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REVIEW ARTICLE

Hydrogel-A Conceptual Overview

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ABSTRACT

Hydrogels have been used extensively in the development of the smart drug delivery systems. In 1960 Wichterle and Lim were discovered hydrogel of poly (2-hydroxyethyl methacrylate). Hydrogels constitute a group of materials which are used in numerous biomedical disciplines, and are still developing for new promising applications. Hydrogels are three-dimensional, hydrophilic, polymeric networks that can swell in water and hold a large amount of water while maintaining the structure. They can be classified in different way as like on the basis of their preparation, biodegradable properties, polymer, sensitivity to surrounding environment and also their application. In this review we are focused on conceptual points of hydrogels related to hygrogel types, their crosslinking, polymers, application, as well as developments.

Key words: Hydrogels, crosslinking, polymers, environmental sensitive, polymerization

INTRODUCTION

Now a day's Pharmaceutical companies are developed different dosages form of drugs with higher rate of drugs release in to systemic circulation from dosage form. Tablet, capsule, injections, microspheres, suspensions, emulsions, ointments, creams, tinctures, powders, pastes, hydrogels, jellies, aerosols, nano particles and transdermal patches are some examples of dosages form with their sub categories for different route of administrations. All these dosages forms are have their own properties and advantages regarding to drug releases rate from dosages form.

Most of the pharmaceutical companies today are oriented toward designing new pharmaceutical dosage forms of existing drugs rather than discovering new drug products. Utilization of the existing resource of marketed and patented drug substances with known therapeutic effects, and modification of their pharmaco-therapeutic characteristics by incorporation in suitable drug delivery system, has been the target of recent pharmaceutical development.

Hydrogels have been used extensively in the development of the smart drug delivery systems. In 1960 Wichterle and Lim were discovered hydrogel of poly(2-hydroxyethyl methacrylate) [1, 7] from that time to till now hydrogels have been of great interest to biomedical scientist and widely involved in development of drug delivery system. Hydrogels are three-dimensional, hydrophilic, polymeric networks that can swell in water and hold a large amount of water while maintaining the structure [2, 3]. Their ability to absorb water is because of its crosslinking network structure which is formed by polymer bearing hydrophilic groups such as –OH, –CONH, –COOH, $–SO_3H$, and $–NH_2$.[1, 4] The networks are composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (tie-points, junctions), or physical crosslinks, such as entanglements or crystallites[5, 6, 11]. In this review we are focused on conceptual points of hydrogels related to hygrogel types, their crosslinking, polymers, application as well as developments.

TYPE OF HYDROGEL

Hydrogel can be classified in different way as like on the basis of their preparation, biodegradable properties, polymer and also their application but classification on the basis of their sensitivity to surrounding environment is more common

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classification of hydrogels. hydrogels can be sensitive to pH, temperature, enzyme, light, electric and other stimuli. (**Table 1**) shows some of environment sensitive hydrogels and their polymer system.

Table 1: Environmental Sensitive Hydrogel and Their Polymer System

S. No	Sensitivity type	Polymer system	Comment	Ref.
1.	pH	poly(methacrylic acid-co-methyl methacrylate)	Hydrogel, 22/78 molar %, with two cross-linking degrees (0.3 and 0.5%)	29
2.	Thermo	poly(N-t butyl acryl amide-co-acrylamide)	Prepared by free-radical cross-linking copolymerization	30
3.	pH	chitosan-alginate, chitosan-carboxymethylcellulose sodium and chitosan-carbopol	Polyelectrolyte complexe hydrogels with prolong drug release systems using Diltiazem HCl	31
4.	Thermo	poly(N-isopropylacrylamide) (PNIPAAm)-poly(ethylene glycol) diacrylate	A fast and reversible phase change with alteration in temperature and able to encapsulate and release various proteins	32
5.	Enzyme	Poly(ethylene glycol)	Formed by Thiol-ene photopolymerization technique to fabricate protein delivery vehicles capable of enzyme-responsive protein release at sites of inflammation	19
6.	pH-thermo	poly-N-isopropylacrylamide	Formed by Electrochemically induced polymerization	33
7.	pH	agarose and carbomer 974P macromers	Highly biocompatible, specifically developed for regenerative medicine applications in spinal cord injury (SCI) repair	34
8.	pH	Poly (acrlyamide-co- acrylic acid)	Superporous hydrogels with fast responsive properties of system	35
9.	IR light	N-isopropylacrylamide	IR light-responsive hydrogel was used to made liquid-based tunable microlenses	36
10.	Thermo	hydroxyethyl methacrylate	Rate controlled rectal Delivery of antipyrine or theophylline. by Cylindrical hydrogels	37
11.	pH	Chitosan–Poly(vinyl alcohol)	Modified pH sensitive swelling	38
12.	Electro	Polydimethylaminopropylacrylamide	Prepared by either cross-linking the water-soluble polymers using radiation or chemical agents	16
13.	Electro	chondroitin4-sulphate	Potential matrices for the electro controlled delivery of peptides and proteins	17

