Chapter 6
Preparation, Properties and Application of Hydrogels: A Review

Sumit Mishra, Priti Rani, Gautam Sen and Kartick Prasad Dey

Abstract Hydrogels are primarily synthesized to retain large amounts of aqueous solution. Depending upon modes of synthesis, the hydrogel materials develop various types of network structure. Recently, popular techniques have been developed for synthesis of hydrogels in the presence of crosslinking agents or multifunctional co-monomer which acts as a crosslinker. It can be categorized according to synthesis techniques, bio-degradability, response to environment and their intended applications. These applications may vary from water retention, conditioner to different aspects of biomedical applications and tissue engineering. Hydrogels contain a number of functional groups which may be utilized as such or modified and used to suit our requirements. In this review article, we have focused on the available synthesis techniques of hydrogels along with their inevitable properties and applications.

Keywords Hydrogel · Radical polymerization · Biomedical application
Tissue engineering

1 Introduction

Polymer hydrogels are well-known materials with widespread usage in many fields, particularly in biomedical, pharmaceutical and agricultural sector. The first water-absorbent polymer was synthesized in 1938 after thermal polymerization of acrylic acid and divinylbenzene in an aqueous medium (Zohuriaan-Mehr 2006). Significant advancement in this field was marked in 1960 when these polymeric hydrogels were widely worked upon exploring their hidden potential (Kumar et al. 2006).

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From the era of 1970s, available literature reports polymeric hydrogels with new chemical structure and resultant better physical properties as well as innovative applications. Advancements in hydrogel properties led to increase its suitability for design and operation of some sophisticated system, like automatic drug delivery systems. Hydrogels need to be smarter to perform necessary function to achieve desired applications. The development of novel hydrogels with their potential applications is in huge demand to suit our requirements.

For example, there are a number of wound-care products available in market today, from injectable foam to hydrocolloid dressings. Recently, hydrogels have found application in wound management systems. Since blood is indispensable for healing process and wounds can damage these blood vessels which may turn fatal, it is important to hold it at the affected areas. For this purpose, the researchers started developing an approach to wound-care management that would rebuild those damaged or dead vessels, creating a matrix of stem cell sponges and hydrogel that develops like skin of a growing foetus. Now, scientists are searching for the best source of such cell sponges, bone marrow and fats seem to be the best options so far. Soon, the clinical trials will be done in which participants will use this advanced hydrogel on diabetic foot ulcers.

More than one million people are suffering from inflammatory bowel disease (IBD) worldwide. The population of patients suffering from this disease is increasing continuously around the world, but its treatment is very limited. People have to depend on daily enemas as a part of therapy which is not comfortable, totally impractical and has great side effects on health. In this regard, clinical development for the effective treatment of chronic and debilitating inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis, is necessary. So, scientists have tried to develop an alternative therapy using disease targeted hydrogel that rapidly sticks to the ulcers and slowly releases the drug to the targeted area only. It is a great breakthrough for the patient for more targeted enema-based therapy in future.

The need to develop smarter hydrogels which can simulate the physiological system to address the biomedical issues is one of the primary objectives of contemporary research. Yet, it is important to understand the fundamental similarities and differences between the two. Such understanding will lead to development of multifunctional hydrogels to suit our requirements. Thus, it is important to review the available literature on synthesis, characterization and available applications of hydrogels along with patents and commercial products.

1.1 What Is Hydrogel?

The term 'hydrogel' bears no specific definition as per updated medical and pharmaceutical encyclopaedia. Hydrogels are three-dimensional materials having capacity to hold excess amount of water to maintain the stability of its dimension. It maintains its 3D integrity in its swollen phase by the virtue of crosslinking

(Williams 1990). Polymer hydrogels are either synthetic or of natural origin, homopolymers or co-polymers (Langer and Peppas 2003). It can also be classified on the basis of nature of crosslinked junction.

(a) Chemically crosslinked with stable networks
(b) Physically bonded networks owing to ionic interactions, hydrogen bonds or hydrophobic interactions, or even polymeric chain entanglements (Jen et al. 1996).

Chemically, hydrogels are synthesized by two different techniques: 'three-dimensional polymerization' occurs in the presence of hydrophilic monomer in addition with either a crosslinking agent indirectly or by direct crosslinking shown in (Fig. 1). Alternatively, polymerization is carried out by employing free radical initiators like benzoyl peroxide, ammonium peroxodisulphate, 2,2-azo-isobutyronitrile (AIBN). This may also be achieved by irradiation with UV rays, gamma rays or electron beam shown in (Fig. 2). In three-dimensional polymerization, product is obtained along with considerable amount of residual monomers. These unreacted monomers are often toxic so they need to be separated out; otherwise, there remains a possibility of leaching from the hydrogels (Khutoryanskiy et al. 2013; Montoro et al. 2014; Mathur et al. 1996).

Rosiak used biopolymers like agar and gelatin as well as synthetic polymers like polyvinyl pyrrolidone (PVP) or polyvinyl alcohol (PVA) which have been crosslinked in the presence of gamma radiation and give sterile hydrogels for wound care (Rosiak et al. 1989). Nowadays, these hydrogels are available in market under brand name 'Kikgel' and 'Aqua-gel' used for dressing of wounds (Rosiak et al. 1989).

Another method for hydrogel synthesis is suggested by Khutoryanskiy. His method synthesizes water-soluble polymers using thermal and microwave radiation in aqueous medium (Khutoryanskiy et al. 2013; Cook et al. 2012). In this process, the aqueous solutions of PVA and poly(methyl vinyl ether-alt-maleic anhydride) are homogenized well at room temperature and kept under microwave radiation and thermal treatment under high pressure through autoclave. These synthesis

