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Hydrogels: An Introduction to a Controlled Drug Delivery Device, Synthesis and Application in Drug Delivery and Tissue Engineering

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Abstract

Hydrogels are the unique three- dimensional polymeric materials that can hold a large fraction of water thus aims to release the drug in a controlled manner. They are the interesting class of material as can be tuned towards the subjected stimuli and can be engineered to imitate the extracellular environment of the body's tissue hence, makes themselves worthy to be used in tissue engineering, drug delivery and in the traditional field of science such as transducer, biosensors and actuators. Here in this review an attempt has been made to present a state-of- art on the hydrogel, its classification on various basis, general synthesis and drug loading with a wide focus on its tuning property towards various stimuli are discussed. Further its application in drug delivery containing the release mechanism with a brief description about how it can be delivered through the different route of administration, application in tissue engineering. Last, some marketed products of hydrogel available in the market are mentioned.

Keywords: Hydrogel; Smart hydrogel; Drug delivery; Controlled drug delivery; Tissue engineering; Scaffold

Introduction

Despite vast and advanced research is going on in the medical field a few candidates are successful clinically attributing good bioavailability [1]. Controlled drug delivery systems that are meant to deliver the drugs at predetermined rate for a pre-programmed period is a good alternative to accomplish and overcome the inadequacy of low bioavailability of conventional dosage form. The most interesting feature of this drug delivery system, attracting the scientist a lot is their release mechanism which is precise and timed controlled from few hours to month [2,3]. Overall it would be highly advantageous if an active agent was released by such system that can sense the signals produced by disease, determined the actual extent of signal and then release the specific amount of drug in response to the need of the physiological condition. In all these respect hydrogels have shown characteristics features of a smart drug delivery system [4]. The kudos goes to the Wichterle and Lim [5] who for the first time led a milestone in the class of hydrogel drug delivery system by proposing the use of hydrophilic poly (2-hydroxyethyl methacrylate) PHEMA for contact lens [6]. Their pioneer work acted as a revolution, since then hydrogels have elaborated their dimensions in several biomedical [7] pharmaceutical [8,9] applications as drug delivery vehicles [10,11] including personal hygiene, contact lenses, lubricating surface coatings, wound healing dressings, three-dimensional (3-D) cell culture substrates, and underwater devices [12-15].

Hydrogels are 3-D macromolecular polymeric chains that can be easily moulded in any form, shape and size. They do not dissolve and can absorb thousand times of their own dry weight in water [16,17]. This fabulous property of their, is imparted by some hydrophilic domains [18,19] for instance OH, -$CONH^-$, $CONH_2^-$, and $-SO_3H$ present in the polymeric structure. These groups assist in absorbing the large fraction of biological fluid or water thus helps in hydrogel formation [20]. One more enthralling characteristics of hydrogels is the porous structure which can be modulated by controlling the density of the cross-links in the gel matrix. Their porosity allows the incorporation of the therapeutic agent into the gel matrix and delivers the active agent at a rate depending manner through the polymeric gel network [21].

Hydrogel Classification

Hydrogels can be classified in various ways which are as follows:

Based on source

Hydrogels can be prepared using either natural or synthetic and the combination of both the polymers as shown in Table 1.

Based on method of polymeric composition

Homopolymer hydrogel: These are composed of one type of hydrophilic monomer. They commonly possess cross-linked backbone structure [22]. Homopolymer hydrogel can be prepared in several possible ways one of the effective ways to form cross-linked homopolymer hydrogel is through photoinduced cross-linking for instance Kadlubowski et al [23] made a hydrogel with glucose sensing property they adopted a novel method of cross-linking through radiation between the polymer Polyvinyl Pyrrolidone (PVP) and Poly (Acrylic Acid) (PAA) containing glucose oxidase as a glucose indicator in deoxygenated aqueous solution with hydrogen peroxide as a free radical source. Cross-linked PAA-PVP gel sensitive to pH was formed successfully by irradiating at a wavelength 200-800 nm. The homopolymeric cross-linked gel containing glucose oxidase is commonly utilized as glucose detector or in glucose sensitive devices.

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Table 1: Hydrophilic polymers used to fabricate hydrogels.

Natural polymer and their derivatives	Synthetic polymer	Combination of both natural and synthetic polymer
Anionic polymers Hyaluronic acid [155], Alginic acid [156], Pectin [157,158], Carrageenan [159].	PEG–PLA–PEG [168],	Collagen-PEG [173],
Cationic polymers Chitosan [160], Polylysine [161].	PEG–PLGA–PEG [169],	Collagen-hydroxyethylmethacrylate [174],
Amphipatic polymers Collagen [162,163], Fibrin [164].	PEG–PCL–PEG [170],	Alginate–Poly(sodium acrylate-coacrylamide) [175],
Neutral polymers Dextran [165], Agarose [166], Pullulan [167].	PLA–PEG–PLA [171,172].	Collagen-g-poly(acrylic acid)/kaolin [176].

