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Hydrogel as a novel drug delivery system: a review

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Abstract

Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature sensitive, which are used for the targeted delivery of drug/proteins to colon, and chemotherapeutic agents to tumors. Recently, controlled and sustained drug delivery has become the standard in modern pharmaceutical design and an intensive research has been undertaken in achieving much better drug product effectiveness, reliability and safety . In this regard, many polymers are very useful with majority of hydrogels, which undergo reversible volume and/or sol-gel phase transitions in response to physiological (temperature, pH and present of ions in organism fluids, blood glucose level) or other external (electric current, light) stimuli.

Key words: Hydrogel, Novel drug delivery, IPN

Introduction

Oral route of drug delivery has been the most convenient and commonly employed route of drug delivery. The oral route is preferred due to its convenience, low cost and better patient compliance. Conventional drug delivery suffer from certain drawbacks like increased fluctuation in the circulatory drug level, more frequency of dosage administration, increased gastrointestinal irritation and dose related side effects. To overcome these

disadvantages, controlled release oral drug delivery systems were designed. Controlled release drug delivery systems are designed for uniform and constant drug release over a prolonged period of time.

The constant drug release is achieved by use of various polymeric systems which act as rate controlling membrane for the release of drug. Researchers have strived to engineer the physical and chemical properties of drug delivery systems (DDS) to specifically regulate their permeability, environmental response, surface functionality, biodegradability and biorecognition sites to produce "intelligent" DDSs. Hydrogels represent a DDS class that are called as intelligent drug delivery [1].

Hydrogels are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amount of water or biological fluid. The networks are composed of homopolymers or copolymers, and are insoluble due to presence of chemical or physical crosslinkages. Hydrogels resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water contents and soft consistency which is similar to natural tissue. The water content which makes hydrogels such a special class of materials is also responsible for their biggest disadvantage of the poor mechanical properties. Hydrogels have been widely used as a drug carrier due to its ease in manufacturing and self application. The production of a large and constant surface area is one of the major merits for them to be widely used for clinical and fundamental applications. Various combinations of polymers are made into hydrogel formulations to investigate their potential as a drug delivery system. The combination of natural and synthetic polymers may provide mechanical stability and biological acceptability, acquiring from synergistic properties of both materials. The hydrogels were found stable and resilient [2]. Various research investigations has shown that a variety of drugs can be delivered effectively via hydrogel based delivery systems [Table 1].

History of Hydrogels

Hydrogels have been used in numerous biomedical disciplines, in ophthalmology as contact lenses and in surgery as absorbable sutures, as well as in many other areas of clinical practice to cure illnesses as diabetes mellitus, osteoporosis, asthma, heart diseases and neoplasms. In 1955, Professors Lim and Wichterle of Prague, Czech Republic, were synthesized the first hydrogel with potential biomedical uses. That hydrogel was made from synthetic poly-2-hydroxyethyl methacrylate and was used in contact lens production [3-5]. The main advantage of that biomaterial was its stability under varying pH, temperature and tonicity conditions. In the 1980s hydrogels were modified for other various applications like cell engineering. Nowadays, hydrogels continue to interest scientists. They are obtained from new materials using the latest techniques to make them safe and non-toxic. The final hydrogel product is present in very advanced applications, e.g. tissue engineering and regeneration, where they can be applied in a non-invasive manner. They can serve in the prevention of thrombosis, post-operative adhesion formation, drug delivery systems, coatings for biosensors and cell transplantation [6-10].

Advantages of Hydrogels

The main advantage of hydrogel is that they possess a degree of flexibility very similar to natural tissue, due to their significant water content. They are biocompatible, biodegradable and can be injected. Hydrogels also possess good transport properties and easy to modify. Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.

Disadvantages of Hydrogels

The main disadvantage of hydrogel is that they are non-adherent and may need to be secured by a secondary dressing and also causes sensation felt by movement of the maggots. Hydrogels have low mechanical strength and difficult to handle and are expensive.