pH sensitive hydrogel:

These hydrogels respond to changes in pH of the external environment. These gels have ionic groups (which are readily ionizable side groups) attached to impart peculiar characteristics and either accept or release protons in response to changes in environmental pH[8]. They can classify as neutral or ionic hydrogel according to their nature. Anionic hydrogel contain negatively charged moieties, cationic hydrogel contain positively charged moieties and neutral hydrogel contain both positively and negatively charged moieties.

Hydrogels made of crosslinked polyelectrolytes display big differences in swelling properties depending on the pH of the environment [9, 10]. The pendant acidic or basic groups on polyelectrolytes undergo ionization. But ionization on polyelectrolytes however, is more difficult due to electrostatic effects exerted by other adjacent ionized groups. The presence of ionizable groups on polymer chains results in swelling of the hydrogels much beyond that can be achievable by nonelectrolyte polymer hydrogels[3]. Since the swelling of polyelectrolyte hydrogels is mainly due to the electrostatic repulsion among charges present on the polymer chain, the extent of swelling is influenced by any condition that reduce electrostatic repulsion such as pH, ionic strength, and type of counterions[3, 8, 9]. If the ionisation of the ionisable component is completed the swelling process stops. Further pH increase only increases the ionic strength. This decreases the osmotic pressure and leads to shrinking of the gel [9].

Temperature sensitive hydrogel:

Temperature sensitive or thermosensitive hydrogels are one of the widely studies type of

hydrogel. They are characterized their hydrophobic groups that are like as methyl, ethyl and proyle groups [1]. Negative thermosensitive (negative temperature dependent), positive thermosensitive (positive temperature dependent), and thermally reversible hydrogel are classified group of temperature sensitive or thermosensitive hydrogels. As the temperature increases, negative thermosensitive hydrogel (negative temperature dependent hydrogel), are shrink due to inter-polymer chain association through hydrophobic interactions resulted decrease their water-solubility [12-14]. While as the temperature increases, positive thermosensitive hydrogel (positive temperature dependent hydrogel) are show just opposite result of negative thermosensitive hydrogel.[12-14] In other hand thermally reversible hydrogel contain non-covalently crosslinked polymer chain and may undergo sol–gel phase transitions, instead of swelling–shrinking transitions. They are inverse temperature dependence and become sol at higher temperatures [12-14].

Electro sensitive hydrogel:

Another type of hydrogel is electro sensitive (electric signal sensitive) hydrogels as the name indicate they are sensitive to electric current. As like pH sensitive hydrogel they are usually made of polyelectrolytes. In the presence of an applied electric field they are undergo shrinking or swelling. Under the influence of an electric field, electro responsive hydrogels generally deswell or bend depending on the shape of the gel and its position relative to the electrodes. Bending occurs when the main axis of the gel lies paralled to (but does not touch) the electrodes whereas deswelling occurs when the hydrogel lies perpendicular to the electrodes [16, 17].

Partially hydrolyzed polyacrylamide hydrogels are directly contacted with the anode and cathode electrodes, now a potential is applied. H+ ions migrate to the region of the cathode, which results in a loss of water at the anode side. Simultaneously, the electrostatic attraction that exists between the anode surface and the negatively charged acrylic acid groups creates a uniaxial stress along the gel axis. These two events lead to shrinking of the hydrogel on the anode side [3, 15].