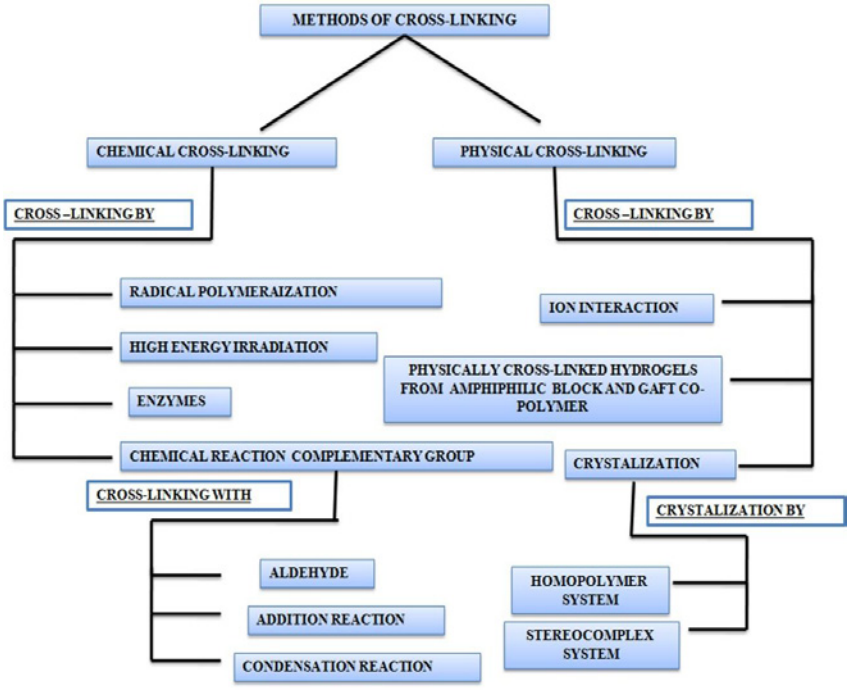

Figure 1: Methods of cross-linking.

Co-polymer hydrogel: It comprises of minimum two co-monomer species in which at least one monomer must be hydrophilic in nature to make it swellable [24]. Laden with a stimuli sensed property hydrogels are in demand and frequently used as smart and intelligent materials [25-28] such as actuators [29], transducer [30], optical fiber humidity sensor [31] and optical biosensor [32]. Fascinating with the above property of smartness, Chen et al. [33] co-polymerized Itaconic acid with N-Vinyl -2-Pyrrolidone (NVP) as a monomer and N, N-methylene-bisacrylamide (MBAAm) and prepared pH sensed hydrogel by ultra-violet induced method. The formed hydrogel was found to be highly pH sensitive. The whole study was based on swelling of the co-polymerized hydrogel whose value increased from 150 to 3011% with the increase in the pH value of the swelling solution which was 4-10. Thus, the pH sensed co-polymerized hydrogel exhibited a promising vehicle for the delivery of Itaconic acid.

Interpenetrating polymer network: An IPN is made up of two polymers that are formed without covalent bond but are cross-linked among similar molecule. Therefore, two meshes with different chemistry integrate to each other. In IPN the bulk of the matrix i.e. polymer act as a reservoir for the active agent and releases it in a long-term manner [34,35].

Interpenetrating polymer network is enriched with the applications in delivering the drug in a constant manner over an extended period [36]. The property to deliver the drug in a controlled manner is actually imparted by the extent of cross-linking [37,38]. To see the release of drug in a controlled manner, Angadi et al. [39] prepared an interpenetrating polymer network blend microsphere of chitosan and hydroxyethyl cellulose containing isoniazid, an anti-tuberculosis drug and cross-linked it with glutaraldehyde. The formed microsphere of isoniazid showed the extended cumulative release up to 16 hours by releasing the drug up to 75% with the encapsulation efficiency of 50- 66%.

Based on physical structure

Amorphous: Here, macromolecular chains are arranged in a random fashion [40].

Semicrystalline: They are recognized by dense regions of macromolecular chains arranged in an ordered manner [40].

Hydrogen bonded or supramolecular/complexation structure: They are well known for their 3-D structure [40].

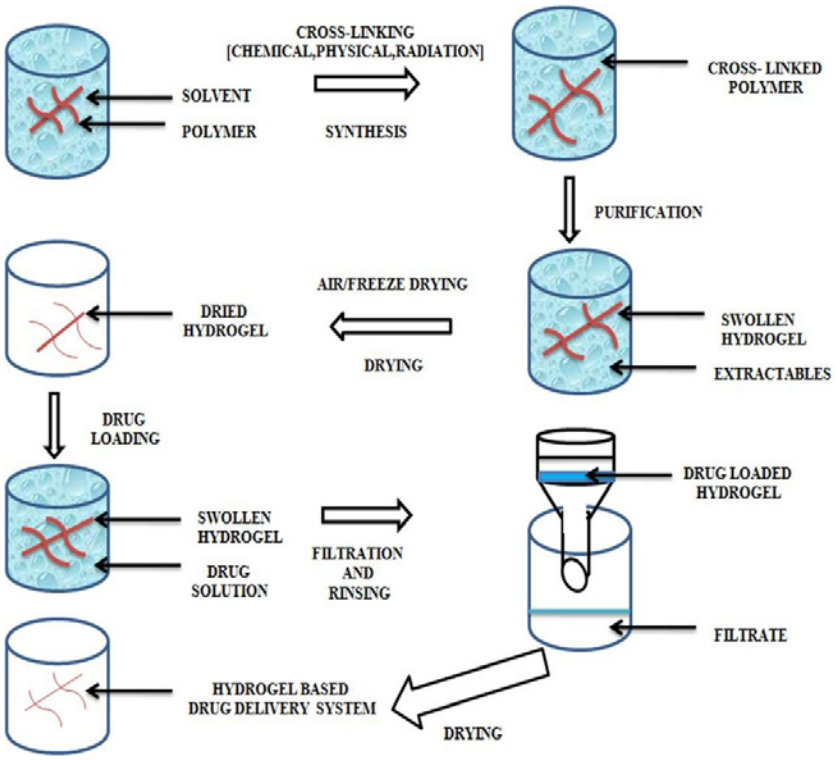

Figure 2: Method of preparation of Hydrogel.

