Faculty of Medical and Health Sciences, University of Poonch Rawalakot
Journal of Pharma and Biomedics
ISSN: 3007-1984(online), 3007-1976 (Print)
https://www.jpbsci.com/index.php/jpbs

An extensive review on hydrogel; Its classification and biomedical application

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Received: February 24, 2024; Revised: April 03, 2024; Accepted: April 11, 2024

A B S T R A C T

This review focuses on the brief introduction of hydrogels that are highly swellable system and have the capacity to absorb large amount of solvent and increase much more in size as compared to their original size. The review comprises of the different types of hydrogels and specifically focuses on the application of the hydrogels in biomedical filed. Hydrogels have the tendency to release the chemical or therapeutic moiety that is loaded inside them through different mechanism. A number of stimuli-based responses of hydrogels have been observed. All of these characteristics make hydrogels a promising system in the field of drug delivery and other biomedical applications.

Keywords: Hydrogels; Stimuli-responsive delivery; Drug release mechanism; Biomedical applications

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INTRODUCTION

Hydrogels are three dimensional polymeric networks capable of imbibing large amount of water and biological fluids and they are insoluble in dissolving medium due to physical or chemical crosslinking of individual polymeric network. The property of hydrogels of greater water absorption is due to functional groups attached to the polymeric backbone, these groups are hydrophilic in nature which impart property of more absorption, while crosslinks between network chains provide them resistance to dissolution. They are rubbery and soft in swollen state, showing excellent biocompatibility while resembling living tissue (Das, 2013; Kim et al., 1992; Lee and Fu, 2003; Lin and Metters, 2006; Mathur et al., 1996).

Networks are homopolymeric or copolymeric in nature, are insoluble due to presence of physical crosslinks, such as crystallites or entanglements or chemical crosslinks (junctions, tie-points) (Peppas et al., 2000b). In recent years, researchers have great interest in development, synthesis and study of environmentally responsive hydrogels, i.e. hydrogel systems that can show swelling and release changes due to temperature, external pH, nature of swelling agent, ionic strength or electromagnetic radiation (Peppas et al., 2000a).

Classification of Hydrogels

Classification According to Source

Hydrogels can be prepared from natural or synthetic polymers. Hydrogels synthesized from both polymeric types have different characteristics and attributes. Hydrogels prepared from synthetic polymer have well defined structures and are modified to yield required functionality and degradability but the synthetic hydrogels do not have inherent bioactive attributes. Natural polymer synthesized hydrogels may often contain diseases causing microorganism or induce inflammatory/ immune responses. Although, natural hydrogel may not provide appropriate mechanical strength but they do offer several characteristics

which are advantageous such as biodegradability, inherent biocompatibility, and biologically familiar moieties that support cellular activities (Lin and Metters, 2006).

Classification According to Polymeric Composition

Homopolymeric Hydrogels

Homopolymeric hydrogels comprised of polymeric network derived from a single monomeric specie, which is a basic structural unit comprising of any polymer network. Homopolymers may have cross-linked polymer skeletal structure depending on polymerization technique and nature of monomer.

Copolymeric Hydrogels

Copolymeric hydrogels referred to polymeric network with at least one hydrophilic component and comprised of two or more different monomer species, arranged in a block random, or alternating configuration along chain of polymeric network (Ahmed, 2015).

Semi-Interpenetrating Polymeric Hydrogels (Semi-IPN)

If one linear polymer overlap or penetrates another cross-linked network when there is no chemical bonding between them so it is called a semi-inter penetrating network (Zhang et al., 2009).

Multi-Polymeric Interpenetrating Polymeric Hydrogels (IPN)

Multipolymeric interpenetrating polymeric hydrogel (IPN), contained a network with two independently cross-linked natural or synthetic polymeric component. An IPN comprise of intimate combination of two polymers in a single network form, at least one of which is cross-linked polymer and other component is a non-cross-linked polymer (Ahmed, 2015; Maolin et al., 2000).

Classification Based on Type of Cross-Linking

Hydrogels can be divided into two categories based on physical and chemical nature of the cross-link junctions.