Table 1: Delivery of variety of drugs via different hydrogel based delivery system

Drug	Therapeutic category	Carrier system	Inference	Reference
Insulin	Hypogylcaemic	Hydrogel	Sustain release of insulin	72
Hydrocortisone	Corticosteroids	Hydrogel	Controlled drug delivery system	73
Riboflavin	Water soluble vitamin	Hydrogel	pH sensitivity to localize drug delivery	74
Salicylic acid	Anti-seborrheics	Hydrogel	pH sensitive drug delivery system	75
Terbinafine hydrochloride	Antifungal	Hydrogel	Controlled drug delivery system	76
Propranolol hydrochloride	Antiadrenergic	Hydrogel	electrically modulated drug delivery	77
5-Fluorouracil & Diclofenac sodium	Antimetabolite & Anti-Inflammatory	Hydrogels	Localized drug delivery	78
Clarithromycin	Anti Helicobacter	Hydrogels	Stomach-specific drug delivery	79
Amoxicillin, metronidazole	Antimicrobial, antiamoebic	Hydrogel	Stomach-specific drug delivery	80
Simvastatin	lipid lowering drug	IPN hydrogel beads	Controlled drug delivery system	81

Characterization of Hydrogels

Hydrogels are characterized by following methods/tests:

Atomic Force Microscopy (AFM): The surface morphology of the hydrogels is studied by a Multimode Atomic Force Microscope.

X-ray Diffraction: X-ray diffraction is used to understand whether the polymers retain their crystalline nature or they get deformed during the pressurization process [11].

Network pore size: Network pore size is measured by a number of techniques like Quasi-elastic laser-light scattering, electron microscopy, mercury porosimetry, rubber elasticity measurements, and equilibrium swelling experiments [11].

Fourier Transform Infrared Spectroscopy: Formation of coil or helix which is indicative of cross linking is evident by appearance of bands near 1648 cm^{-1} FTIR. Any change in the morphology of hydrogels changes their IR absorption spectra [12].

Rheology: Hydrogels are evaluated for viscosity under constant temperature (4°C) by using Cone Plate viscometer.

Swelling Behavior: Hydrogels are allowed to immerse in aqueous medium or medium of specific pH to know their swellability. These polymers show increase in dimensions related to swelling [13, 14].

Cross-linking and mechanical strength is measured by Ultimate compressive strength, change in polymer solubility with time [15, 16].

Classification of Hydrogel

1. Based on the methods of preparation
2. Stimuli-sensitive hydrogels
3. Based on mechanism of release

1. Based on the methods of preparation

Hydrogels may be classified as:

Homo-polymeric Hydrogel

A polymer network which has been derived from single species of monomer is known as homopolymers [17]. Homopolymers have cross-linked skeletal structure depending on the nature of the monomer and polymerization method. Cross-linked homopolymers are mainly used in drug delivery system and for the preparation of contact lenses. Homo-polymeric hydrogel film is prepared by the use of poly (2-hydroxyethyl methacrylate) (polyHEMA) as a monomer, polyethylene glycol dimethacrylate as cross-linking agent and benzoin isobutyl ether as the UV-sensitive initiator. Another low molecular weight cross-linking agent (1, 1, 1-trimethylol propane trimethacrylate) is used in the synthesis of Homo-polymeric hydrogel. The hydrogel prepared with this cross-linking agent is soft in nature and contains 30-40 % of water and has high oxygen permeability. For these properties it is used in contact lenses, as matrices for drug delivery system and soft tissue implants.

Other polymers, which are used for the preparation of homo-polymeric hydrogel, are Polyetheleneglycol (PEG), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), polyacrylic acid (PAA). Polyacrylic acid (PAA) is another homopolymeric hydrogel [18]. Its commercial version comprises of 2.5 % of PAA and 97.5 % of water. It is stable and has optimal elasticity property.

Co-polymeric hydrogel

Co-polymeric hydrogels are prepared from two types of monomer in which at least one is hydrophilic. Gong *et al*. synthesized the biodegradable co-polymeric hydrogel composed of triblock poly (ethylene glycol)-poly (ε-caprolactone) – poly (ethylene glycol) (PECE) for the development of drug delivery system. In this triblock preparation PEG was used as initiator, stannous octoate as catalyst and hexamethylene diisocyanate as coupling agent. This co-polymeric block has capability to form hydrogel when it is applied *in-situ*. It also has capability of releasing both types of drugs, hydrophobic and

hydrophilic in nature including proteins over a sustained period of time. Thomas *et al*. prepared co-polymeric hydrogels by the use of two monomers namely acrylamide and acrylic acid with N, *N*-methylenebisacrylamide and potassium persulfate as the cross-linker and initiator respectively. Kim et al prepared copolymers of methacrylic acid (MAA) with PEG-PEGMA using tetra (ethylene glycol) dimethacrylate as cross-linker.