Based on cross-linking: Hydrogels based on types of cross-linking are divided into two classes physical cross-linking and chemical cross-linking [41] shown in Figure 1.

Polymers possessing covalent bond between them are termed as the cross-linked polymer. Chemical cross-linking provides a good mechanical strength [42]. While physical cross-linking forms non-covalent interactions between the polymers [43].

Based on ionic charges

Hydrogels based on ionic charges are of four types [44].

a. Neutral hydrogel (non-ionic)

b. Cationic hydrogel

c. Anionic hydrogel

d. Ampholytic hydrogel

Preparation of Hydrogel

Fabrication of hydrogel includes physical and chemical cross-linking methods. The cross-linking is formed by either covalent [45,46] or non-covalent interaction [47-49]. Hydrogel possessing covalent interactions are termed as chemical gel while non-covalent gels are called as physical [50]. A general description of the synthesis of a hydrogel is presented in Figure (2).

Hydrogel Drug Loading

Loading of the drug in hydrogel generally involves two methods. In the first approach, the polymer to be used for hydrogel is mixed with the drug, an initiator and a cross-linker if required, are allowed

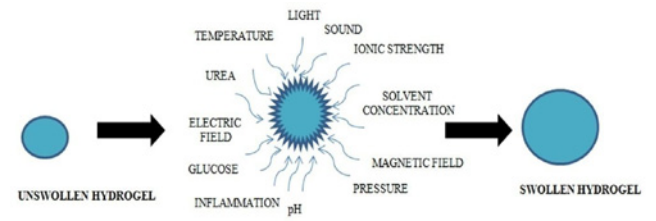

Figure 3: Schematic presentation of stimuli sensed hydrogel.

to polymerize having the drug within the matrix [51]. However, in the second approach, an already formed hydrogel is allowed to swell in a drug solution till equilibrium. In both the mechanism i.e. after loading of drug the hydrogel is dried. Drug loading within hydrogel is affected by several factors viz. interaction between polymer and solvent, cross-linking density of the polymeric network, the presence of a solvent etc. All these parameters influence the extent of swelling to a great extent. The drug loading per unit mass of a polymer can be calculated from the following expression [52].

(Swollen polymer weight-Dry polymer weight)/(Dry polymer weight).

Smart Hydrogel

Smart hydrogels are the hydrogels that sense and act quickly according to the stimuli or signals perceived. They expand or shrink in their volume with respect to changes in the environment such as the change in temperature, pH, glucose, light, electric current, sound etc. as shown in Figure 3. They are also termed as intelligent as they have an excellent ability to return in their primordial form after an

Table 2: Examples of different types of thermoresponsive polymers.

Polymer	Types of polymer
Poly(N-isopropylacrylamide) (PNIPAM)	L
Poly(N-n-propylacrylamide) (PNNPAM)	L
Poly(N-cyclopropylacrylamide) (PNCPAM)	L
Poly(N,N-diethylacrylamide) (PDEAM)	L
Poly(N-(1 hydroxymethyl)propylmethacrylamide) (PHMPMA)	L
Poly(N-acryloylglycinamide) (PNAGA)	U
Poly(N-acryloylasparaginamide) (PNAAAM)	U
Poly(methacrylamide) (PMAAm)	U
Poly(acrylonitrile-co-acrylamide) (P(An-co-AM))	U

over of the external stimulus to which they have been exposed [53-55].

Temperature sensitive hydrogel

Hydrogels exhibiting response towards the change in temperature are known as thermosensitive or temperature sensitive hydrogel. The sole stimulus of their sensitivity is temperature, which is required for its gelation [8,56]. Temperature sensitive polymers manifest a transition such as lower or upper critical solution temperature in the aqueous environment. In the case of polymers with Low Critical Solution Temperature (LCST), they remained water soluble below the LCST, but changes to water insoluble or sparingly water soluble at a temperature termed as upper critical solution temperature (UCST) [57]. Some typical examples of thermo responsive polymers are shown in Table 2 labeling "L" as LCST and "U" as UCST [58].

The phenomenon of conversion from solution to gel is termed as a sol-gel transition [59-61]. When a polymer remains in water three types of interaction take place i.e. between molecules of water, between molecules of polymer and water and between molecules of polymer. Polymers showing lower critical solution temperature, when undergoes increase in temperature results in negative free energy which makes association of water and polymer unfavourable, promoting the other two types of interaction. The thermodynamics behind this can be expressed as

$$\Delta G=\Delta H-T\Delta S.$$

This negative free energy (ΔG) is attributed to the higher entropy (ΔS) in response to change in enthalpy (ΔH). The increase in entropy occurs due to the association between water molecules (The major factor for the cause of interaction). This phenomenon is termed as hydrophobic effect [59,62,63]. Resultant, a conformational change in a polymer at a critical solution temperature occurs that leads to the reversible linking of the polymer chain and therefore the gel turns to the solution form as the thermal stimulus is removed.

pH sensitive hydrogel

pH sensitive hydrogel is a gel composition that responds to the pH of the environment. The principle of the gel is a structure that either shrinks or swells in response to the pH of the system [64]. pH sensitive polymers contain acidic or basic side groups attached to their backbone that may accept or release the proton with respect to the change in the surrounding pH [65,66]. Polymers with a wide range of ionizable group are called as the polyelectrolyte. In the case of anionic/acidic group, volume of hydrogel increases as the pH of the media increases while declines for polymer containing cationic/basic groups [67]. Polymers typically used for fabricating pH responsive hydrogel are poly (hydroxyethyl methacrylate-co-acrylic acid) [68], Polyvinyl Pyrrolidine (PVP) [69], chitosan [70], Poly (methacrylic acid) [71].