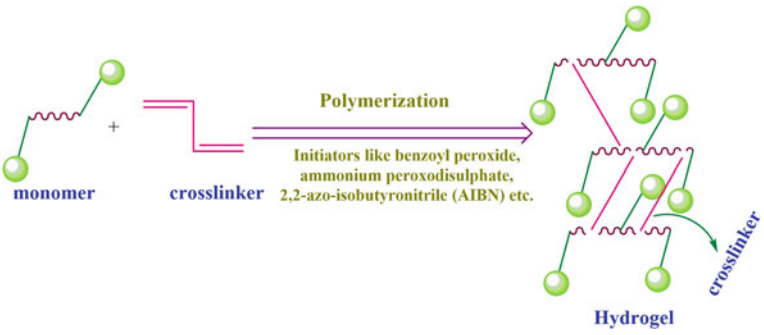

Fig. 1 Schematic representation of hydrogel formation by initiators

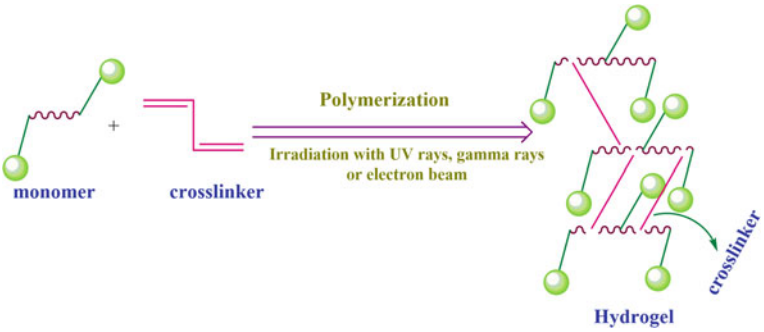

Fig. 2 Schematic representation of hydrogel formation by irradiation

techniques using irradiation as well as thermal procedures are cheap, safe and free from purification steps. They result in formation of hydrogels in the presence of hydrophilic polymers in suitable combination.

1.2 History of Hydrogel

According to Lee, Kwon and Park, the word 'hydrogel' was used in a number of articles since 1894 (Wei and Charlotte 2014). The material ascribed at that time was a colloidal gel made up of inorganic salts rather than a hydrogel. In 1960, the first developed crosslinked network material having hydrogel properties as well as high water affinity was polyhydroxyethylmethacrylate (PHEMA) hydrogel. This was intended to be used in a much-awaited project of permanent contact lens production. Hydrogel was the first soft material developed to be used inside any patient (Nierzwicki and Prins 1975; Wichterle and Lim 1960). Broadly, the history of hydrogels can be categorized (Buwalda et al. 2014) as follows:

- The first era of hydrogel development history involved a wide range of random crosslinking experimental procedures. These involved using initiators for the chemical modifications. The primary objective was to synthesize materials with high swelling index and reasonable mechanical properties.
- The second generation of materials involved optimizing response to specific stimuli like variation in pH, temperature, pressure or even concentration of solvent molecules. These stimuli were used to initiate specific phenomenon like polymerization of monomer, drug delivery. (Buwalda et al. 2014).
- Finally, the third generation of hydrogels led to further advancement. It focused on the development of stereo-complexed materials, e.g. PEG-PLA interaction (Yom-Tov et al. 2014; Abebe and Fujiwara 2012), and hydrogels crosslinked with other physical interaction, e.g. cyclodextrins (Chung et al. 2008; Kirakci et al. 2014).

In 1980, Lim and Sun modified hydrogels and designed calcium alginate microcapsules for cell engineering. Later, Yanna and co-workers (Lim and Sun 1980) worked upon collagen and shark cartilage tissues as natural raw materials for novel dressing which reduced the healing burn. Both natural and synthetic hydrogel generated an interest for encapsulation of cells (Yannas et al. 1989) and have become a popular choice in the field of 'tissue engineering'. Here, they serve as matrices for repairing of tissues and regeneration of tissues and organs (Sefton et al. 2000). It is helpful in the prevention of thrombosis, in drug delivery systems, as biosensor coatings as well as in cell transplants (Nguyen and West 2002; Peppas and Bures 2000; Sawhney and Pathak 1994; Miyata et al. 2002; Chang et al. 2010).

The tunable properties, hydrophilic character, biocompatibility and response to stimuli focus the interest of scientists in the development of the 'smart hydrogels' for many years (Park et al. 1993).

1.3 Types of Hydrogel

Hydrogels can be broadly categorized on the basis of various features. This may include their synthesis procedures and routes, biodegradable properties, applications or their response to various stimuli and some other parameters. Hydrogels are found to exhibit variations with respect to changes in pH, temperature, light, enzyme, electric and other stimuli. Hydrogels showing some environmentally sensitive properties along with their parent polymers are shown in Table 1.

2 Synthesis Procedures of Hydrogels

Therefore, hydrogels may be categorized as homo-polymers, co-polymers, interpenetrating networks and semi-interpenetrating network based on synthesis techniques and routes.

2.1 Homopolymers

Homopolymers are developed from single monomer. It provides a basic structural and functional unit to any polymeric network (Iizawa et al. 2007). Homopolymer crosslinked frame structure depends upon polymerization technique and nature of the monomer. The possible way to prepare homopolymeric hydrogel is by use of PHEMA {poly(2-hydroxyethyl methacrylate)} as monomer, polyethylene glycol dimethacrylate as crosslinking agent and benzoin isobutyl ether as a UV-sensitive initiator. This film was kept in de-ionized water under UV radiation (λ = 253.7 nm). The film was immersed in water to remove toxic or unreacted

Table 1 Classification of hydrogels with respect to response to stimuli

Response to stimuli	Parent polymer	Source
pH	Poly(methacrylic acid-co-methyl methacrylate); chitosan–carboxymethylcellulose, chitosan–alginate, sodium and chitosan–carbopol Poly(acrlyamide-co-acrylic acid) Chitosan–poly(vinyl alcohol)	Segundo et al. (2008) Saleem et al. (2012) Gemeinhart et al. (2000) Gunasekaran and Chai (2006)
Temperature	Poly(*N*-t butyl acryl amide-co-acrylamide); poly(*N*-isopropylacrylamide) (PNIPAAm)-poly(ethylene glycol) diacrylate	Okay and Ozturk (2002) Derwent and Mieler (2008)
Enzyme	Poly(ethylene glycol)	Aimetti et al. (2009)
pH-thermo	Poly-*N*-isopropylacrylamide	Johannsmann and Bunsow (2008)
IR light	*N*-isopropylacrylamide	Zeng and Jiang (2008)
Electro	Polydimethylaminopropylacrylamide Chondroitin 4-sulphate	Murdan (2003) Masteikova et al. (2003)

substances. PHEMA is used in artificial skin manufacturing and wound dressing besides the contact lenses to provide good healing conditions. PHEMA can also be synthesized by low molecular weight crosslinking agents like trimethylolpropane trimethacrylate. These hydrogels are soft in nature like PMMA and have high oxygen permeability. So, they can also be used for manufacture of contact lenses, as drug delivery matrices and tissue implants. Its application can further be improved upon by increasing its mechanical strength. Cretu has improved the hydrogel properties by introducing hydrophobic compound (caprolactone) into its structures or synthesizing amphiphilic material (Cretu et al. 2004).