Semi- Inter Penetrating Network (Semi-IPN)

In the semi-inter penetrating network one polymer is linear and penetrates another cross-linked network without any other chemical bonds [19]. Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature due to the absence of restricting interpenetrating elastic network. It also has benefits like modified pore size & slow drug release etc.

One example of semi-inter penetrating network is the entrapment of linear cationic polyallylammonium chloride in acrylamide/ acrylic acid copolymer hydrogel, which has both higher mechanical strength and fully reversible pH switching of theophylline release. This pH sensitive semi-IPN was prepared by template copolymerization in the presence of *N*, *N*′-methylene bisacrylamide as a cross-linking agent [20]. This semi-inter penetrating network contained both covalent and ionic bonds. The covalent bonds retained the three-dimensional structure of hydrogel and the ionic bonds imparted the hydrogel with higher mechanical strength and pH responsive reversibility. Semi-IPN hydrogels, composed of alginateand amine-terminated Poly (N-isopropylacrylamide) (PNIPAAm), was synthesized by crosslinking with calcium chloride. This alginate/PNIPAAm semi-IPN hydrogels has sensitivity towards temperature, pH and ionic strength of swelling medium [21].

Inter Penetrating Network (IPN)

IPNs are defined as intimate combination of two polymers, in which at least one is synthesized or cross-linked in the immediate presence of the other [22]. This is prepared by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. IPN method has advantage because it can overcome thermodynamic incompatibility occurs due to the permanent interlocking of network segments and limited phase separation can be obtained with it. The interlocked structure of the cross-linked IPN components is believed to ensure stability of the bulk and surface morphology [23].

The main advantages of IPNs is that relatively dense hydrogel matrices can be produced which has tougher mechanical properties, controllable physical properties and more efficient drug loading compared to conventional hydrogels. IPN pore sizes can also be controlled to tune the drug release kinetics, interaction between the hydrogel and the surrounding tissues along with its mechanical properties [24].

Kim *et al*. were synthesized the IPN of PU and polyacrylamide (PAA), which can control water absorption [25]. The PU and PAA were mixed together and the respective cross-linking agent vinylpyrrolidone and methylenebisacrylamide were added followed by exposure of the mixture to UV radiation. Liu *et al*. were synthesized series of IPN hydrogels to impart sensitiveness towards temperature and pH fluctuations [26]. The investigators have incorporated one pH sensitive polymer, polyaspartic acid into the PNIPAAm hydrogel system for improving its response rate to environmental temperature.

2. Stimuli-Sensitive Hydrogels

Stimuli-sensitive hydrogel has capability to swell and de-swell according to conditions, for this ability they are used as new intelligent materials. Applications of Stimuli-sensitive hydrogel for biomedical

fields have three functions: sensing an external signal (sensor function), evaluation (processor function) and action (actuator function), due to these they were developed as "intelligent gels" or "smart gels".

They can be used in controlled drug delivery to achieve constant concentration of therapeutically active compounds in the blood with minimum fluctuations and predictable and reproducible release rates over a long period of time. With this type of hydrogels elimination of side-effects, waste of drug, frequent dosing and optimized therapy and better patient compliance are also achieved.

Stimuli-sensitive hydrogel have been divided into following types according to stimuli:

Temperature-sensitive hydrogels

Temperature-sensitive hydrogels are the most studied class of stimuli sensitive polymer in drug delivery system. These hydrogels have ability to swell or de-swell due to change in the temperature of the surrounding fluid. They are classified into three types: negatively thermosensitive, positively thermosensitive and thermally reversible gels.

Hydrogels containing polymers, such as pNIPAM, methyl cellulose, pluronics, tetronics, and *N*-vinyl caprolactam, are characterized by the temperature dependent sol–gel transition, which corresponds to the lower critical solution temperature (LCST), and by the gel-sol transition temperature, which corresponds to the upper critical solution temperature (UCST) to dissipation or precipitation of a gel [27].