Physically Cross-Linked Hydrogels

Physical processes are involved like aggregation, complexation, association, crystallization, and hydrogen bonding for the synthesis of physical hydrogels. Physical networks have transient junctions that arise from physical interactions such as hydrogen bonding, ionic interactions, hydrophobic interactions or either from polymer chain entanglements.

Chemically Cross-Linked Hydrogels

To prepare chemical hydrogels, chemical processes are used i.e., chemical covalent crosslinking method. Chemically cross-linked hydrogels have permanent junctions (Ahmed, 2015; Omidian and Park, 2012).

Classification According to Polymer Nature

Natural Polymer Hydrogels

Natural polymers are normally used in the formulation of hydrogels prepared by chemical cross-linking. Natural polymers of proteins, nucleic acids, polysaccharides are available. Natural polymer can be modified to produce many derivatives but modification property is small in comparison with synthetic polymer.

Synthetic Polymer Hydrogels

Hydrogels synthesized from synthetic polymer have low degradation rates. Generally synthetic polymers are mechanically strong and hydrophobic in nature and they do not have inherent biocompatibility properties. Synthetic polymers can be altered easily by modification in their molecular weight and chemical composition which modifies the physicochemical properties of hydrogels (Tabata, 2009).

Classification Based on Network Electrical Charge

Hydrogels can be classified as ionic, neutral, or depending on the nature of side group chains (Peppas et al., 2000b).

Preparation of Hydrogels

Three main parts are involved in synthesis of hydrogel i.e. monomer, initiator and cross linker (Ahmed, 2015). The main materials used for synthesis and preparation of PHG are polymer and monomers and polymers can be of natural origin or of synthetic source (Laftah et al., 2011). To control final hydrogel attributes and heat of vaporization diluents can be used such as aqueous solutions or water. Synthesized hydrogels require washing to remove impurities produced during preparation. Washing will remove the non-reacted monomers, cross-linkers, initiators, as well as unwanted product produced by side reactions (Omidian and Park, 2010).

Drug Release Mechanism

Most of the hydrogels are glassy in their appearance in dried/dehydrated state. When a glassy hydrogel comes in contact with water or thermodynamically compatible solvents, medium penetrates in free spaces between macromolecular chains surfaces. Drug release from hydrogel involves absorption of water or biocompatible fluids and desorption of therapeutic agents/drugs. In hydrogel drug delivery system, rate controlling factor is polymer resistance toward imbibing fluids as resistance to change in shape or volume. When enough solvent penetrates, dried matrix, polymer glass transition temperature drops to level of experimental temperature. Stress development in glassy polymer matrix due to adsorption of fluid is maintained by an increase in end-to-end distance and radius of gyration of polymer molecules matrix while outcomes appear macroscopically as swelling. Solvent molecules movement into dried polymer matrix with glassy appearance takes place and simultaneous

increase in the thickness of rubbery or swollen region increases with time. The time taken for increase in polymer molecules radius of gyration is a characteristic for a particular polymer/solvent system which is a relaxation phenomenon (Gupta et al., 2002; Rao and Devi, 1988). Hydrogels with high water content typically results in relatively rapid drug release from gel matrix particularly in case of hydrophilic drugs over period of hours or days (Hoare and Kohane, 2008).

Drug Release Mechanisms from Hydrogel Devices

Hydrogels with hydrophilic polymer characteristics have ability to imbibe large amount of water so their release mechanism vary from hydrophobic polymer. Hydrogels have a combination of unique characteristics that make them suitable for drug delivery systems. Different developed models have been used to predict and analyze drug release mechanism from hydrogel as a function of time. These models are based on rate- limiting step for controlled release and are described as follows:

- Diffusion-controlled delivery systems
- Swelling-controlled delivery systems
- Chemically-controlled delivery system

Diffusion Controlled Delivery System

Diffusion-controlled mechanism is the most commonly used for drug release from hydrogels. Fick's law of diffusion used in modeling diffusion-controlled release with either constant or variable diffusion coefficients. Drug diffusivities are generally determined empirically or estimated as free volume, hydrodynamic, or obstruction-based theories (Lin and Metters, 2006).