The technique for the synthesis of these macromolecular architectures by an elegant utilization of 'click chemistry' was first made by Hilborn and co-workers in 2006 (Ossipov and Hilborn 2006). They synthesized poly(vinyl alcohols) functionalized with acetylene or azide groups. Hydrogel was formed immediately after addition of $CuSO_4$/Na ascorbate. Lin and Anseth also synthesized PEG hydrogel through click chemistry (Benamer et al. 2006). This technique is based on a step-growth synthesis process. In this reaction, monomers having azide and alkyne functional groups remain bonded with each other by the virtue of catalysts to form stable covalent bonds. PEG hydrogel obtained by this method has good mechanical properties and permits modulation of physicochemical characteristics of the PEG hydrogels.

Polyvinylpyrrolidone hydrogels are synthesized by irradiation technique (Benamer et al. 2006). This is done by irradiating the reaction mixture with 60 Co source at a dose rate of 3.2 Gy/min. It can also be used for wound healing.

Polyacrylic acid (PAA) is also a homopolymeric hydrogel (Christensen et al. 2006). It contains 2.5% PAA and 97.5% water in its commercially available grade. It is stable and possesses fairly elastic properties. It is non-toxic, non-inflammatory and simulates the human physiological environment of soft tissue for the application in endoprosthesis.

2.2 Co-polymers

Co-polymers consist of multimonomer systems with one hydrophilic monomer, managed in any standard arrangement like random, block or alternating along with the polymer chain (Kopecek and Yang 2009). Ring opening co-polymerization of a-caprolactone to poly(ethylene glycol)-poly(a-caprolactone)-poly(ethylene glycol) co-polymeric hydrogel was given by Gong for establishment of drug delivery system (Gong et al. 2009; Kim and Peppas 2003). In triblock synthesis mPEG, stannous octoate and hexamethylene diisocyanate were used as initiator, catalyst and coupling agent. When this co-polymeric block is applied in situ, it is capable to form hydrogel. This hydrogel can release both hydrophilic and hydrophobic drugs including proteins.

Carboxymethyl cellulose (CMC) is known to be water soluble and bio-compatible. Wang suggested blending CMC with cellulose or with PVP to form PVP/CMC hydrogel (Wang et al. 2007). The blended PVP/CMC hydrogels possessed good mechanical properties. Its high water retention capacity improved its bio-degradability and also made it suitable as dressing material.

Later on, Thomas developed free radical co-polymerization. This hydrogel has been synthesized using acrylamide and acrylic acid as monomers and *N*,*N*-methylene bisacrylamide and potassium persulfate in aqueous medium (Thomas et al. 2007). This hydrogel was transparent and embedded silver nanoparticles. This silver embedded nano-composite hydrogel possessed antimicrobial activity which could be used further in various applications.

Synthesis of a thermoplastic hydrogel was reported by polymerization of a-benzyl L-glutamate (BLG) *N*-carboxyanhydride. This reaction was carried out using diamine groups placed at the ends of poly(ethylene oxide) chains of the poloxamer. This hydrogel was pH-sensitive and thermosensitive in nature and used for drug delivery applications (Oh et al. 2003).

Multistep gelation process synthesizes hydrogel with multimembrane 'onion-like structure' under controlled physicochemical conditions by Ladet as shown in Fig. 3. He reported synthesis of a multilayered material based on physical hydrogels of amphiphilic polymers. These were synthesized without any external crosslinker by using chitosan and alginate. These novel three-dimensional multimembrane structures are useful in biomedical applications (Ladet et al. 2008).

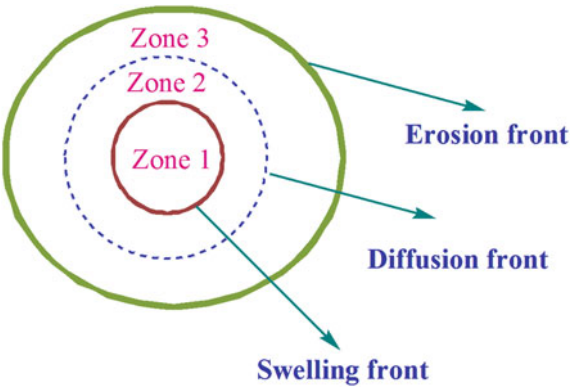

Fig. 3 Schematic representation of swellable matrix tablet during drug release

2.3 *Semi-interPenetrating Networks (Semi-IPNs)*

Semi-interpenetrating networks are formed without any chemical bonds between them. Here, (Semi-IPN) one straight chain polymer penetrates another crosslinked network (Zhang et al. 2009). Semi-IPNs are reported to have fast response rates towards pH and temperature as given by their kinetic studies. The polymerization of cationic polyallylammonium chloride (linear) in acrylamide or acrylic acid is an example of (Semi-IPN) co-polymer hydrogel. It has higher mechanical strength which led to theophylline release by pH variation. This type of semi-IPN was prepared by using *N*,*N*-methylene bisacrylamide as a crosslinker by means of template co-polymerization. (Zhang et al. 2005). The IPN network consists of both covalent and ionic bonds, and 3D structure is formed due to covalent bonds. The ionic bonds were responsible for better mechanical properties and pH reversible property.

Also, a semi-IPN hydrogel network was synthesized for its suitability in nano-level systems. Here, production and stabilization of silver nanoparticles were achieved (3–5 nm size) (Murthy et al. 2008). PVP chains were dispersed physically throughout PAA network. This silver nano-architecture was found to have significant antibacterial effects.

Crosslinked co-polymer of PHEMA and semi-IPN of gum arabic was prepared by the use of ammonium persulfate as initiator and *N*,*N*-methylene bisacrylamide as crosslinker (Gils et al. 2010). The hydrogel was embedded with silver nanoparticles using silver nitrate with trisodium citrate as reducing agent. This led to appreciable antibacterial activity due to the presence of silver nanoparticles inside the hydrogel network.

Some semi-IPN hydrogels of alginate and poly(*N*-isopropylacrylamide) (PNIPAAm) were synthesized using calcium chloride as crosslinker (Ju et al. 2002). Swelling behaviour of semi-IPNs was observed at different pH at higher temperatures, and the formation of a polyelectrolyte complex was reported. It forms by the reaction of carboxyl groups of alginate and amino groups of modified PNIPAAm. It was sensitive towards pH, temperature and ionic strength of solvent.