Negative temperature-sensitive hydrogels have a lower critical solution temperature (LCST), means the critical temperature below which the polymer swells in the solution while above it the polymer contracts. Below the LCST, the enthalpy term, related to the hydrogen bonding between the polymer and the water molecules, is responsible for the polymer swelling. When the temperature is raised above the LCST, the entropy term (hydrophobic interactions) dominates and polymer contraction may occur.

The polymers, which are used to prepare temperature-sensitive hydrogel, respond to a lower critical solution temperature (LCST) are Poly (*N*-isopropylacrylamide) (PNIPAM) Poly (*N,N*-diethylacrylamide) (PDEAM) Poly (*N*-ethylmethacrylamide) (PNEMAM) Poly (methyl vinyl ether) (PMVE) Poly (2-ethoxyethyl vinyl ether) (PEOVE) Ploy (*N*-vinylcaprolactam (PNVCa) Poly (*N*-vinylisobutyramide) (PNVIBAM) Poly (*N*-vinyl-*n*-butyramide) (PNVIBAM).

Positive temperature-sensitive hydrogels have an upper critical solution temperature (UCST). Upon cooling below the UCST, contraction may occur. Polymer networks of poly (acrylic acid) (PAA) and polyacrylamide (PAAm) or poly (acrylamide-co-butylmethacrylate) exhibit positive temperature dependence of swelling [28].

A thermo responsive copolymer hydrogel utilize keto-enol tautomerization. This copolymer is a composite stimuli-responsive polymer which has both an UCST and a LCST within various temperature ranges, and also responds to hydrogen ion concentration. Accordingly, it can be effectively used for chemovalve, for separation, drug delivery systems, catheters, artificial muscles, etc. [29].

pH-sensitive hydrogels

pH-sensitive polymers are mainly water-soluble with ionizing functional groups. Their physical properties like solubility change in terms of pH. PH-Sensitive hydrogels have two main classes: cationic hydrogels and anionic hydrogels.

Cationic hydrogels swell and release the drug into a lower pH environment of stomach. Cationic hydrogels are mainly used for the development of self-regulated insulin delivery system, which releases the insulin in response to change in the glucose concentration.

Anionic hydrogels swell and release the drug into a higher pH environment so swelling of this type of hydrogels is minimal in the stomach and the drug release is also minimal. Anionic hydrogels are used in

the preparation of intelligent controlled release systems for site-specific drug delivery of therapeutic proteins to the large intestine, where the biological activity of the proteins are prolonged,

Most commonly used ionic polymers for pH-responsive properties are poly (acrylamide) (PAAm), poly (acrylic acid) (PAA), poly (methacrylic acid) (PMAA), poly (diethylaminoethyl methacrylate) (PDEAEMA) and poly (dimethylaminoethyl methacrylate) (PDMAEMA) [30].

Dual pH-thermal sensitive systems

Some hydrogels are also known which have both pH and thermal sensitivities. It was prepared by copolymerizing a temperature-sensitive monomer, usually *N*-isopropylacrylamide, into a pH-sensitive monomer such as acrylic acid. Hydrogels prepared from poly (*N*-isopropylacrylamide) PNIPAAm and PAA exhibited dual sensitivities [31], PNIPAAm shows temperature-sensitivity, whereas PAA shows pH-sensitive swelling. This hydrogels was able to respond rapidly to both temperature and pH changes. Kim *et al.* proposed their use for the delivery of calcitonin and insulin [32].

Other stimuli-sensitive hydrogels

Several stimuli, other than pH and temperature, can also stimulate the release of some therapeutically active agent from a depot. These include physical stimuli, such as light, magnetic field, electric current and ultrasound, which can be applied to the systems externally and chemical stimuli, like ionic species, certain chemical substances and biological compounds. [33]

Ultrasound is widely used as a drug permeation enhancer through biological barriers. Pulsatile drug release can be obtained by the on/off application of ultrasound to an ultrasound-sensitive hydrogel. Pulsatile release of insulin was achieved only after ultrasonic exposure for 1 minute, which causing release of insulin [34].

