin for binding with concanavalin A. Any increment in glucose level would result in the dissociation of glycosylated insulin from its complex with concanavalin A leading to insulin release (57, 61).

Phenylboronic acids are non-biological compounds that have the ability to form complexes with glucose as well as other polyol compounds (55, 61). These complexes are strong but they are unstable at pH of 7.4 (which is the physiological pH) (55, 61). Therefore the addition of amine group to the hydrogel loaded with phenylboronic acid is required to insure the stability of the produced complex at physiological pH (55, 61). In addition, glucose could dissociate from the complex if another polyol with higher affinity toward phenylboronic acid is present. Numerous approaches have been suggested to utilise this phenomenon in the fabrication of glucose-sensitive insulin carrier systems (55, 61).

7. Enzyme triggered *in situ* gelation

The human body is rich in various enzymes that are responsible for catalysing normal biological reaction. Some of these enzymes may become over expressed or over reactive in certain pathological conditions such as malignancy, rheumatoid arthritis and other inflammatory conditions (63, 64). This concept of pathological elevated enzyme activity has fascinated the attention of scientists to develop smart hydrogels based drug delivery systems that exploit enzyme-catalysed reactions to elicit the cross-linking between the polymeric chains and thus leading to gelation at the targeted site (65, 66). Fibrin and fibrinogen hydrogels are examples of enzyme responsive hydrogels in which the *in situ* gelation mediated by the enzymatic activity of transglutaminases which belong to a group of enzymes

that accelerate the formation of the isopeptide linkages between the amine group of lysine amino acid and the amide group on glutamine's side chain (64).

Another class of enzymes that is exploited in smart hydrogel fabrication are the hydrogen peroxidase, which can trigger chemical cross-linking among tyramine moieties of hyaluronic acid (of tyramine-functionalised type) as well as other glycopolymer based copolymers (64). This reaction involves oxidative coupling of these moieties that occur in the presence of hydrogen peroxide. Similar hydrogen peroxidase mediated oxidation is responsible for the *in situ* cross-linking of polyethylene glycol and gelatine based hydrogels (64).

8. Other triggering stimuli for *in situ* gelation

Numerous triggering factors have recognised such as magnetic field, antigens and others. However, these triggering elements could be used for the development of hydrogels used in diagnostic applications such as in bioassays or biosensor and have limited benefits in the drug delivery field (67, 68).

Conclusion

The current review in the field of smart materials along with their fascinating properties and biomedical applications have been centred around the type of the polymer (whether natural or synthetic) that possess intelligent behaviour and the fundamental mechanism of sol-gel transition. These polymers have the ability to respond to different stimuli. Of these stimulating factors, temperature, pH and ionic strength are the most beneficial for the adventure of drug delivery systems as well as other biomedical applications.

Recommendations

Further research is required toward the scope of applications of intelligent hydrogels in biomedical field. The method of production of synthetic polymers along with their properties and advantages is worthy to be studied. Investigations that are focusing on the polymers that possess dual responsive properties with their potential benefits are interesting as well.

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