Glucose sensitive hydrogel

Glucose sensitive hydrogel are composed of polymers such as N-(2-(dimethylamino) ethyl)-methacrylamide [72], N,N-(dimethylacrylamide) [73] that can model the function of sensitive organs and tissue such as pancreas whose function is to release insulin [74]. The strategy of mimicking the natural response of the pancreas in a diabetic patient via. glucose sensitive polymers involves the appropriate delivery of insulin in response to the variation of glucose level in the body [75,76]. The mechanism behind the controlled release of insulin from the system to maintain its level in a diabetic patient involves an enzyme substrate reaction where glucose reacts with glucose oxidase forming gluconic acid, resulting in a decrease in the pH of the environment. With the change in pH, the gel swells or shrink depending on the characteristics of the particular polymer of the system. Insulin is released from the system with the change in the pores size of the polymer [77].

Light sensitive hydrogel

The light sensitive hydrogel has been extensively used in various biotechnological application such as light controlled enzymatic bioprocessing system [27], photo triggered targeted drug delivery systems [78], and photo controlled separation/recovery systems in bioMEMs (Biological microelectro mechanical system) formats. These hydrogels are supposed to deliver the light in a controlled way with accuracy. The light sensitive hydrogel is applicable in the fabrication of optical switches, display unit, and especially in optical drug delivery system [79,80].

Electric current sensitive hydrogel

Electric current induced hydrogel are basically composed of polyelectrolyte and shrinks or swells in response to an applied electric field [81]. Polymers contain a large number of the ionizable group on their backbone chain thus sensitive towards both pH and electricity [82]. Various reports are already existing stating about the use of electric current *in vivo* in the form, for instance, iontophoresis and electroporation in the application of dermal and transdermal drug delivery [83-85]. Lin et al. [86] reported, synthesis, structure and electric field sensitive conductive IPN hydrogel of polyacrylate/polyaniline (PAA/PANI) and poly (2-acrylamido-2-methyl propylsulfonic acid-acrylic acid)/polyaniline [P(AMPSAA)/ PANI] for its application in drug delivery, switches, sensors and for actuators. The fabricated conductive IPN hydrogel showed a porous structure of numerous PANI nanofibers. To observe its affinity towards electric field they subjected the hydrogel in an aqueous solution of NaCl resulted in its bending towards the anode and as soon as the stimulus was removed the hydrogel returned to its real position.

Sound sensitive hydrogel

Ultrasound sensitive hydrogel is potential to deliver the drug in an

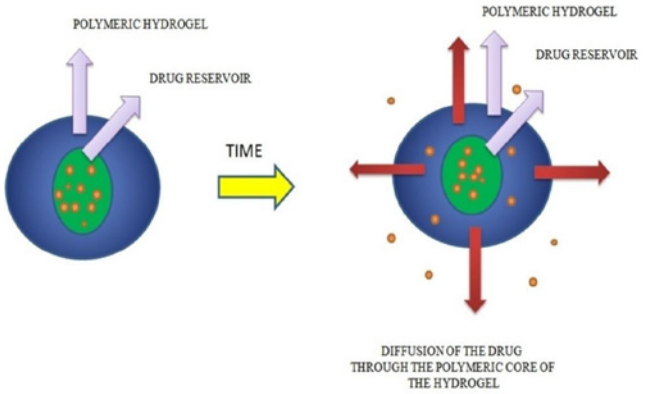

Figure 4: Diffusion controlled release mechanism of drug through reservoir system.

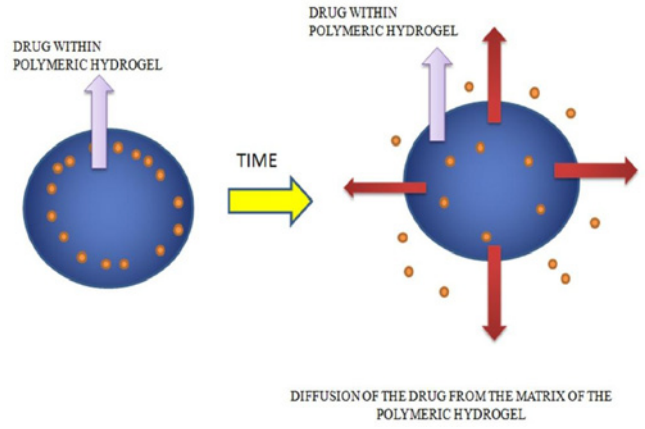

Figure 5: Diffusion controlled release mechanism of drug through matrix system.

"on-off switch" manner. For these system sound acts as a permeation enhancer and helps the drug to cross the biological barrier. For instance, Kwok et al [87] prepared a self assembled ultrasound sensitive system made up of methylene chain where the drug insulin present within the polymer (co-polymer of 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate). The whole system was so sound sensitive that it showed the pulsatile release of insulin just in one minute when got exposed to the ultrasonic exposure that resulted in disruption of the ordered methylene chain hence, controlled release of insulin.