Light sensitive hydrogel:

Since the stimulus of light can be imposed instantaneously and can be delivered in specific amounts with high accuracy, it renders light-responsive hydrogels highly advantageous over others. Also, the capacity for instantaneous delivery of the sol–gel stimulus renders light-responsive polymers potentially applicable for the development of optical switches, display units and ophthalmic drug delivery systems.[3, 15] Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscle or as the *in situ* forming gels for cartilage tissue engineering. In the last study gels that may undergo transdermal photopolymerization after subcutaneous injection were found to be applicable for drug release devices [3, 17]. Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. Unlike UV light, visible light is readily available, inexpensive, safe, clean and easily manipulated [3, 15].

Enzyme sensitive hydrogel:

A type of hydrogel mainly used in targeting the drug to colon is enzyme sensitive hydrogel. The presence of pH sensitive monomer and azo crosslinking agent in the structure is mainly responsible for colon specificity of enzyme sensitive hydrogels.[18] The hydrogels psss through GI tract, the swelling capacity of hydrogels increase with the pH due to presence of pH sensitive polymer. Upon arrival in the colon, the hydrogel have reached a degree of swelling, that make cross linking accessible to the enzyme (azo reductase) or mediator. Subsequently the hydrogel network is progressively degraded by the cleavage of cross-linking and the drug entrapped is thus released [18, 19].

Glucose sensitive hydrogel:

One of the most challenging problems in controlled drug delivery area is the development of self-regulated (modulated) insulin delivery systems. Delivery of insulin is different from delivery of other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Thus, self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for modulating insulin delivery, and all of them have a glucose sensor built into the system [3, 18].

Intelligent stimuli-responsive delivery systems using hydrogels that can release insulin have been investigated. Cationic pH-sensitive polymers containing immobilized insulin and glucose oxidase can swell in response to blood glucose level releasing the entrapped insulin in a pulsatile fashion [17, 18]. Another approach is based on competitive binding of insulin or insulin and

glucose to a fixed number of binding sites in concanavalin A. Lectins, which are carbohydrate-binding proteins, interact with glycoproteins and glycolipids on the cell surface and induce various effects, such as cell agglutination, cell adhesion to surfaces, and hormone-like action. The unique carbohydrate-binding properties of lectins are very useful for the fabrication of glucose-sensitive systems. Therefore, some researchers have focused on the glucose-binding properties of concanavalin A (Con A), a lectin possessing four binding sites [17, 18]. Out of these two, the synthetic hydrogels with a phenylboronic acid group is also consider as an approach in development of Intelligent stimuli-responsive delivery systems[20] Hydrogels can be made to undergo sol–gel phase transformations depending on the glucose concentration in the environment. Reversible sol–gel phase transformations require glucose-responsive crosslinking.

Pressure-sensitive hydrogels:

The concept that hydrogels may undergo pressure induced volume phase transition came from thermo dynamic calculations based on uncharged hydrogel theory. According to the theory, hydrogels which are collapsed at low pressure would expand at higher pressure [3].

PREPARATION OF HYDROGEL

Solution polymerization/ cross-linking, suspension polymerization, polymerization by radiation, chemically cross-linking, and physical cross-linking are methods of hydrogel preparation by utilization of different monomer, polymer as well as copolymers. (**Table 2**) consists of method of preparation with commonly used polymers in these methods and (**Table 3**) has examples of hydrogel prepared by different methods.