Diffusion-controlled delivery systems divided in two major types: matrix devices and reservoir devices. In matrix devices, drug is dispersed throughout hydrogel polymeric structure. Reservoir systems consist of a polymeric outer membrane surrounding a core containing drug inside. Drug release from each type of system occurs by diffusion through water filled pores or macromolecular mesh. Fick's law of diffusion is widely used in diffusion-controlled release modelling systems. For a reservoir system where drug depot is encoded by a polymeric hydrogel matrix, Fick's first law of diffusion describe drug release through the membrane;

$$J_i = -D_{ip}\frac{dC_i}{dX} \qquad \text{(Eq. 1)}$$

J_i is molar flux of drug (mol/cm^{2}s), C_i is concentration of drug, and D_{ip} is diffusion coefficient of drug in polymer. Equation 1 is integrated to give following expression.

$$J_i = K\frac{D_{ip}\Delta C_i}{\delta} \qquad \text{(Eq. 2)}$$

K is partition coefficient, δ is thickness of hydrogel membrane. For constant flux of drug from the reservoir, concentration difference should remain constant. Designed device with these attributes follow zero-order release. For a matrix system where drug in polymer matrix is uniformly dispersed, unsteady-state drug diffusion through matrix can be described by the Fick's second law;

$$\frac{\partial Ci}{\partial t} = \frac{\partial}{\partial x}\left[D_{ip}\frac{\partial C_i}{\partial x}\right] \qquad \text{(Eq. 3)}$$

This equation represent one-dimensional transport with non-moving boundaries (Ganji and Vasheghani-Farahani, 2009).

Swelling Controlled Delivery Systems

Swelling-controlled release occurs when hydrogel swelling is slower than diffusion of drug. In swelling, control release molecules release from swollen hydrogels at the glassy and rubbery interface and modeling of this mechanism usually involves moving boundary conditions (Lin and Metters, 2006; Siepmann and Peppas, 2001).

When polymeric hydrogels are brought in contact with release medium like physiological fluids or water then swelling starts and hydrogel internal structure changes accordingly from a glassy (dried) to rubbery state. During polymeric swelling phenomenon three moving boundaries may form: swelling front, erosion front and diffusion front. The swelling front separates rubbery portion from glassy one, and moves towards the glassy core. The erosion front splits the rubbery portion from external release medium. Finally, the diffusion front separates regions of dissolved and undissolved drug, and follows the swelling front in its motion. The example of swelling controlled system is drug release from hydroxypropyl methylcellulose (HPMC) based hydrogels. HPMC based preparations undergoes phase transitions from glassy to rubbery state after absorbing liquid at phase transitions temperature thus causing release of loaded drug (Coviello et al., 2005).

Chemically Controlled Delivery Systems

Chemically-controlled release involves understanding of reactions occurring within a delivery matrix for molecule release. Reactions involve polymer chain cleavage through enzymatic or hydrolytic degradation or reversible or irreversible reactions occurring between releasable drug and polymer network (Lin and Metters, 2006).

There are two major types of chemically-controlled release systems; pendant chain systems, and erodible drug delivery systems. In pendant chain systems, drug is affixed to polymer backbone and has degradable linkages with polymer. As these degradable linkages break, drug is released. In erodible systems, drug release occurs due to degradation or dissolution of hydrogel. Erodible drug delivery systems can be reservoir or matrix system. In

matrix devices, drug is thoroughly dispersed within polymer network of hydrogel. Reservoir systems consist of a polymeric outer membrane surrounding a core containing drug inside. Drug diffuses out by polymer erosion or through gel (Ganji and Vasheghani-Farahani, 2009).