Light-responsive hydrogels are utilized in developing photo-responsive devices, especially in ophthalmic drug delivery systems [34]. These possess a potential of becoming truly biomimetic sensors [35]. Photo induced self-healing polymers can mimic the biological systems in which damage triggers a self-healing response. These materials can be used to repair fiber fracture, delamination or propagation of microcracks of polymeric components used in a variety of applications, extending the functional life and safety of the polymeric components [36].

Electric current can also be used as an environmental signal for stimulate the hydrogels. Hydrogels, which have electric current sensitivity, are usually made of polyelectrolytes. An electric field as an external stimulus has some advantages, like the availability of equipment, which allows precise control with regards to the magnitude of current, duration of electric pulses, intervals between pulses, etc. [37].

3. Based on mechanism of release

Hydrogels are classified on the basis of mechanism of release from the device as - diffusion controlled systems, swelling controlled system, chemically controlled system, and environmental responsive systems.

Diffusion controlled systems-

Diffusion is the most common mechanism for controlling the release in drug delivery system. They are of two types: -reservoir devices and matrices devices

Reservoir devices

This type of devices is composed of a core containing drug, which is surrounded by a polymeric membrane. Typical examples of reservoir devices are capsules, cylinders, slabs or spheres etc. Diffusion is the rate limiting step for drug release through the outer membrane of the device. One disadvantage of this device is that the outer membrane is ruptured sometime and the entire content of the device are delivered instantaneously. Care must be taken while preparing this device to ensure that the device does not contain pin holes which may lead to rupture.

Matrix devices

In this type of devices the drug is dispersed throughout the 3D-structure of the hydrogel. Release take place due to diffusion of the drug throughout the macro molecular mesh or water filled pores. In these systems the drug is dispersed within a glassy polymer. The polymer begins to swell upon contact with biological fluid. As the penetrant enters the glassy polymer, the glass transition temperature of the polymer is lowered, allowing for relaxations of the macro molecular chains.

Swelling Controlled Release Systems- They are of two types:

Erodible Drug Delivery Systems

Erodible drug delivery systems (either matrix or reservoir), are also known as degradable or absorbable release systems. From these systems drug release is mediated by the rate of surface erosion. In reservoir devices; the drug core is surrounded by an erodible membrane and in matrix devices; the drug is dispersed within the 3D- structure of the hydrogel. Drug release is controlled by drug diffusion through the gel or erosion of the polymer and as the polymer erodes, the drug begins to release [38].

Pendant Chain Systems

In this system the drug molecules are chemically linked to the backbone of a polymer. In the presence of enzymes or fluids, chemical or enzymatic hydrolysis occurs which leads to concomitant release of the drug at a controlled rate. The drug may be linked directly to the polymer or can be linked via a "spacer" group. In the biodegradable system, the polymer is gradually decomposed and control release of drug is obtained. The drug is uniformly dispersed throughout the polymer and is slowly released as the polymer disintegrates. The degradation rate of the polymer drug linkage is used to determine the release of covalently attached drugs. These linkages are generally degraded by hydrolysis allowing degradation and release rates are determined by simple first-order kinetic relationships [39].

Chemically Controlled Release Systems

It is also known as degradable or absorbable release system. These can be either matrix or reservoir type. In reservoir type systems, the membrane erodes significantly and drug is released by diffusion mechanism. Zero order release can be obtained by this system.

Environmental responsive systems-

These systems mainly include temperature and pH responsive hydrogel. Physical and chemical stimuli also stimulate the release of drug from hydrogel. Physical stimuli include light, magnetic field, electric current and ultrasound, which can be applied to the systems externally and chemical stimuli include ionic species, certain chemical substances and biological compounds.

Preparation methods of hydrogel

Hydrogels, generally have hydrophilic properties, so they are prepared from hydrophilic monomers, but sometimes hydrophobic monomers are also used in hydrogels preparation to regulate the properties for specific applications [40]. Basically, the three integral parts for the hydrogels preparation are monomer, initiator, and crosslinker. Diluents as water or other aqueous solutions can be used to control the heat of polymerization and the final hydrogels properties.

Hydrogels have been synthesized and prepared by several polymerization techniques such as solution polymerization or aqueous polymer solution [41], radiation polymerization [42] or photopolymerization [43], suspension polymerization [44], reversible addition-fragmentation chain transfer (RAFT) polymerization and free radical polymerization [45-46]. But generally, Hydrogels are synthesized by solution polymerization, suspension polymerization and radiation polymerization techniques [47].