Table 2: Method Of Preparation And Commonly Used Polymers [1, 21-24]

S. No.	Method of preparation	Compatible monomer/polymers for methods	Comments
1	Solution polymerization /cross-linking	Poly(2-hydroxyethyl methacrylate), methacylic acid, N-isopropylacrylamide	pH or thermo sensitive and also a great verity of hydrogels have been prepared by this method
2	Suspension polymerization	Poly(vinyl alcohol), poly(hydroxyl ethyl methacrylate)	Spherical hydrogel microparticles with range of 1μm to 1mm can prepared
3	Polymerization by radiation	Poly(vinyl alcohol), poly(ethylene glycol), poly(acrylic acid)	Hydrogel of unsaturated compound can prepared
4	By chemically cross-linking	Poly(methacrylic acid), poly(ethylene glycol)	Highly toxicity of cross-linking agent is a problem hence unreacted agent have to extracted
5	By physical cross-linking	Chitosan, poly(acrylic acid)	A method to overcome the problem of cross-linking agent toxicity and prepared biodegradable hydrogel

Table 3: Example of Hydrogel Prepared By Different Method

S. No	Preparation method	Type	Polymer system	Ref.
1.	Solution polymerization/ cross-linking by radox initiator	pH	Poly(methacrylic acid-co-methyl methacrylate)	29
2.	Solution polymerization/ cross-linking by radox initiator	Thermo	Poly(N-t butyl acryl amide-co acrylamide)	30
3.	By physical cross-linking	pH	Chitosan-alginate, chitosan carboxymethylcellulose sodium and chitosan-carbopol	31
4.	Solution polymerization/ cross-linking by radox initiator	Thermo	Poly(N-isopropylacrylamide) (PNIPAAm)-poly(ethylene glycol) diacrylate	32
5.	Polymerization by radiation	pH	Agarose and carbomer 974P macromers	34
6.	Solution polymerization/ cross-linking by radox initiator	pH	Poly (acrlyamide-co- acrylic acid)	35
7.	Solution polymerization/ cross-linking by radox initiator	Thermo	N-allyl maleamic acid (AMA) with acrylamide and acrylic acid	21
8.	Solution polymerization/ cross-linking by thermal initiator	Thermo	N-allyl maleamic acid (AMA) with acrylamide and acrylic acid	21
9.	Solution polymerization/ cross-linking by UV-induced initiation	pH	Poly(ethylene glycol) methacrylate-graft-poly(glutamic acid)	24
10.	gamma radiation	Ion	Acrylamide/2-hydroxyethyl methacrylate	23

Solution polymerization/ cross-linking:

In solution copolymerzation/ cross-linking, the ionic or neutral monomers are mixed with the multifunctional crossing agent.[1] The polymerization is initiated thermally[21], by UV light[24], or by radox initiator[21, 22] system. The

presence of solvent serves as heat sink and minimized temperature control problem. The resulted hydrogel washed with distilled water to remove un-reacted monomers.

Suspension polymerization:

This method is employed to prepare spherical hydrogel micropartical with size range of 1µm to 1mm. in this method the monomer solution is dispersed in non-solvent forming fine droplet, which is stabilized by stabilizer. The polymerization initiated by thermal decomposition of free radical. The prepared micropartical washed to remove un-reacted monomers cross-linking reagent and initiator [1].

Polymerization by radiation:

High energy radiations like gamma and electron beam have been used to prepare hydrogel of unsaturated compound. The irradiation of aqueous polymer solution results in the formation of radical on the polymer chain. Also radiolysis of water molecule results in the formation of hydroxyl radicals, which also attack the polymer chain resulting in formation of the macroradicals. Recombination of macroradical on different chain results in the formation of covalent bond and finely a cross-linking structure formed [1, 23].

Chemically cross-linking:

Polymers containing functional groups like –OH, –COOH, $–NH_2$, are soluble in water. The presence of these functional groups in polymer can be used in preparation of hydrogel by forming covalent linkage between the polymer chains and complementary reactivity [1, 21].

Physical cross-linking:

The hydrogel can be prepare be reversible ionic cross-linking. This is a method to overcome the problem of toxicity of covalent cross-linking agent and to avoid purification step. Chitosan (poly-cationic polymer) can react with positively charged component, either ion or molecule, forming a network through ionic bridge between polymeric chain [1, 21].

MONOMER AND POLYMERS USED IN PREPARATION OF HYDROGELS

Hydrogels consist of elastic networks with interstitial spaces that contain as much as 90-99% w/w water. Different monomers and polymers used in hydrogels formulation can be of either synthetic or natural origin, homopolymers or copolymers. **(Fig 1**) content name and structures of some of them.