Water in Hydrogels

Water contents play an important role in the fate of nutrients and cellular component movement in gel. Hydrogels have capacity to imbibe large amount of water. Then water content becomes determining factor in overall nutrients absorption in cellular components out from the gel. When glassy hydrogel starts to absorb water or other fluids, first water molecule leads to establishment of 'primary bound water' by first hydrating hydrophilic and polar groups. Polymeric matrix swells after hydration of polar groups which exposes the hydrophobic groups. Hydrophobic groups will lead to formation of 'secondary bound water' by interacting with water molecule which also called hydrophobically-bound water. Primary and secondary bound water called 'total bound water'. After hydrophilic and hydrophobic sites have interacted with and bound water molecules, swollen network matrix will further absorb water due to osmotic driving force of the network chains towards infinite dilution. Network crosslinking either covalent or physical nature will inhibit further water imbibition to control swelling which will lead to formation of elastic polymer network with retraction force and network matrix will reach equilibrium state of swelling. The additional swelling water called 'bulk water or free water' and it is supposed to cover spaces between network chains, macropores, voids or center of larger pores, that is absorbed after hydrophobic, ionic, hydrophilic and polar groups become saturated with bound water. If polymeric crosslinks or networks are degradable then gel will become to dissolve and disintegrate at composition dependent rate as swelling starts (Hoffman, 2002).

Smart Hydrogels

On the basis of hydrogel response toward stimulus, hydrogels may be:

- Conventional Hydrogels
- Smart or stimuli responsive hydrogels

Conventional Hydrogels

Basic limitation which conventional drug delivery system is facing is least harmonization between actual release profile of drug showed by the dosage form and required time for therapeutically effective plasma drug concentrations (Gupta et al., 2002).

Smart or Stimuli Responsive Hydrogels

Hydrogels are 'intelligent' or 'smart' in the sense that they can respond by showing changes in their chemical or physical behavior by recognizing the prevailing stimuli like pH, temperature, ionic composition, resulting in controlled release of drug entrapped in polymeric network. Many progresses in polymer-based controlled-release systems have been seen in the past few years. Several products with decreasing or constant release rates have advanced from the laboratory to clinic in short duration. Most of these systems have therapeutic benefits but do not have any response toward varying metabolic states of body. There was a need of system which respond to changed physiological conditions. An ideal drug delivery system should respond to metabolic changes, physiological requirements, accordingly alter and maintained drug-release profile. Above all, if drug has some side effects and its release is not required then body's metabolic system will be burdened drug release when not required poses an extra burden on the body's metabolic system. Thus, drug delivery mechanism should be optimized for self-regulated or pulsed mechanism (Gupta et al., 2002).

Solid–liquid coexistent materials and polymer gels, depending on many external physicochemical factors, such as pH, temperature, ionic concentration, solvent composition can change their shape and volume reversibly (Kim et al., 1999). Hydrogels have ability to protect drug from hostile environments in stomach like low pH and presence of enzymes. By sensing any environmental stimuli hydrogels bring changes in gel structure and can control drug release. Hydrogels containing 'sensor' properties and upon minor variations in environmental conditions can undergo gel–sol phase transitions or reversible volume phase transitions. Types of hydrogels which are environment sensitive also called smart or intelligent hydrogel (Qiu and Park, 2001). Stimuli responsive hydrogels can be classified into following types based on their responses to different stimuli.

1. Temperature Sensitive Hydrogels
2. pH-Sensitive Hydrogels
3. Glucose Sensitive Hydrogels
4. Electric Signal-Sensitive Hydrogels
5. Light Sensitive Hydrogels
6. Enzyme-Sensitive Hydrogels
7. Antigen Sensitive Hydrogels

Temperature Sensitive Hydrogels

Hydrogels exhibit response toward environment varying temperature are called temperature sensitive hydrogels. The presence of hydrophobic groups, such as methyl, ethyl and propyl groups characterizes temperature sensitive polymers (Beltran et al., 1991). Polymeric system which are

temperature dependent at least one of their components should have temperature dependent solubility in dissolving medium. A critical solution temperature may be defined as a temperature at which the polymer solution undergoes separation from one phase to other phase (Bajpai et al., 2008). Hydrogel with temperature dependent swelling in water, their components should be insoluble below or above some specific temperature, called the lower or upper critical solution temperature (LCST or UCST), respectively (Bromberg and Ron, 1998). Temperature sensitive hydrogels are further divided as positive temperature hydrogels, negative temperature hydrogels and thermos-reversible hydrogels.