Semi-IPN hydrogels have also been investigated for delivery in stomach. They show more swelling index in acidic conditions. These studies have been carried out for the delivery of amoxicillin and metronidazole antibiotics. These drugs are used for the treatment of helicobacter pylori infestation in stomach. A guar gum (GG)-based semi-IPN hydrogel and poly(methacrylic acid) are also reported (Li and Liu 2008). The minimum swelling index was observed in acidic pH condition for hydrogel loaded with 5-aminosalicylic acid (5-ASA).

In acidic pH conditions, the model drug 5-ASA formed complex hydrogen-bonded structure with the polymeric network structure. The maximum swelling index is observed for these hydrogels at pH 7.4 due to the electrostatic repulsion of the carboxylic groups. It resulted in minimum release of 5-ASA from the hydrogel network at pH 2.2. In vitro study showed that concentration of crosslinker and amount of GG affected degradation. This enzymatic degradation of hydrogels by cecal bacteria accelerates the release of 5-ASA from hydrogel at pH 7.4.

PVP-based hydrogel (Lu et al. 2010a, b) was synthesized as very promising thermosensitive material. The most vital shortcoming of PVP hydrogel as thermosensitive material is that it did not exhibit thermosensitivity under normal conditions. PVP and CMC resulted in the formation semi-IPN hydrogel having application as volume-phase transition temperature (VPTT). This study explained that the VPTT was significantly dependent on CMC content and pH of the swelling medium. VPTT behaviour is reflected in buffer solution of pH 1.2 but not in alkaline medium. In vitro drug release was studied at various buffer solutions using bovine serum albumin (BSA) as a model drug. These studies suggested that PVP/CMC semi-IPN hydrogels could work as suitable candidates for the delivery of protein drug in the intestine.

2.4 InterPenetrating Networks (IPNs)

An interpenetrating polymer network (IPN) consists of two or more polymeric chains in any network. The synthesis is done by immersing a pre-polymerized hydrogel into a solution of monomers and a polymerization initiator. These are not covalently bonded to each other but partially interconnected with each other on a polymer scale (Lipatov 2002). These networks cannot be distributed unless chemical bonds are broken. In this hydrogel, two or more networks can be arranged in such a manner that they are coupled and cannot be separated from each other. These hydrogels are often referred as ‘intelligent polymers’ or ‘hungry network’ (Shivashankar and Mandal 2012). The benefits of using IPNs are its compact matrices, strong mechanical properties, modifiable physical properties and fairly good candidature for drug delivery systems as compared to conventional hydrogels (Mohamadnia et al. 2007). As of now, it is the centre of immense interest for scientific research due to its unexplored potential in a large number of applications, particularly in medicine, industry, biology and environmental areas.

IPN has tailor-made properties. Its pore size and surface chemistry can be tuned for specific drug release kinetics. This is a result of interaction between hydrogel and the surrounding tissues (Li et al. 2007). Chivukula synthesized highly crosslinked IPN hydrogel network that restricts the swelling response of pH-sensitive hydrogel. It allows linear swelling with an abrupt pH change from 7.4 to 2 suited for oral drug delivery application (Chivukula et al. 2006). Chitosan crosslinked/PNIPAM IPN network has been studied with diclofenac (Alvarez et al. 2005).

Polyurethane (PU) is also a biomaterial. IPN of PU and polyacrylamide controlled water absorption (Abraham et al. 2001). They are mixed together by addition of crosslinking agents vinyl pyrrolidone and methylenebisacrylamide. Then, the reaction mixture is exposed to UV radiation. This type of IPN hydrogels finds application as wound dressing material, artificial muscles, sensor systems and bio-separators.

Series of IPN hydrogels were reported to affect sensitivity towards temperature and pH fluctuations (Liu et al. 2012). This synthesis involved incorporation of polyaspartic acid which is a pH-sensitive polymer, into PNIPAAm hydrogel system. The swelling mechanism confirmed that IPN hydrogels possessed swift shrinking and re-swelling properties with respect to the concentration ratio of two components. These fast responsive properties of hydrogels enhance its applications in biomedical fields.

Next series of hydrogels include in situ polymerization approaches. Calcium alginate (Ca–Alg) and dextran methacrylate derivative (Dex-MA) hydrogels showed potential application in pharmaceutical field (Matricardi et al. 2008). The semi-IPN synthesized by the dispersion of Dex-MA chains into Ca–Alg hydrogel forms a hydrogel having different rheological properties than original Ca–Alg precursor. This enhanced its chances through use in injection of the semi-IPN through hypodermic needle. The IPN synthesized by UV treatment of semi-IPN forms hydrogels which are strong enough for delivery of bioactive molecules like protein.

3 Significant Properties of Hydrogel

3.1 Swelling Properties

The swelling properties of hydrogel matrix are important features that govern its future applications in pharmaceutical, biomedical, ophthalmology and tissue engineering fields. The polymer chains present in hydrogel interact with solvent molecules and start expanding to the fully relaxed and solvated state till they attain equilibrium state. The crosslinked network, on the other hand, applies an opposite force that pulls the chains inside. When these two forces acting in opposite directions balance each other, equilibrium is attained. This equilibrium ratio (Eq. 1.) generally illustrates the swelling behaviour of hydrogels.

$$\text{Equilibrium swelling ratio} = \frac{W_{\text{Swollen}}}{W_{\text{dry}}} \quad (1)$$

where

W_{swollen} weight of the swollen hydrogel
W_{dry} weight of the dry gel

The swelling kinetics of the hydrogels can be determined from the swelling kinetics. First, the weight of the dry hydrogel (W_{dry}) is determined. Then, this dried hydrogel is immersed in water until the swelling equilibrium is reached. This is followed by weighing the swollen hydrogel (W_{swollen}) after removing the excess water. The swelling ratio is given as (Eq. 2).

$$\text{Swelling ratio} = \frac{W_{\text{Swollen}} - W_{\text{dry}}}{W_{\text{dry}}} \quad (2)$$

Many research groups have assessed the swelling/shrinking kinetics of PNIPAAm hydrogel with temperature variations. Yoshida and co-workers have discussed the shrinking kinetics of PNIPAAm hydrogel. They explained that comb-type PNIPAAm hydrogels collapsed fist followed by the hydrogels without grafted side chains. (Yoshida et al. 1995; Kaneko et al. 1995). They also mentioned a comb-type grafted hydrogel synthesized by PEO graft chains in the crosslinked PNIPAAm network (Kaneko et al. 1998). The swelling characteristics are of utmost importance for hydrogels in biomedical and pharmaceutical applications. The equilibrium swelling ratio is an important parameter which affects the solute diffusion coefficient, surface wettability and mechanical properties of the hydrogel. The swelling properties are affected by many factors like nature of monomer, crosslinker concentration and other environmental factors like temperature, pH and ionic strength.