Drug Delivery

Polymeric hydrogels are drawing attention since the 1950s [88]. Being blessed with the boon of smartness, it can be triggered externally and exhibits spatiotemporal release mechanism [89]. Owed with rapid and controllable diffusion rate [90], they have been considered as a promising vehicle for the encapsulation and controlled release in numerous physiological conditions for instance [91] cancer therapy [92-94], osteoarthritis [95], diabetes [96,97], viral and bacterial infection [98], cardiac disease [99] etc. The main benefit proffered by hydrogel in drug delivery application is their drug delivery in controlled manner for a long period thus enabling the active pharmaceutical ingredient over a longer duration [100]. As hydrogels possess excellent property to imbibe water, that is even greater than 90% of their own weight. This unique hydrophilic property makes them classic from other drug delivery systems. Delivery of therapeutic agent from hydrogel occurs mainly through three mechanisms diffusion-controlled systems, swelling-controlled systems and chemically controlled systems [101].

The diffusion controlled release system is the most accepted and commonest among all the drug release mechanism models available for describing the drug release from the hydrogel, and are divided as reservoir device (Figure 4) and matrix device (Figure 5) [102]. In reservoir system, the drug remains within a core, surrounded by a polymeric membrane. Drug release from such system through polymeric membrane follows Fick's First law of diffusion [103-105].

$$J(i = -D\_ip\ (dC\_i)/dX)$$

Where J_i molar flux of the drug is is, D_ip is the diffusion coefficient of the drug in the polymeric membrane.

To perpetuate release of drug from such system at a constant flux the device must be fabricated by incorporating the drug in higher concentration in the core or center resultant letting the drug release at a constant rate [106]. Matrix system involves uniform distribution of drug in the overall structure of the hydrogel. Concerning with the reservoir type, matrix system releases the drug through the macromolecular pores in the polymeric hydrogel rather than from the core as in reservoir system. Here, in this case, the release rate is proportional to the square root of time which is constant and time independent in reservoir system [106].

In swelling controlled mechanism drug diffusion is faster than hydrogel expansion. Here the release of the drug from the hydrogel significantly depends on the stretched volume of the device [103,107]. The chemically controlled release mechanism is influenced by chemical reactions occurring within the device. The release of the drug from the system depends on reactions, for instance, polymeric chain cleavage via hydrolytic or enzymatic degradation reaction or reversible or irreversible reactions taking place between the polymeric network and the releasing drug [102,108]. Table 3 summarizes some of the experimental studies done for hydrogel drug delivery.

The release of drug in a controlled manner and further its delivery to the ocular route is one of the challenging tasks for a pharmaceutical engineer due to the inherent protective nature of eyes such as blinking and tear flow that actively supports rapid clearance and low bioavailability thus low therapeutic response [109]. Concerning the above mentioned problems various steps have been taken such as fabrication of ointments [110], suspension [111], emulsion [112], micro [113], nanocarrier systems [114,115], inserts [116,117] and liposomes [118,119] etc. Although they have been proven to be successful in increasing the bioavailability however, they are stacked with several limitations too, for instance, viscous nature of ointment leading to the blurring vision [120] or non-homogeneity, cake formation or aggregation of the suspended particle in the suspension [121]. The same limitation with the ocuserts, as they pose a problem in inserting and removal especially in the geriatric patient [122,123]. Hydrogel as smart emerging technology could be a useful device for ocular drug delivery. Presently pharmaceutical engineers are giving their vigorous effort towards fabrication and evaluation of such ocular

Table 3: Application of hydrogel in drug delivery.

Polymer used for fabricating hydrogel	Drug carried within system	Application	Reference
Mixture of chitosan and alginate	Bevacizumab	Ocular dug delivery	147
Polyacrylic acid and gelatin	Vancomycin hydrochloride Gentamycin sulphate	Local drug delivery for antibiotic	148
P(MAA-g-EG) and P(MAA-co-NVP)	Anti-TNF- α	Transmucosal drug delivery	149
Poly(ethylene glycol)-grafted-chitosan	Cyclosporine A	Subcutaneous drug delivery	152
Copolymer of polyethylene glycol (PEG) onto phthaloyl chitosan	Ciprofloxacin	Pulmonary drug delivery	158
Quaternized chitosan and poly(ethylene glycol)	Insulin	Nasal drug delivery	160

Table 4: Different Growth factors in Tissue engineering.

Growth factor	Tissues to be treated	Function
Ang-1	Blood vessel, heart, muscle	Blood vessel maturation and stability
Ang-2	Blood vessel	Destabilize, regress and disassociate endothelial cells from surrounding tissues
FGF-2	Blood vessel, bone, skin, nerve, spine	Migration, proliferation and survival of endothelial cells
BMP-2	Bone, cartilage	Differentiation and migration of osteoblasts
BMP-7	Bone, cartilage, kidney	Differentiation and migration of osteoblasts, renal development
EGF	Skin, nerve	Regulation of epithelial cell growth, proliferation and differentiation
EPO	Nerve, spine, wound Healing	Promoting the survival of red blood cells and Development of precursors to red blood cells
HGF	Bone, liver, muscle	Proliferation, migration and differentiation of mesenchymal stem cells
VEGF	Blood vessel	Migration, proliferation and survival of endothelial cells