Positive temperature hydrogels have the upper critical solution temperature (UCST). This means at higher temperature than UCST swelling take place while at lower temperature than UCST gel contract and releases fluids or solvents from polymeric matrix.

Negative temperature hydrogels have lower critical solution temperature (LCST). This means that hydrogel will exhibit swelling phenomena at lower LCST while contraction at higher LCST.

Unlike positive and negative hydrogels thermos-reversible gels follow sol-gel phase transition phenomena rather than swelling and deswelling. Sol-gel transformation is dependent on surrounding medium glucose concentration. Tetronic and Pluronics compound possess thermos-reversible gel properties (Laftah et al., 2011).

Of the many temperature-sensitive polymers, poly(N-iso-propylacrylamide) (PNIPAAm) used widely shows a lower critical solution temperature while Poly(N N-diethylacrylamide (PDEAAm) is also used commonly because of its lower critical solution temperature (LCST) in the range of 25–32ºC,close to the body temperature (Beltran et al., 1991; Hoffman, 1991; Zhang et al., 2009).

pH-Sensitive Hydrogels

All pH-responsive polymers contain pendant acidic (e.g., ammonium salts) or basic (e.g., carboxylic and sulfonic acids) groups that either release or accept protons in response to varying pH in external environment. Hydrogels that contain (co)monomers with weak basic or weak acidic side groups, respond to pH change. These weak acidic basic groups are ionizable and their charge will be function of pH (Bae et al., 1989). For example, pH-responsive hydrogels composed of PEG-containing ionic networks have been applied for oral delivery of proteins such as insulin and calcitonin (Peppas et al., 2006).

Glucose Sensitive Hydrogels

Many hydrogels system have been developed which are glucose sensitive. These systems can be used for regulating insulin level in diabetes. Glucose oxidase enzyme is mostly used for glucose sensing in body. In pH responsive hydrogel systems containing glucose oxidase, glucose is oxidized to gluconic acid and this oxidation consequences lowering in environmental pH. Insulin release can be controlled by swelling of pH sensitive hydrogels. Many methods have been utilized to develop system by combining pH-sensitive hydrogels with glucose oxidase. Hydrogel synthesized by polycations membrane such as PDEAEM. When pH lowers then swelling of hydrogel takes place due to ionization of PDEAEM. More drug releases from hydrogels as membrane swells, than in less swollen condition (Bae et al., 1989; Miyata et al., 2002; Qiu and Park, 2001).

Electric Signal-Sensitive Hydrogels

Hydrogels which respond to electric current as an environmental signal called electro-sensitive hydrogels. Electric current sensitive hydrogels are made of insoluble polymer with swellable properties which carries anions and cations associated with polyelectrolytes. Electric current sensitive polymeric hydrogels exhibit bending of structure due to swelling and de-swelling and bending phenomena in presence of electric field (Kim et al., 1999; Qiu and Park, 2001).

Polyelectrolyte hydrogels exhibit de-swelling phenomena due to removal of water from gel on application of electric field. Gels with cationic side chains show shrinking phenomena at cathode while anionic gels at anode (Ramanathan and Block, 2001).

Polyelectrolyte hydrogel mechanical response toward an electric field can be used to modify and controlled release of drug. Gels can be synthesized either by introducing drug during synthesis of hydrogel or after synthesis. Different mechanisms of drug release from polyelectrolyte hydrogels are employed as diffusion electrophoresis, erosion of electro-erodible gels while most main mechanism involved is forced convection of drug from the network (Murdan, 2003).

Light Sensitive Hydrogel

Light responsiveness getting increased attention due to development of materials sensitive to electromagnetic radiations. Light sensitive hydrogels can be further classified into visible light sensitive hydrogel and UV sensitive hydrogels. Light-sensitive chromophore (e.g., tri-sodium salt of copper chlorophyllin) are used in synthesis of visible light-sensitive hydrogels. When light is applied to hydrogel, chromophore absorb light, temperature rises of the system changing swelling behavior of system. Poly(N-iso-propylacrylamide) hydrogels show this behavior. Leuco

derivative molecule, bis(4-di- methylamino)phenylmethyl leucocyanide are employed in synthesis of UV-sensitive hydrogels.