Kiil developed a mathematical model to explain the water-induced swelling, drug dissolution, external and internal mass transport resistance of dissolved drug in an HPMC matrix (Kiil and Dam-Johansen 2003). The main purpose of this model was to determine the position of three distinct moving fronts (Fig. 3).

3.2 Mechanical Properties of Hydrogel

The mechanical strength of the hydrogel network depends upon the composition and structure of hydrogels (Shibayama 2012). In general, the polymer hydrogels are very weak, soft, brittle and cannot withstand large deformation. These mechanical properties of hydrogels are very important parameters for pharmaceutical and biomedical applications. The assessment of mechanical property is important for biomedical applications, e.g. ligament and tendon repair, wound dressing material,

matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties are suitable to maintain its physical texture during delivery of therapeutic moieties. Hydrogel is a tailor-made material which can be optimized mechanically by tuning its crosslinking parameters. Higher degree of crosslinking results in formation of a strong hydrogel, but it reduces the percentage elongation of hydrogel and forms more brittle structure. Therefore, optimum degree of crosslinking has been achieved for relatively strong and elastic hydrogel. The mechanical characterization involved relaxation experiments based on generalized Maxwell model. Crosslinking density of hydrogel was determined by Flory's theory and Young modulus. This value was then used to determine the average polymeric mesh size according to the equivalent network theory (Schurz 1991).

Recently, a hydrogel having capacity for the large deformation and development of a slide-ring (SR) gel was given by Okumura and Ito. The process involved the crosslinking of polyrotaxane (Okumura et al. 2001).

3.3 Bio-compatible Properties

Bio-compatibility and non-toxicity is an important property for the hydrogel to make it appreciable in the field of biomedical studies. Most of the hydrogels used for this application have to pass cytotoxicity and in-vivo toxicity tests (Grodzinski 2009). Biocompatibility of the material signifies its suitable response in a specific application. It is divided into two components:

(a) bio-safety: the absence of cytotoxicity, mutagenesis carcinogenesis and related things
(b) bio-functionality: ability of material to perform the specified task for which it is intended (Grodzinski 2009)

This is relevant for tissue engineering applications since the tissue continuously interacts with the body. In case of synthetic hydrogel synthesis, any chemical used in polymerization may cause challenge for in vivo biocompatibility. Further, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and crosslinkers may also be toxic to host cells (Bryant et al. 2000). Thus, removal of hazardous chemicals from preformed hydrogels is important. This may involve a number of purification processes like solvent washing or dialysis. In situ gelation of scaffolds presents a unique challenge since reactants which are used to synthesize the gel are injected into the body in the pre-polymer solution form. The utilization of this technique is ideal but needs precaution that all components used in the reaction are safe and non-toxic. Earlier, natural polymers were believed to be better than synthetic ones in terms of biocompatibility; still the presence of synthetic crosslinkers and initiators seems to have the same toxicity concerns as purely synthetic hydrogels.

4 Characterization of Hydrogels

Different types of characterization techniques have been developed for understanding the hydrogel network structure and physical or chemical properties. The physical properties of hydrogels network structure depend upon the equilibrium and dynamic swelling ratios. It depends on volume fraction of polymer, effective molecular weight of the polymer chain in between two crosslinking points and the correlation between two adjacent crosslinks (Lin and Metters 2006; Peppas et al. 2006). Flory (1942) and Huggins (1942) were the first to develop independently the theoretical base 70 years ago for understanding the polymer solutions.

Hydrogels have numerous properties, like absorption capacity, swelling behaviour, permeability, surface properties, optical properties and mechanical properties. All these properties make hydrogel a promising material for a wide variety of applications. The properties of the polymer chains and the crosslinking structures in these aqueous solutions play a vital role in the outcome of the properties of the hydrogel. Hydrogels are characterized by following methods/tests.

4.1 Fourier Transform Infrared Spectroscopy

FTIR analysis provides a reliable information about the crosslinking which is confirmed by appearance of IR bands near 1648 cm^{-1} region. IR absorption spectra give an idea about morphology of hydrogels.

4.2 Atomic Force Microscopy (AFM)

A multimode atomic force microscope helps to examine the surface morphology of the hydrogels.

4.3 Network Pore Size

Pore size determination is an important technique for hydrogel characterization. Different techniques like Quasi-elastic laser light scattering, electron microscopy, mercury porosimetry, rubber elasticity measurements, and equilibrium swelling experiments are used to determine the network pore size of hydrogel.

4.4 X-ray Diffraction

X-ray diffraction studies provide useful insight into the crystalline nature of hydrogel, whether the hydrogels retain their crystallinity or they get deformed during the synthesis procedures

4.5 Swelling Behaviour

Data of specific swelling studies is a must to determine its potential use as a hydrogel, and many researchers have successfully worked upon it.

4.6 Crosslinking and Mechanical Strength

The mechanical strength of the hydrogel depends upon the crosslinker density inside the network structure. Generally, the mechanical strength of the hydrogel increases with increase in the crosslinker concentration.

4.7 Rheology

It depends on the type of interactions based on structural properties (i.e. association, entanglement and crosslinks) present in the system. Polymer solutions are essentially viscous at low frequencies and tend to fit the scaling laws: $G' \sim \omega^2$ and $G'' \sim \omega$. At high frequencies, elasticity dominates ($G' > G''$). This corresponds to Maxwell-type behaviour with a single relaxation time, which may be determined from the crossover point, and this relaxation time increases with concentration. Crosslinked microgel dispersions exhibit G' and G'' that are almost independent of oscillation frequency.

All these characterization techniques give an account for the confirmation of intended crosslinking results, formation of hydrogel, used further for different applications.

5 Application of Smart Hydrogel

In the last few decades due to its hydrophilic character, biocompatibility and initiate stimuli hydrogels received considerable attention towards several applications. These applications are discussed in the following subsections.