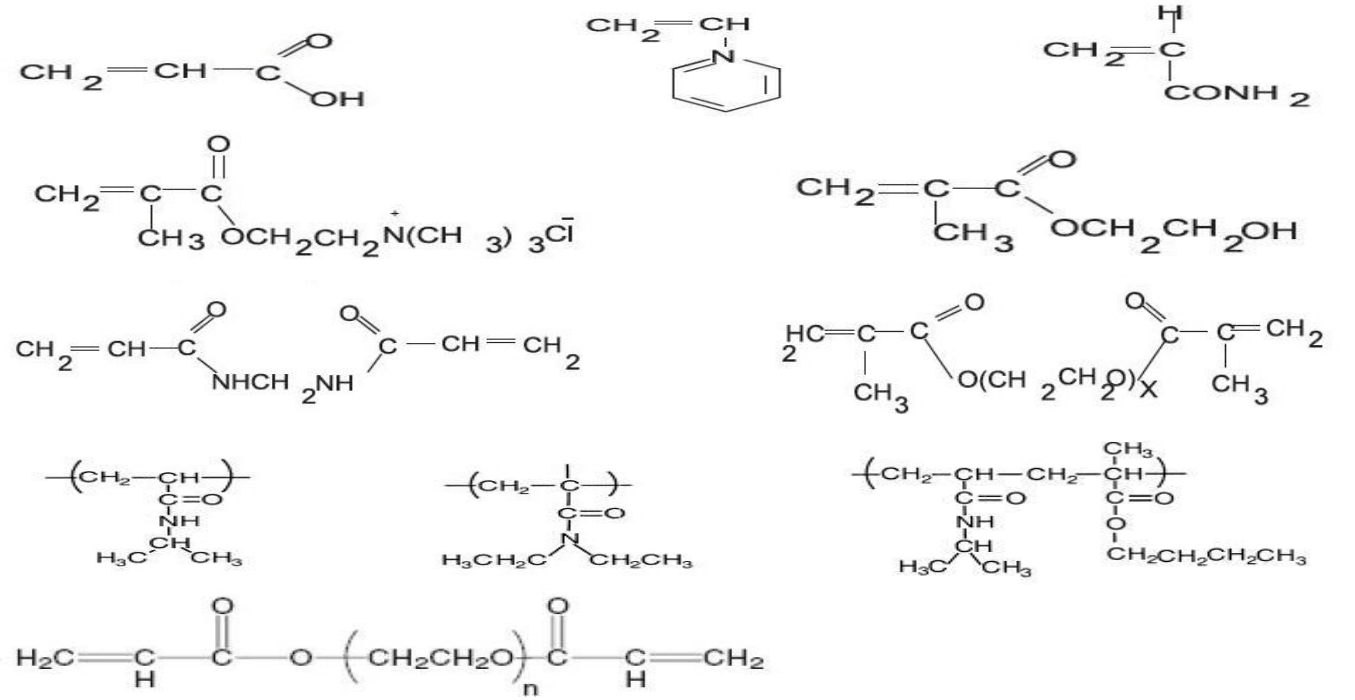

Fig 1: Acrylic acid, Vinyl pyridine, Acrylamide, 2-methacryloyloxy-trimethyl ammonium chloride, 2-hydroxyethyl methacrylate, N,N methylene bisacrylamide, Ethylene glycol di-methacrylate, poly(*N*-isopropylacrylamide) (PNIPAAm), Poly(*N*,*N*-diethylacrylamide) (PDEAAm), (*N*-isopropylacrylamide)-co- butyl methacrylate P(NIPAAm-co-BMA) and polyethylene glycol diacrylate (PEGDA) respectively

Polymer properties for pH sensitive hydrogel:

With large number of ionizable group, Polyelectrolyte polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH[3, 8]. These polylectrolytes are used in preparation of pH sensitive hydrogels. Cationic polyelectrolytes, such as poly(*N*,*N*9 - diethylaminoethyl meth acrylate (PDEAEM), dissolve more, or swell more if cross linked, at low pH due to ionization. On the other hand,

polyanions, such as poly(acrylic acid) (PAA), dissolve more at high pH[8, 9]. (**Fig 2**) is shows pH sensitive ionization of polyelectrolytes with example of polyacrylic acid and poly (N, N-diethylamino ethyl metacylate) (in figure 1).