Light stimulus hydrogels have many benefits over pH sensitive hydrogel and temperature sensitive hydrogels as both are limitized by hydrogen ion diffusion and thermal diffusion respectively but these advantageous as can be applied at required time in required amount and are capable of sol-gel transformation in stimulus response (Qiu and Park, 2001). Some light-responsive delivery systems produce reversible structural change (drug releases in pulsatile manner while some triggers irreversible change that release drug in single dose (Alvarez-Lorenzo et al., 2009).

Enzyme-Sensitive Hydrogels

Enzymes-sensitive hydrogels are advancing as enzyme sensitive DDS and as enzyme sensor. Hydrogel system can be developed from biodegradable polymer while biodegradable polymer are promising candidates in biomedical field as have characteristics for drug delivery system and tissue engineering. Biodegradable polymers can be breakdown by many enzymes and these enzymes are helpful in diagnosis of many physiological and pathological conditions in the body. Many enzymes can be used as signal for site specific drug release as microbial enzymes in colon (Miyata et al., 2002).

Antigen Sensitive Hydrogels

Novel antigen-sensitive hydrogels have been developed which show varying swelling behavior toward specific antigen. This hydrogel system synthesized by employing antigen-antibody bonds in hydrogels at cross-linking sites. An antibody has recognition site for specific antigen and bonded with antigen by many interactions as van der Waals interactions, hydrophobic interactions, hydrogen bonds, hydrogen bonds, non-covalent bonds and electrostatic interactions. Characteristics of antibodies are linked to immune responses in body. Antibodies are employed in detection of physiological variations by involving in immunological assays which uses their versatility and specificity. Antibody specific antigen recognition property provide a platform for development of various sensor for various function of antigen sensing and immunoassay. Specific antigen presence become responsible for volume change in hydrogel structure (Bae et al., 1989; Miyata et al., 2002).

Applications of Hydrogels

Hydrogels in Drug Delivery

Biomaterials are used as devices or implants that will use in physiological and pathological conditions to interact with biological fluids. Biomaterials field not only construct materials that are immunologically and structurally sound but also try to design a system which is biomimetic that can interact through cellular indications to physiological environment. Hydrogels are suitable biomaterials due to their innate capacity to absorb large volume of physiological fluids and their molecular structure. In tissue engineering and drug delivery field there is great progress while using smart hydrogels. Intelligent or stimuli-responsive hydrogels are hydrophilic cross linked polymeric network that are chemically and physically cross linked and undergo a change in structure as bond breakage, phase volume change or sol gel transition on reaching stimulus (Chen et al., 2003; Knipe and Peppas, 2014).

For suitable and efficient drug therapy there was a need of delivery system. Among them, hydrogel considered as efficient candidate as controlled delivery devices, targetable devices of therapeutic agent and bio-adhesives devices. Many sites are available for hydrogel drug delivery as oral, rectal, epidermal, ocular, subcutaneous routes (Sri et al., 2012).

Per-Oral Drug Delivery

Hydrogels have common application of drug delivery is by oral route. Mouth, stomach, small intestine and colon are the four specific sites for drug delivery by hydrogel system. Hydrogels can be presented as controlled drug delivery system by modifying their bioadhesive and swelling characteristics in physiological fluids. Mucoadhesive hydrogel system have ability of adhering locally to increase absorption and concentration at site of release (Sri et al., 2012).

Drug Delivery in Oral Cavity

Many diseases of oral cavity as periodontal disease, fungal and viral infection and oral cavity cancers can be treated by locally administration of drug delivery system. Mucoadhesive systems are required in copious flow of saliva for long term release of drugs locally. Bioadhesive hydrogel, systems for this purpose are now marketed as Aftachw is a bioadhesive tablet made up of poly (acrylic) acid and hydroxypropyl cellulose. For treatment of aphthous ulcer it is delivery of triamcinolone acetonide locally (Sri et al., 2012).