Ang: Angiopoietin; bFGF: Basic Fibroblast Growth Factor; BMP: Bone Morphogenetic Protein; EGF: Epidermal Growth Factor; FGF: Fibroblast Growth Factor; HGF: Hepatocyte Growth Factor; VEGF: Vascular Endothelial Growth Factor.

delivery system carrying numerous desired properties such as easy application, decreased dosing frequency, patient compliance. On all these parameters hydrogels stand as a standard [124]. For instance, Xu et al. [125] proposed an in situ injectable polysaccharide cross-linked hydrogel for the ocular delivery of Avastin®. Commercially Avastin®, chemically named as Bevacizumab is available for treating age related macular degeneration and proliferative diabetic retinopathy. Since the drug is suffering from short elimination half-life time resultant, it requires repeated administration. The fabricated in situ hydrogel loaded with Avastin was prepared by mixing glycol chitosan and oxidized alginate aqueous solution. Through experiment, it was found that encapsulated Avastin showed an initial burst release at its initial stage within four hours followed by sustained release for a period of three days. The main reason behind the slow release of drug from hydrogel was dependent upon increased alginate concentration present as oxidized form.

Hydrogel implants for the release of antibiotics are now becoming a trend. Treating chronic infections through conventional manner i.e. administration of antibiotic via oral or systemic route might pose a fluctuation in serum concentration. To avoid this, local application is found to be suitable as it provides the maximum concentration of drug at the site of infection with minimum side effects. Numerous local delivery devices for antibiotics have been taken into consideration and are mostly composed of non degradable polymers. Application of such non-degradable polymer actually is the main problem due to its undetermined period of antibiotic release from drug delivery device composed of a synthetic polymer. To show the importance of delivery of antibiotic in a controlled manner from hydrogel made up of natural polymer Changez et al [126] prepared an Interpenetrating Polymer Network (IPN) implant device loaded with Vancomycin hydrochloride (VCI) and Gentamicin sulphate (GS) with polymers poly (acrylic acid) and gelatin cross-linked using 0.3 mol % of N,N-methylene bisacrylamide and 1% w/w of glutaraldehyde, respectively. The blank and the drug loaded hydrogel implant were applied for treating osteomyelitis in the rabbit. They divided twelve rabbits into four groups and each group were treated with the following combination i.e. 12±1 mg of cross-linked acrylic acid and gelatin named as 1a containing 22% w/w of GS, 12±1 mg of cross-linked acrylic acid and gelatin named as 1b containing 44% w/w GS, 16±1 mg of cross-linked acrylic acid and gelatin named as 1b containing 44% w/w GS and 16±1 mg of cross-linked acrylic acid and gelatin labelled as 1c containing 44% w/w VCl. The drug concentration was measured following its implantation in the adjacent tissue of femoral cavity, and serum. Authors through their experiments observed that among all the four implanted device, no drug was found after 21 days at the treated local site with the implanted device in group 1a and 1b (12±1 mg), however after 6 weeks the drug Gentamicin sulphate and Vancomycin hydrochloride in a quantity of 16±1 mg 1b (44% w/w GS) and 16±1 mg of 1c (44% w/w VCl) respectively within implanted IPN hydrogel device were detected at the treatment site that revealed to be the best and cured the infection within 6 weeks.

Another application involving the release of drug through this device is oral administration of monoclonal antibodies (mAbs) in GI tract and systemic disease. Developing an oral delivery of mAbs is a challenging task as they lose their biological activity because of physical and chemical instability *in vivo*. However Carrillo-Conde et al. [127] took this challenge and designed a pH sensed hydrogel with outstanding transmucosal delivery of anti-TNF- α for Inflammatory Bowel Disease in the GIT and systemically to be used for rheumatoid arthritis. The polymer used for the experiments were P(MAA-g-EG)

and P(MAA-co-NVP). Hydrogel composed of these two polymers showed an outstanding swelling behaviour, with improved protein loading and release at neutral pH imitating the small intestine conditions, as well as, these hydrogel systems maintained the antibody bioactivity upon release resulting in the systemic circulation enabling effectively performing its biological function.

Thermosensitive hydrogel meant for sol-gel transition for implant drug delivery based on the natural polymer is of keen interest. Their sol form helps in injectable administration and gel form in controlled release [128,129]. For instance Jiang et al. [130] prepared poly(ethylene glycol)-grafted-chitosan (PEG-g-CS) hydrogel and examined the cytotoxicity of cyclosporine A, *in vivo* degradation and its release from grafted polymer. Cytotoxicity was experimented using L929 murine fibrosarcoma cell line. Degradation and drug release *in vivo* were evaluated by subcutaneous injection of the hydrogel into Sprague-Dawley rats. It was observed that PEG-g-CS polymer exhibited no significant cytotoxicity when the drug concentration was below 3 mg ml−1. Upon implantation, PEG-g-CS hydrogel maintained its integrity for two weeks and in the third week collapsed, and merged into the tissue. The hydrogel exhibited sustained release of cyclosporine A for three weeks with no significant burst release *in vitro* and achieved the effective drug concentration *in vivo* for more than five weeks, showing almost the same bioavailability to chitosan/glycerophosphate hydrogel.