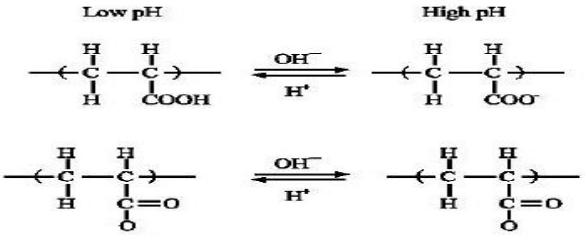

Fig 2: pH sensitive ionization of polyacrylic acid and poly (N, N- diethylamino ethyl metacylate) respectively

Polymer properties for temperature sensitive hydrogel:

Temperature-sensitive hydrogels are probably the most commonly studied class of environmentally sensitive polymer systems in drug delivery research. Polymers used in synthesis of temperature-sensitive hydrogels contain hydrophobic groups such as methyl, ethyl and propyl groups. Many polymers exhibit a temperature-responsive phase transition property. Temperature-sensitive hydrogels contain hydrophobic groups. Polymers with LCST however, decrease their water-solubility as the temperature increases [12, 14, 15].

Polymer properties for Electro sensitive hydrogel:

As like pH sensitive hydrogels, polyelectrolyte polymers are used in synthesis of electro sensitive hydrogel. Due to presence of polyelectrolyte, the electro sensitive hydrogels undergo shrinking or swelling in the presence of an applied electric field [15, 16].

Polymer properties for light sensitive hydrogel:

The capacity for instantaneous delivery of the sol–gel stimulus renders light-responsive polymers is characteristic behavior of polymer used in synthesis of light sensitive hydrogels as well as potentially applicable for the development of optical switches, display units and ophthalmic drug delivery systems [3]. Light responsive polymers may be UV or visible light sensitive; however, visible light-responsive polymers and the hydrogels prepared from them are more beneficial just because of their safety, inexpensiveness, readily availability, clean and easily manipulation [15, 17]. its property can be explain with hydrogels synthesized by introducing a leuco derivative molecule, bis(4-di-methylamino)phenylmethyl leucocyanide, into the polymer network. Triphenylmethane leuco (**Fig 3**) derivatives are normally neutral but dissociate into ion pairs under ultraviolet irradiation producing triphenylmethyl cations.

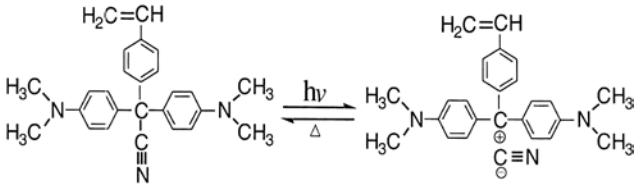

Fig 3:- Structure of leuco derivative molecule bis(4-(dimethylamino)phenyl)(4-vinylphenyl)methylleucocyanide

Polymer properties for Enzyme sensitive hydrogel:

pH sensitive monomer and azo cross-linking agent are involved in synthesis of enzyme sensitive hydrogel. Enzyme sensitive hydrogel are mainly used in targating the drug to colon. The presence of pH sensitive monomer and azo cross-linking agent in hydrogel structure in required for this colon specificity [19].

Polymer properties for glucose sensitive hydrogel:

One of the most challenging problems is the development of self-regulated (modulated) insulin delivery systems. Self-regulated (modulated) insulin delivery systems required glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for intermodulating insulin delivery. First one is pH sensitive membrane system used glucose oxidase enzyme resulting oxidation of glucose in gluconic acid followed by change in environmental pH. This process make possible by use different types of pH sensitive hydrogels. Second system is Sol–gel phase reversible hydrogel systems. Hydrogels can be made to undergo sol–gel phase transformations depending on the glucose concentration in the environment. Reversible sol–gel phase transformations require glucose-responsive cross-linking. A highly specific interaction between glucose and Con A was used to form cross-links between glucose-containing polymer chains [17, 18]. **(Fig 4)** shows sol–gel phase-transition of a phenylborate polymer. At alkaline pH, phenylborate polymer interacts with poly (vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to induce a transition from the gel to the sol phase.