Drug Delivery in GI Tract

GI tract has large surface for systemic absorption and most commonly used route for drug administration. Efficient and effective drug delivery system is required due to complexity of GIT tract. In peptic ulcer disease treatment of Helicobacter pylori infection is required. Hydrogels with antibiotic drug delivery which are stomach specific are now

marketed. Cationic hydrogel with pH sensitive release and swelling properties have developed for drug delivery in acidic environment of stomach locally. IPN hydrogels were composed of freeze-dried chitosan-poly (ethyleneoxide) materials and incorporated with amoxicillin and metronidazole are used with modified characteristics based on pH change (Sri et al., 2012).

Ocular Delivery

Various physiological limitations result in unsuccessful drug supply to eye due to its defensive mechanism such as blinking, low permeability of cornea and effective tear drainage. Therefore, conventional eye drops lead to poor absorption and exhibit limited ophthalmic bioavailability. Moreover, short retention time in ocular delivery needs frequent dosing for durable therapeutic efficacy. These problems have motivated researchers to advance drug delivery systems that offer an extended ocular retention time of drugs. Ointments and suspension can retain in eye but causes unpleasant feelings. Hydrogels provide ocular drainage resistant device because of their elastic properties and give better feelings and less gritty sensations. Specifically, *in-situ*- forming hydrogels are attractive as an ocular drug delivery system due to their capability in dosing as a liquid, and their durable retention property as a gel after dosing (Sri et al., 2012).

Transdermal Delivery

Traditionally transdermal route used for skin disinfection or to treat skin diseases by topical administration of dermatological drugs. Transdermal route involves many advantages as hepatic first pass metabolism bypass, delivery of drug for longer duration at constant rate and discontinuation of therapy by removing device at any inconvenience. Now a day's transdermal route considered as site for drug delivery systematically. Hydrogel in comparison to conventional patches and ointment give good feeling to skin due to large content of water (Sri et al., 2012).

Subcutaneous Delivery

Hydrogels possess an extensive variety of potential pharmaceutical applications. Among them, their significant applications may originate in subcutaneously inserted implantable therapeutics. Exogenous materials may induce possibly unwanted body response such as immunogenicity, inflammation and carcinogenicity. Biocompatibility is the requirement which makes materials implantable. Biocompatibility of hydrogels is because of presence of high water contents. They have several considerable properties e.g., wide acceptability for drugs with different molecular sizes and hydrophilicities, mechanical irritation and prevention of cell adhesion and protein absorption as a result of low interfacial tension between hydrogel and water (Sri et al., 2012).

Topical Delivery

Some of the active pharmaceutical ingredients (API) are delivered by hydrogels e.g., desonide, a synthetic corticosteroid. A better patient compliance can be achieved by formulation of hydrogels than conventional creams. Dryness and scaling can be treated due to moisturizing properties of hydrogels. Cotrimazole, an antifungal has been formulated as hydrogel drug delivery system for vaginitis which shows more absorption than conventional creams. Protein drug delivery interleukins are now delivered as hydrogels which have improved the patient compliance. Hydrogels cause slow release of proteins by forming *insitu* polymeric network. Hydrogels undergo biodegradation and are biocompatible (Sri et al., 2012).

Rectal Delivery

Rectal route is used for drug delivery to locally associated disease treatment in rectum such as hemorrhoids. Drugs delivered by rectum directly drain into systemic circulation. Conventional dosage forms have uncontrolled diffusion of drug which causes bioavailability variations. Hydrogels are developed with bio-adhesive properties for prolonging drug release after rectal administration to overcome problems associated with conventional dosage forms (Sri et al., 2012).