5.1 Biomaterial Application

5.1.1 Soft Contact Lenses

Soft contact lenses remain one of the most widely used applications of hydrogels. Hydrogels have the adaptability towards the global ocular curvature and permit the atmospheric oxygen to reach up to cornea by dissolving the water of the lens (Lum et al. 2013). PHEMA was the first ever synthetic hydrogel prepared by DuPont scientists in 1936 (Strain et al. 1939). It was established as a promising and wonderful candidate for manufacture of contact lens by Wichterle and Lim (1960) due to their biocompatibility and mechanical properties. Nowadays, a number of hydrogel contact lens materials have been developed containing various monomers such as N-VP, MAA, MMA and glyceryl methacrylate. These are incorporated to increase the water content of hydrogel contact lens and also to enhance its mechanical properties to allow them to hold the force of the eyelid along with an elevated permeability to oxygen (Lum et al. 2013) (Fig. 4).

5.1.2 Tissue Regeneration and Tissue Engineering Applications

Globally, many people suffer from the loss of an organ or chronic failure of any organ function as a result of some severe disease, accident, etc., every year. This necessitates the need of tissue and organ transplantations, but they are difficult to be carried out due to lesser availability of donors, legal norms, social norms, etc. (Lee and Mooney 2001).

The term 'tissue engineering' came in practice in 1988 as an engineered application. The beautiful combination of fundamental principles of basic

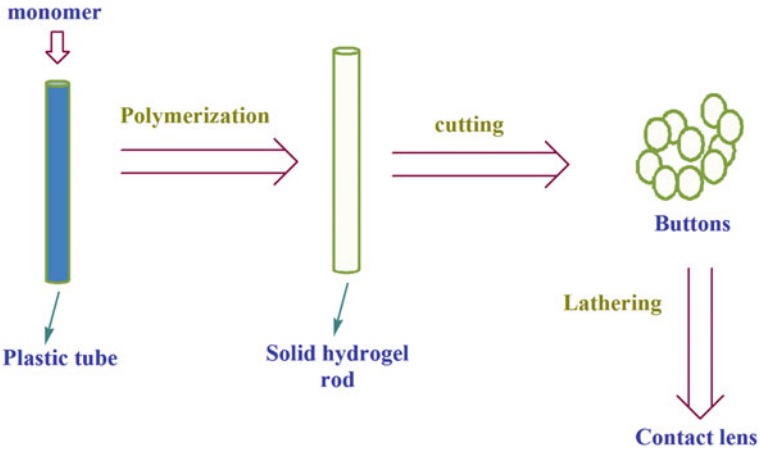

Fig. 4 Schematic representation of lathe-cutting technique

engineering and life sciences towards understanding human physiology and solving its problems by developing substitutes for tissues or organ system was a major breakthrough in the history of mankind. This helped in reviving a hope towards extension of life by regenerating specific tissues and organ systems using engineered materials and suitable synthetic strategies (Chapekar 2000).

Thus, tissue engineering has developed a hope for design of an ideal living substitute which mimics the properties of living tissues in human system (Langer and Vacanti 1993). Scaffolds act as three-dimensional artificial templates in which the tissue targeted for reconstruction is cultured to grow. The highly porous nature of hydrogel allows it for the diffusion of cells during migration. It also transfers the nutrients and excludes the waste products from cellular membranes (Loh and Choong 2013).

Now, both synthetic as well as natural hydrogels are used as scaffolds for various tissue engineering applications. These include repair of tendon, ligament, cartilage, blood vessels, skin and even heart valves (Ma 2004). The synthetic hydrogels targeted to be used as scaffolds are polyurethanes (PU), PVA, PEO, PNIPAAm, PAAc and poly(propylene fumarate-*co*-ethylene glycol) [P(PFco-EG)]. The natural hydrogels to be used in these applications include agarose, alginate, collagen, chitosan, gelatin, fibrin and hyaluronic acid (HA).

The micron-sized hydrogels (microgels) are also used to deliver macromolecules like phagosomes into cytoplasm of antigen-presenting cells. This release is triggered on due to acidic conditions within the tissues. These hydrogels mould themselves according to the pattern of membranes, tissues and possess considerable mechanical strength. This property of hydrogels is also used in cartilage repair (Bindu et al. 2012). Presently, the following hydrogels have been successfully used in tissue engineering applications:

(a) Collagen-coated tissue culture: They are used for implant of cornea, trachea gland cells, etc. (Pal et al. 2009).
(b) Poly(lactic-co-glycolic acid) (PLGA) polymer: They are used in conjunction with preadipocytes for epithelial cell culture of breast cells (Pal et al. 2009).
(c) Porous scaffolding: These are coated with fibrillar collagen, used for the culture of liver cells, to be used in liver implants (Pal et al. 2009).

Nowadays, scientists are expanding the application of hydrogels in the regeneration of the central nervous system. For this application, chemically crosslinked PHEMA tubes have been developed by synthesizing centrifugal force; the outer diameter of these tubes is 2.4 mm, and wall thickness is 40–400 μm, which could be used for guided regeneration in the nervous system (Lum et al. 2013).

5.1.3 Wound Dressing

From early 1980s investigations are going on to promote the skin healing potential of hydrogels and its application in clinical setting. At first, the hydrogels absorb and

retain wound exudates. Afterwards, fibroblast proliferation and keratinocyte migration are done for completion of epithelialization of the wound or wound healing. [Bullock et al. 2010; Ribeiro et al. 2009) The dense matrices of hydrogels (100 nm in swollen state) not only check the entry of bacteria but also permit transport of bioactive molecules (e.g. antimicrobial agents or drugs) to the targeted wound site to be healed (Drury and Mooney 2003). Such molecules can be easily entrapped in the polymeric network during the gel formation process, which is gradually released on the wound site as hydrogel absorbs its exudate and swells (Burd 2007; Boonkaew et al. 2014; Chakavala et al. 2012; Kumar et al. 2012a, b; Cui et al. 2011). The unique and tunable mechanical properties of hydrogels increase its suitability towards elasticity and flexibility to adapt with wounds caused in different body sites.

Hydrogels bring immediate relief to patients in distress, as compared to conventional bandages, pads or gauzes. Even, in case of burns, hydrogels are good alternatives for running water. It acts as a coolant to localized wound also reduces the pain and recovers the extent of resultant damage and reduces pain (Cuttle et al. 2009; Coats et al. 2002). The high water retention ability of hydrogels makes them particularly soothing on the wound. Non-adhesive nature of hydrogels causes less pain and discomfort to patient, as cells do not attach firmly to hydrophilic surfaces. Transparency of hydrogel provides an advantage over traditional bandages causing less pain during peeling it off.