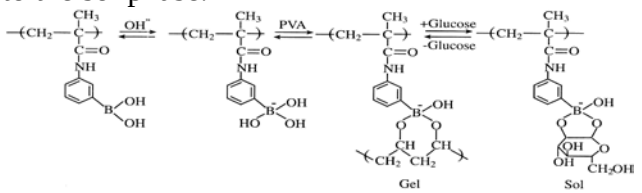

Fig 4: Sol–gel phase-transition of a phenylborate polymer. At alkaline pH, phenylborate polymer interacts with poly(vinyl alcohol) (PVA) to form a gel. Glucose replaces PVA to induce a transition from the gel to the sol phase

Polymer properties for Pressure-sensitive hydrogels:

The concept that hydrogels may undergo pressure induced volume phase transition came from thermodynamic calculations based on uncharged hydrogel theory. According to the theory, hydrogels which are collapsed at low pressure would expand at higher pressure. The pressure sensitivity appeared to be a common characteristic of temperature-sensitive gels. It was concluded that the pressure sensitivity of the temperature-sensitive gels was due to an increase in their LCST value with pressure. The degree of swelling of poly(*N*-isopropylacrylamide) hydrogels increased under hydrostatic pressure when the temperature is close to its LCST. Other hydrogels, such as poly(*N*-n-propylacrylamide), poly(*N*,*N*-diethylacrylamide), all showed the pressure sensitivity near their LCSTs[3].

DRUG RELEASE MECHANISAM FROM HYDROGEL

Due to hydrophilicity of hydrogels they can imbibe large amounts of water. Thereforethe molecule release mechanisms from hydrogels are not as like hydrophobic polymers. For hydrogels, both simple and sophisticated models have been previously developed to predict the release of an active agent from a hydrogel device as a function of time. These models are based on the ratelimiting step for controlled release and are therefore categorized as follows:

Diffusion-controlled:

Most commonly applicable mechanism for describing drug release from hydrogels is Diffusion-controlled. Fick's law of diffusion with either constant or variable diffusion coefficients is commonly used in modeling diffusion-controlled release.[2, 13, 25, 26] Drug diffusivities are generally determined empirically or estimated a priori using free volume, hydrodynamic, or obstruction-based theories[2, 13, 25, 26].

Swelling-controlled:

Swelling-controlled release occurs when diffusion of drug is faster than hydrogel swelling. The modeling of this mechanism usually involves moving boundary conditions where molecules are released at the interface of rubbery and glassy phases of swollen hydrogels[2, 13, 25, 26].

Chemically-controlled:

Chemically-controlled release is used to describe molecule release determined by reactions occurring within a delivery matrix. The most common reactions that occur within hydrogel delivery systems are cleavage of polymer chains via hydrolytic or enzymatic degradation or reversible or irreversible reactions occurring between the polymer network and releasable drug. Under certain conditions the surface or bulk erosion of hydrogels will control the rate of drug release. Alternatively, if drug-binding moieties are incorporated in the hydrogels, the binding equilibrium may determine the drug release rate. Chemically-controlled release can be further categorized according to the type of chemical reaction occurring during drug release. Generally, the liberation of encapsulated or tethered drugs can occur through the degradation of pendant chains or during surface erosion or bulk-degradation of the polymer backbone [2, 13, 27, 28].

APPLICATION OF HYDROGELS

hydrogels have attention as excellent candidates for controlled release devices, bioadhesive devices, or targetable devices of therapeutic agents that can be used for oral, rectal, ocular, epidermal and subcutaneous application.