Pulmonary drug delivery is considered as the most useful means of drug delivery because of its large surface area for absorption and high solute permeability [131]. In the case of respiratory diseases such as asthma or cystic fibrosis [132], requires local administration of antibiotics in a sustained release manner [133,134]. Though these kind of formulations are quite effective but not enough to release the drug in a sustained way as they exhibit rapid clearance of inhaled particles mainly through alveolar macrophage uptake [135]. Hence to show an effective delivery of drug to lungs so as to increase its residence time Du et al. [136] prepared swellable Ciprofloxacin-loaded nano-in-micro hydrogel particles for local lung drug delivery. The basic concept behind this work was to develop swellable and respirable system because the particles when inhaled initially remains in aerodynamic size in a dry state but get swell and increases in size as soon as it moves towards the wet respiratory tract. To get such micro hydrogel embedded with the nano-sized drug they grafted copolymer of Polyethylene Glycol (PEG) onto Phthaloyl Chitosan (PEG-g-PHCs) self [135] assembled with the model drug Ciprofloxacin to form the drug loaded nanoparticle. Further, these nanoparticles were then encapsulated into Ca^{2+} cross-linked alginate hydrogel microparticle. Finally the formed formulation was then evaluated for size *in vitro* release study and *in vivo* pharmacokinetic studies that revealed the loaded drug in nanosize range of 218 nm embedded within 3.9 micron hydrogel particles exhibited a rapid initial swelling within 2 minutes and showed rapid initial release of ciprofloxacin within the first 5 hours followed by a relatively slow release up to 144 hours. Whereas *in vivo* pharmacokinetic studies performed with formulations delivered to rats Ciprofloxacin concentrations in plasma, lung tissue and lavage were measured up to 7 hours.

Nasal drug delivery in the recent year has been used as a popular and alternative route for systemic medication because of various advantages such as avoidance of first pass metabolism, large surface area, porosity in the endothelial membrane etc. [137]. Taking such tremendous properties of nasal drug delivery in a view Wu et al. [138] prepared a thermosensitive hydrogel of quaternized chitosan and poly (ethylene glycol) to deliver Insulin as a model drug through nasal route. Giving Insulin through this alternative route was beneficial and compatible rather than receiving it through a painful means i.e. via injection in the patients suffering from Insulin-Dependent Diabetes Mellitus (IDDM). The thermosensitive hydrogel by just mixing N-[(2-Hydroxy-3-Trimethylammonium) Propyl] Chitosan Chloride (HTCC) and Poly (Ethylene Glycol) (PEG) with a little amount of α-β-Glycerophosphate (α-β-GP). The formed formulation then showed a transition from solution to non-flowing hydrogel around 37°C for several minutes. Due to the low viscosity at room temperature, it can be dropped or sprayed quickly into nasal cavity and spread on the nasal mucosa in the solution state. After administered into the nasal cavity, the solution transforms into viscous hydrogel at body temperature, which decreases nasal mucociliary clearance rate and the drug release. Further during animal testing too, the hydrogel formulation was found to reduce 40–50% of initial blood glucose concentration blood glucose concentration for at least 4–5 hours after administration, and no cytotoxicity was found after application.

Tissue Engineering Applications of Hydrogel

Tissue engineering is rapidly emerging and extensive multidisciplinary field including biomedical science, cell biology, cell material interaction and surface characterization [139]. Tissue engineering shows its awesome effect when a single part or the entire tissue or organ fails. Although several strategies are there for the treatment for instance repair or replacement with a natural or synthetic substitute. However, synthetic substitutes might pose a problem when used during surgical method or implant application [124]. Tissue regeneration strategies include four components (i) selection and isolation of tissue of interest (ii) scaffolds either natural or synthetic acting as a platform for cell function and transplantation, (iii) signalling molecule as protein or growth factors showing the cellular function of interest, and (iv) bioreactors hosting, nurturing and providing a biologically active environment for cell expansion and differentiation [139]. Some of the recent applications of hydrogel in tissue engineering are as follows.

Hydrogel as stem cell transplantation carrier

Hydrogel for stem cell transplantation has been emerged out as an extraordinary achievement in tissue engineering. This unique 3-D matrix epitomizes the existing natural extracellular matrix and provides a simulated natural environment for the cell behaviour and leaving the limitations associated with the conventional cell based therapies [140]. Their high water content helps in exchange of ions, metabolites, and nutrients with the fluids of the surrounding tissue thus maintain the viability of the transplanted cell [141]. Recently efforts have been poured towards injectable hydrogels for the repair and replacement of body tissues [142]. For example, Wang et al. [143] prepared an injectable biodegradable hydrogel made up of Oligo [Poly (Ethylene Glycol) Fumarate] (OPF) to encapsulate the mouse embryonic stem cell to treat Myocardial Infarction (MI). The embryonic stem cell encapsulated in OPF hydrogel is injected into the left ventricular wall in the rat MI model. Under observation of the

Table 5: Different commercially available products of hydrogel.