A wide variety of hydrogels for wound dressings is commercially available in the market for treatment of minor burns and other skin wounds. They are available in numerous forms like amorphous gels, gel-impregnated gauzes, sheets or plasters (Burd 2007; Grippaudo et al. 2010). Amorphous gels are generally prescribed for superficial burn like cavity wounds, sheets and gel-impregnated gauzes (Winter et al. 1962). Plaster-like hydrogel dressings (e.g. MySkin®) are very user-friendly and attractive, as it can be well positioned on the wound without the use of adhesives and bandages. The development of hydrogel formulations is attaining new heights (Table 2), to address different aspects of wound healing and management (e.g. reduction in infection control, easy dressing).

5.1.4 Drug Delivery

Hydrogels have unique properties that make it useful in drug delivery application. Due to its hydrophilicity, it can hold excessive amounts of water. Hence, it can be used for design of drug delivery systems that control release of solute over a given time period. Many biomaterials have been explored for this purpose, which act by two mechanisms: (1) controlled release may be achieved by varying the crosslinker concentration and controlling the ratio of hydrophilic to hydrophobic monomers. (2) The interaction of hydrogels with drugs is very less, so it is better to release large fraction of active molecules drugs (protein and peptides) through hydrogel carriers. Controlled and targeted drug delivery would decrease the unwanted side effects and aid the recovery aspects. Several mechanisms describe the release of

Table 2 List of various hydrogels used in wound dressing

Burn depth	Hydrogel precursors	Additional components	Source
Partial-thickness	AMPS/ PEGDA	–	Nalampang et al. (2013)
	AMPS	Silver nanoparticles	Boonkaew et al. (2014a), Boonkaew et al. (2014b)
	Chitin	ZnO nanoparticles	Kumar et al. (2012a, b)
	Chitosan	–	Lu et al. (2010a, b)
	PVP/PEG	Honey	Mohd et al. (2012)
	Laponite®/ alginate	Mafenide	Ghadiri et al. (2014)
	PVA/ chitosan	Silver sulfadiazine	Chakavala et al. (2012)
	PVA	Silver nanoparticles	Oliveira et al. (2014)
Full-thickness	Chitosan/ collagen	Lysostaphin	Cui et al. (2011)
	Collagen/ PEG/fibrin	–	Natesan et al. (2013)
	Dextran/ PEGDA	–	Sun et al. (2011)
	Dextran	Chitosan microparticles with EGF and VEGF	Ribeiro et al. (2013)

drug from hydrogel: (a) diffusion, (b) chemical control, (c) swelling and environmentally responsive release.

The diffusion-controlled release systems can be represented by matrix devices. This may be available as vacant chambers in form of a capsule, cylinders or sphere. This system carries drugs covered with a hydrogel membrane as shown in Fig. 5.

In this system, a continuous drug release system is maintained due to high concentration of drug in the centre of system (Peppas and Lowman 1999). Other matrix systems include dispersion or uniform dissolution of drug throughout the

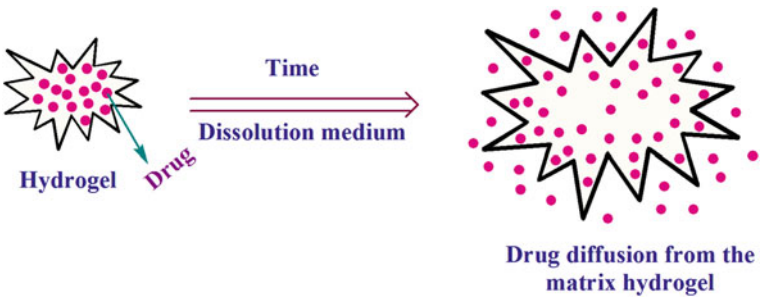

Fig. 5 Schematic representation of drug release from hydrogel matrix

three-dimensional space of hydrogel as shown in Fig. 5. Here, drug release is carried out by the macromolecular pores. In this system, the initial rate of drug release is proportional to the square root of time (Peppas and Lowman 1999).

In the swelling-controlled release devices, the drug is loaded in a glassy polymer and it starts swelling on contact with a bio-fluid. Afterwards, hydrogel starts expanding beyond its boundary and allows the drug to diffuse with the relaxation of polymeric chains. This is called Case II transport mechanism, and it shows constant, time-independent release kinetics. It is called as 'anomalous transport', combining swelling-controlled release with diffusion (Peppas and Lowman 1999).

'Smart' hydrogels are promising materials for controlled release of drug, since they change their properties in response to specific stimuli. Right after the discovery of hydrogels, it has been used as anticancer and antibiotic delivery. Various research experiments have focus on the variety of drugs that can be delivered efficiently through the hydrogel based on the delivery systems shown in Table 3.

5.2 *Industrial Applications*

Hydrogels are significantly used for the adsorption of methylene blue dye from the industrial effluent. Hydrogels beads are used for the adsorption of dioxins.

Table 3 Drug delivery via different hydrogel-based system

S. No.	Carrier medium	Drug	Therapeutic category	Analysis	Ref.
1	Hydrogel	Insulin	Hypogylcemic	Sustain release of insulin	Brown et al. (1996)
2	Hydrogel	Riboflavin water	Soluble vitamin	pH sensitive to localize drug delivery	Amiji (1997)
3	Hydrogel	Salicylic acid	Antiseborrheics	pH-sensitive drug delivery system	Ferreira (2000)
4	Hydrogel	Terbinafine hydrochloride	Antifungal	Controlled drug delivery system	Şen et al. (2000)
5	Hydrogel	5-fluorouracil and diclofenac sodium	Antimetabolite and antiinflammatory	Localized drug delivery	Zhang et al. (2014)
6	IPN hydrogel beads	Simvastatin	Lipid lowering drug	Controlled drug delivery system	Boppana et al. (2010)

A numbers of researchers are trying to develop techniques to sieze the metal ions. Irani and the co-workers synthesized a polyethylene-*g*-poly(acrylic acid)-co-starch/OMMT (LLDPE-g-PAA-co-starch/OMMT) hydrogel composite for PbI (II) removal (Joint et al. 2010; Irani et al. 2015).

Yan and co-workers performed etherification and functionalization of chitosan beads resulting in carboxymethylated chitosan having adsorption capacity of metal ions. These beads selectively adsorb specific ions like Cu(II), Pu(II) and Mg(II) (Yan et al. 2011). This property increases its potential towards dye removal after magnetic doping of hydrogel microsphere with IPN structures (Yan et al. 2011).