Application of pH sensitive hydrogel:

pH-sensitive hydrogels have been most frequently used to develop controlled release formulations for oral administration. pH-sensitive hydrogels have involved in development of biodegradable drug delivery systems[24]. These type of hydrogels would be ideal for localized delivery of antibiotics, such as amoxicillin and metronidazole in the the stomach for the treatment of *Helicobacter pylori.* pH-sensitive hydrogels were placed inside capsules or silicone matrices to modulate the drug release as squeezing hydrogel system. pH-sensitive hydrogels have also been used in making biosensors and permeation switches[9].

Application of temperature sensitive hydrogel:

These thermo- sensitive gels are specific, controllable and biocompatible drug delivery devices. They could be biodegradable also. The drugs which are widely been explored for such devices are usually from category of anticancer, antidiabetic, hormones or proteins. They are able to give a dense, less permeable surface layer of gel, described as a skin-type barrier. It used to develop reservoir type microcapsule drug delivery system. Thermo-sensitive macrocapsules of nanoparticles have been developed recently. Temperature-sensitive hydrogels can also be

placed inside a rigid capsule containing holes or apertures such a device is called a squeezing hydrogel device. Commonly used thermoreversible gels are Pluronics and Tetronics. Some of them have been approved by FDA and EPA for applications in food additives, pharmaceutical ingredients and ag ricultural products [1, 3, 12].

Application of electro-sensitive hydrogel:

Electro-sensitive hydrogels have been applied in controlled drug delivery. Electro-sensitive hydrogels, which are basically pH-sensitive hydrogels, are able to convert chemical energy to mechanical energy. Those systems can serve as actuators or artificial muscles in many applications. Application of an oscillating electrode polarity could lead the hydrogel to quickly repeat its oscillatory motion, leading to a worm-like motion [3, 15-17].

Application of light sensitive hydrogel:

Light-sensitive hydrogels can be used in the development of photo-responsive artificial muscles, switches and memory devices. Light-sensitive hydrogels are used to develop Ophthalmic Light Sensitive Nanocarrier Systems [26]. The potential application of visible light-responsive hydrogels for temporal drug delivery was also proposed, based on the response of crosslinked hyaluronic acid hydrogels that undergo photosensitized degradation in the presence of methylene blue [3, 15].

Application of enzyme sensitive hydrogel:

Enzyme sensitive hydrogels have become increasingly important in biomedical fields because of their high potential for tissue engineering, drug delivery systems, etc.[18] for that they are developed as biodegradable Enzyme sensitive hydrogels by using Biodegradable polymers. Enzyme sensitive hydrogels are promising candidates as enzyme sensors and enzyme-sensitive drug delivery systems.[18] Enzyme sensitive hydrogels can protect protein drugs against digestion by proteolytic enzymes in the stomach, due to their low swelling ratio at a low pH[18, 19].

Application of glucose sensitive hydrogel:

One of the most challenging problems in controlled drug delivery area is the development of self-regulated (modulated) insulin delivery systems. Glucose sensitive nanoparticles for controlled insulin delivery have been developed with glucose sensitive hydrogel[27]. A glucose-sensitive hydraulic flow controller can be designed using a porous membrane system consisting of a porous filter grafted with polyanions and immobilized glucose oxidase.[18] Glucose sensitive hydrogel are use to develop squeezing hydrogel device system from insulin. It applicable as Reversible sol–gel phase transformations depending on the glucose concentration in the environment [18].

CONCLUSION

There are numerous applications of these hydrogels, in particular in the medical and pharmaceutical sectors. The network structure and the thermodynamic nature of the components of these networks play a key role in their diffusional behavior, molecular mesh size changes (especially in environmentally responsive hydrogels), and the associated molecular stability of the incorporated bioactive agents. Due to their high water contents and soft consistency hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. Recent advances in the development of neutral and ionic hydrogels for drug delivery applications have concentrated on several aspects of their synthesis, characterization and behavior. In the last few years, there have been new creative methods of preparation of hydrophilic polymers and hydrogels that may be used in the future in drug delivery applications. Synthesis of new polymers and crosslinkers with more biocompatibility and better biodegradability would be essential for successful applications. Development of environmentally sensitive hydrogels with such properties is a formidable challenge. If the achievements of the past can be extrapolated into the future, however, it is highly likely that responsive hydrogels with a wide array of desirable properties can be made.

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