Product	Product Type	Main chemical Constituent	Characteristic
Aquasorb	Wound dressing	Polyvinyl pyrrollidone and water	A sterile transparent hydrogel that provides a moist, cooling and pain relieving environment to the wound. [177].
SAF-Gel	Wound dressing	Alginate	It is especially useful for dry wounds. Provides an optimum moist environment as well as help in autolytic debridement to the wound. [178].
Vigilon	Hydrogel sheet	Polyethylene oxide and 96% water	It is a non-adherent hydrogel sheet. Applicable for skin tears, minor burns and radiation reaction. Once applied gives moist environment to the wound. Further cross-linking of polyethylene provides an additional support to the dressing. [179].
Flexigel	Hydrogel sheet	Polyacrylamide with hydrophilic polysaccharide particle	It inhibits the physical separation between the wounds and protects it from external environment to control the bacterial infection. [180].
Derma Gran	Impregnated gauze	Zinc and source of vitamins such as vitamin A, B_6 and C	It is a kind of hydrophilic wound dressing. This acts as a filler and with its hydrogel property absorbs wound exudates and creates moist environment. [181].
Curafil	Impregnated gauze	Glycerine, Propylene glycol	It consists of a gauze sponge, filled with transparent hydrogel that provides a natural moist environment to the wound [182].
Restore	Impregnated gauze	Calcium alginate	This kind of wound dressing provides not only superior absorbency but also excellent wet strength. [183].
Transeal	Moisture vapour permeable film	Polyurethane	It is a clear, permeable to the gas and moisture and allows skin breathable kind of wound dressing that provides a possible moist environment to the wound helping it in quick cure. [184].
Acuvue	Contact lens	Silicone hydrogel	These contact lenses are available in various pack sizes. All products of Acuvue contact lens aim is to provide at least 96% of oxygen permeability to the eyes in order to give feeling of smoothness in every blink. [185].
Biofinity	Contact lens	Silicone hydrogel	This contact lens provides a natural wettability so that no need to add additional drop to make it moist. [186].
Air Optix	Contact lens	Silicone hydrogel	These contact lenses maintain and sustains the moisture for almost all and every day. [187].

four weeks, OPF hydrogel was found to reduce the infarct size and collagen deposition improved the cardiac function.

Hydrogel as space filling scaffold carrier

Scaffolds are the simplest form of space filling agent and are used in various applications including bulking material, also termed as bioactive 'glue'. Scaffolds function is to provide a large volume for vascularization, new tissue production and remodelling so as to make easy the host tissue integration upon implantation. A desirable scaffold for tissue engineering should have the potential to provide an Extracellular Matrix (ECM) simulated environment so as to interact with the surrounding native cells and tissue [144]. Hydrogels offer as an attractive scaffold biomaterial because of resemblance with the tissue ECM as well as their delivery in a minimum invasive manner [145]. For instance Park et al. [146] made a biodegradable hydrogel scaffold of water soluble Poly (Ethylene) Glycol (PEG) and water insoluble Poly(ε-Caprolactone) (PCL) and used it as a vehicle for delivering rabbit chondrocytes to form neocartilage. The scaffolds were prepared by salt leaching method. It was found that hydrogel possessing a low amount of PEG showed less chondrocyte differentiation while high content exhibited better chondrocyte differentiation.

Hydrogel for growth factor delivery in tissue engineering

Growth factors are signaling molecules that command the cell and helps in tissue regeneration by controlling overgrowth factor delivery [147]. Various examples of growth factors and their functions are enlisted in Table 4 [148].

Exogenous administration of growth factors in tissue engineering suffers a lot of problems because of its inactivation or elimination after intravenous delivery [149,150]. Hydrogels can be a good alternative for such problems [151]. Delivery of growth factors through this device in a spatiotemporal method provides a targeted location and avoids undesirable side effects [152,153]. To study the delivery of signaling molecule as protein, Sun et al. [154] developed new hybrid hydrogel for delivery of Bone Morphogenetic Protein (BMP). The biodegradable, and cell compatible hydrogel was formed by combining the properties of arginine and gelatin methacrylamide through UV photo-cross linking method. The formed hydrogel of Gelatin Methacrylamide (Gel-MA) and arginine based unsaturated non-peptide polycations (Arg-UPEA) carrying BMP showed an outstanding cell attachment and proliferation and also released the protein drug in controlled and sustained release manner.

Marketed Products of Hydrogel

Currently, hydrogel has spread its wing from research laboratory to market. Some of its widely used marketed products are shown in Table 5.

Conclusion

In the past few years, hydrogel as a drug delivery system has undergone an extreme advancement. The main property that makes it unique from another delivery system is its quick responsiveness towards different stimuli which is nowadays is of significant consideration for pharmaceutical engineers. Their application is not only limited to drug delivery but is widely applicable in the traditional field of science such as sensing, transducing and actuating etc. Further with the advent and degree of cross-linking methods significant changes can be seen in the physical properties of the hydrogel polymer such as elasticity as they can reform to their original form, decrease in the viscosity as it will prevent polymers to flow etc. all these changes in physical property certainly affect the formulation according to the need. Being biocompatible and biodegradable in nature they have shown their potential and sustainable ability in delivering the drug and protein over a long period of time. Another drastic achievement that has been imparted by the hydrogel, is in the area of tissue engineering. Hydrogel has acted as an excellent biomaterial for cell delivery as it can mimic the same structural and compositional property with the existing natural extracellular matrix so as to provide firm integrity to the tissue constructs. Thus, it can

be predicted that the hydrogel system which is full of versatility will certainly open new arenas in drug delivery.

Future Prospective

Hydrogel controlled drug delivery system has a bright future and scope in the field of pharmaceutical and tissue engineering. The use of 'smart' hydrophilic polymers will certainly bring a great revolution for the delivery of therapeutics. Utilization and synthesis of novel polymers or grafting the existing natural polymer is an another approach to proceed towards the success. Their soft nature and biocompatibility are one of the important and demanding feature covering not only almost the entire area of pharmaceutics as well as biomedical but also are used in biosensing device, microchips etc. In addition to this exhibiting intelligence in its surrounding will surely provide improved methods for delivering thermolabile substances too. With such inherent properties, versatile nature and further advancements, hydrogel must be going to show more potential and remarkable application in biomedical and pharmaceutical technology.

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