Novel and porous bio-absorbent xylan-based hydrogel has been developed by Xin after graft co-polymerization of acrylic acid (AA) and xylan-rich hemicelluloses. It has many applications towards adsorption of heavy metal ions (Pd^{2+}, Cd^{2+} and Zn^{2+}) from aqueous solutions.

The maximum adsorption capacities of Pd^{2+}, Cd^{2+} and Zn^{2+} were reported to be 859, 495 and 274 mg/g, respectively (Peng et al. 2012).

5.3 Environmental Applications

Hydrogels are polymeric chains of repeating units with high water absorbing capability. Some hydrogels have capability to absorb water 500 times more than their weight. These superabsorbent properties of hydrogel enhance its potential to conserve water and to solve other environmental issues.

5.3.1 Hydrogels for the Prevention of Soil Erosion

Soil erosion has been controlled since a decade by reducing erosion and increasing water retention and permeability of finely textured agricultural soils. Water-soluble hydrogels have been used to reduce erosion and improve water infiltration among fine-textured agricultural soils. The water-soluble PAM hydrogels play an important role in preventing soil erosion by forming a thin film that covers the soil surface. During irrigation, this film protects the soil from washing away and maintains the optimum moisture conditions within the soil system, so that irrigation water can permeate easily. Several studies have proved that PAM hydrogels are efficient agents used to combat soil erosion.

5.3.2 Use of Hydrogels for Agricultural Purposes

Hydrogel uniqueness enhances its potential towards the field of agriculture also. It is reported that anionic herbicide 2,4-D encapsulated in carboxymethylcellulose (CMC) gel is suitable for the controlled release of herbicide. More perfection in this process has been attained by the addition of bentonite in the gel formulation by

insinuating inorganic or organic cations in between of Na^+ saturated bentonite for the slow release rate of herbicide in water and soil (Li et al. 2009).

Nowadays, clay-loaded hydrogels are also gaining more interest because of its unique properties and broad applications. Nano-composite-based hydrogels have been developed to release macro- and micronutrients in slow and controlled manner into independent or concurrent systems. Its physicochemical properties and water uptake capacity improved 5000 times more than its weight by producing nanocomposite by underwent hydrolysis treatment. These nanocomposites had great swelling degree, so they were formulated with high calcium montmorillonite (MMt) contents for agricultural applications (e.g. carriers for nutrient release) (Bortolin et al. 2016).

6 Patents on Hydrogels

As a result of high potential and tailor-made properties of hydrogels, researchers have obtained various patents in its various spheres of utilization. The recent available patents are listed in Table 4.

Table 4 Patents on application of hydrogels

Application	Patent no	Title of patent	Year	Ref.
Biomaterial application	United State Patent US 6861123	Silicone hydrogel contact lens	2005	Turner et al. (2005)
	United State Patent US 3679504	Method of forming colour effects in hydrogel contact lenses and ophthalmic prostheses	2005	Ketelson et al. (2005)
	United State Patent US 4472327	Method of making hydrogel cosmetic contact lenses	1984	Neefe (1984)
	United State Patent US 3808178	Oxygen-permeable contact lens composition, methods and article of manufacture	1974	Gaylord (1974)
	United State Patent US 5423737	Transparent hydrogel wound dressing with release tab	1995	Cartmell et al. (1995)
	United State Patent US 8431151	Antimicrobial nano-structured hydrogel web containing silver	2013	Mather et al. (2013)
	United State Patent US 8409606	Drug delivery through hydrogel plugs	2013	Sawhney et al. (2013)

(continued)

Table 4 (continued)

Application	Patent no	Title of patent	Year	Ref.
	United State Patent US 5514380	Biodegradable hydrogel co-polymer as drug delivery matrix		Song et al. (1996)
	United State Patent US 8383153	Poly(amidoamine) oligomer hydrogel for drug delivery and drug carrier using the same	2013	Lee et al. (2013)
	United State Patent WO 1998043615	Method for oral delivery of proteins	1998	Lowman et al. (1998)
	United Sate Patent US 7066904	Triggered release hydrogel drug delivery system	2006	Arthur et al. (2006)
	United State Patent US 9255178	Photocrosslinkable poly (caprolactone fumarate)	2016	Wang et al. (2016)
	United State Patent US 4654039	Hydrogel-forming polymer compositions for use in absorbent structures	1987	Brandt et al. (1987)
	United State Patent US 5147343	Absorbent products containing hydrogels with ability to swell against pressure	1992	Kellenberger (1992)
	European Patent EP 2646002	Hydrogels microcapsules	2013	Mistry et al. (2013)
Industrial application	European Patent EP 2172475	Lipid peptide for use as hydrogels	2015	Miyaji et al. (2015)
	United State Patent US 6960617	Hydrogels having enhanced elasticity and mechanical strength properties	2005	Omidian et al. (2005)
	United State Patent US 5847089	Carboxyl-modified superabsorbent protein hydrogel	1998	Damodaran and Hwang (1998)
	United State Patent US 7304098	Hydrogel for use in down hole seal applications	2007	Li and Zhou (2007)
	United State Patent US 8244078	Hydrogel-based sensor probe for detecting an environmental state	2012	Hendriks et al. (2012)

(continued)

Table 4 (continued)

Application	Patent no	Title of patent	Year	Ref.
Environmental application	United State Patent 8840839	Environmentally responsive hydrogel	2012	Iordanov et al. (2014)
	United State Patent US 8840839	Hydrogel-based device for detecting an environmental state	2014	Sidney et al. (1993)
	United Sate Patent US 5185024	Application of agricultural polyammonium acrylate or polyacrylamide hydrogels	1993	Aqua source Inc. (1993)
	European Patent EP 2535359	Controlled release agricultural products	2012	Sannino et al. (2012)

7 Conclusion

The hydrogel materials have a great ability to serve as response to stimuli materials. Hydrogels have immense hidden potential in various applications. They are successfully being used in biomedical field in adverse environmental conditions like low pH and high temperatures, in human metabolism. A large numbers of hydrogel materials have been investigated for controlled drug release for drug formulation purpose. This bio-compatible nature of hydrogels makes them a promising candidate for future applications as well as for the development of next generation of materials for biomedical application also environmental field.

A major weakness of all these hydrogels is the need for optimization of their response time, which is either too slow or too fast. These optimized hydrogels as per their response time are in huge demand for various emerging applications. Future hydrogels are in the process of development with perfect control over their structure–property relationships even at micro- and nano-levels. So, practically they are used as smart materials. This relationship is further expected to result in a new range of hydrogels which are specifically suited for an application and unlock a new era of human imagination.

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