Solution Polymerization

In this method, hydrogels are synthesized by mixing the ionic or neutral monomers with the multifunctional cross-linking agent. UV-irradiation or a redox initiator system is used to initiate the polymerization reaction. The presence of solvent is the major advantage of this polymerization method. The prepared hydrogel has been washed with distilled water for the removal of unreacted monomers, cross-linking agent, initiator, and other impurities. When the amount of water during polymerization is more than the water content corresponding to the equilibrium swelling [48] phase separation occurs and the heterogeneous hydrogels are formed.

Suspension Polymerization

In this polymerization method, the monomer solution is dispersed in the non-solvent, forming fine monomer droplets, which are stabilized by the addition of stabilizer. Radicals from thermal decomposition of an initiator are used to initiate the polymerization reaction. The newly formed micro-particles have been washed to remove unreacted monomers, cross-linking agent, and initiator. The viscosity of monomer phase affected the shape of particles produced, while the size of particles can be controlled by the hydrophilic-lipophilic balance (HLB) of each type of suspending agent [49, 50]. This is one of the most successful methods used to prepare spherical hydrogels with a size range of 1 *m*m to 1 mm.

Polymerization by Irradiation

This method is used for the preparation of hydrogel from the unsaturated compounds and polymerization reaction has been initiated by ionizing high energy radiation, such as gamma rays and electron beams. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains and radiolysis of water molecules results in the formation of hydroxyl radicals, which also attack the polymer chains resulting in the formation of macro-radicals. Recombination of the macro-radicals on different chains leads to forming of covalent bonds and finally a cross-linked structure. During radiation, polymerization macroradicals can interact with oxygen, and as a result, radiation is performed in an inert atmosphere using nitrogen or argon gas. Examples of polymers cross-linked by this method are poly (vinyl alcohol), poly (ethylene glycol) and poly (acrylic acid). The major advantage of the radiation initiation over the chemical initiations is that the production is relatively pure and initiators free [51-53].

Dosage forms of hydrogel

The route of administration is decided the dosage forms for hydrogel based drug delivery systems. The preparation of hydrogels mainly involves cross-linking of polymers within a mould to impart the desired shape suitable for administration into the body. For various routes of administration different shapes of hydrogels are developed. For peroral route hydrogels are prepared in the form of spherical, cylinders and

discs [54], for implants in the form of drum-shaped [54], disc-shaped [55] and cylindrical preparations [56], for rectal route in the form of cylinders [57], and for vaginal administration cylindrical [58] and torpedo-shaped devices [59] are developed.

Application of Hydrogel

1. The main reason for wide applications of hydrogels are their unique properties such as absorption, swelling and de-swelling behavior, hydrophilicity, and biocompatibility [60, 61]. Hydrogels have special application in pharmaceuticals field including diagnostic, therapeutic, and implantable devices such as catheters, biosensors [62], artificial skin [63], and tissue engineering [64]. Natural polymers generally have better biocompatibility and less latent toxicity than other synthetic polymer [65, 66], therefore, hydrogel of natural polymers have more attraction as excellent candidates for controlled release device, bio-adhesive device, and targetable therapeutic devices.
2. PH-sensitive hydrogel have ability to convert chemical energy into mechanical energy. Therefore, these systems can serve as actuators or artificial muscles in many applications [67].
3. Light-sensitive hydrogel have been use to develop photo-response artificial muscles, switches and memory devices [68] and electro-sensitive hydrogel have been applied in controlled drug delivery.
4. In addition, hydrogels are initially used to be developed as ocular lenses. Recently the ocular lens made of hydrogels was commercialized as soft contact lenses (SCL), which have been used widely as an adaptor for drug delivery system. The reason for wide acceptance is the ability of these lenses to release and control the amount of drug over an extended period during treatment [69].
5. Hydrogels have special application for control-release fertilizers [70], to reduce environmental pollution [69, 71], reduce irrigation water consumption, improve fertilizer retention in soil, eliminates the leaching of nutrients, increase soil aeration and diminishes soil density. The function of hydrogel in the soil is to absorb water from rainfall or irrigation and release it slowly to meet the need of plant growth and to enhance the production in terms of quality and quantity.

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