Hydrogels in Diagnostic Devices

Hydrogels play an important role in micro-devices which are used for diagnostic purposes. Hydrogels can be inserted in micro-devices using many approaches as molding and photolithographic process. Biosensor and valves which are environment sensitive, hydrogels used as integral component of micro-devices. PEG based pH-sensitive photo cross-linker based hydrogels work in microfluidic channels as functional valves by modifying their actuation by swelling changes which made possible after sensing change in solution pH. Intelligent materials such as chemically or electrically sensitive polymer, photosensitive polymer is now investigating for modified actuated valves which modify their physicochemical properties by sensing stimulus in exTernal environment. PEG fabricated hydrogels used in controlled microreactors for controlling protein location within microfluidic channel (Peppas et al., 2006).

Hydrogels in Controlled Drug Delivery

Hydrogels have been used in controlled delivery of drugs as smart carriers. Researchers have modified physical and chemical characteristics of hydrogels for their use as smart carriers in controlled drug delivery systems. Engineered

attributes of hydrogels involve optimum permeability, surface functionality, biodegradability, enviro-responsive nature, surface bio-recognition for application of controlled release. Controlled swelling characteristics of hydrogels can be used as tool to modify or trigger drug release as PEG and PVA based hydrogel system can control drug release by changing polymer composition, polymer chain length, and initial concentration. Improved drug release made possible by mucoadhesive and bioadhesive system by improving residence time after interacting with biological fluids. Hydrogel systems with molecular recognition used for controlled, targeted, and delayed delivery of drugs. Biomimetic systems that resemble physiological processes have potential for drug release applications and hydrogels are getting attraction in this field (Peppas et al., 2006).

Hydrogels in Tissue Engineering

Tissue engineering targets to replace, regenerate repair tissues or organ and aims to generate artificial organs for transplantation. Hydrogels which are cell laden work as scaffolds. Scaffolds used in tissue engineering help out cell adhesion and proliferation. Scaffolds manufactured should be bio erodible as resulting structure made from physiological components after tissue growth. Cell-laden hydrogels resemble natural tissues due to their biocompatibility, water contents and high mechanical strength and have major applications in tissue engineering (Peppas et al., 2006).

Hydrogels in Diagnostic Imaging

Targeting required location and administering accurate dose of imaging agent are critically important for proper diagnosis in medical imaging. Hydrogels are emerging as required tool with similar attributes in controlled drug delivery system. Hydrogels can be used as suitable carrier with release attributes as coating with stealth properties, as coating with targeting properties or combination of both (Peppas et al., 2006).

CONCLUSION

Hydrogels are highly swellable system which are capable of encapsulating a number of chemical and therapeutic moieties in their cavities. They have the tendencies to encapsulate both hydrophilic and hydrophobic moieties and have the capability to deliver the drug either diffusion controlled, swelling controlled or swelling controlled mechanism. Based on their significant response to different stimuli, they have the property to deliver the loaded drug upon exposure to various stimuli. All of these characteristics make hydrogels as one of the promising delivery systems.

ACKNOWLEDGEMENT

All the authors are really thankful to Faculty of Pharmacy, The University of Lahore and Faculty of Pharmacy, The Islamia University of Bahawalpur for providing facilities for completing the review.

REFERENCES

Ahmed, E.M., 2015. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research 6, 105-121.

Alvarez-Lorenzo, C., Bromberg, L., Concheiro, A., 2009. Light-sensitive intelligent drug delivery systems. Photochemistry and Photobiology 85, 848-860.

Bae, Y.H., Okano, T., Kim, S.W., 1989. Insulin permeation through thermo-sensitive hydrogels. Journal of Controlled Release 9, 271-279.

Bajpai, A., Shukla, S.K., Bhanu, S., Kankane, S., 2008. Responsive polymers in controlled drug delivery. Progress in Polymer Science 33, 1088-1118.

Beltran, S., Baker, J.P., Hooper, H.H., Blanch, H.W., Prausnitz, J.M., 1991. Swelling equilibria for weakly ionizable, temperature-sensitive hydrogels. Macromolecules 24, 549-551.

Bromberg, L.E., Ron, E.S., 1998. Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery. Advanced Drug Delivery Reviews 31, 197-221.

Chen, T., Embree, H.D., Brown, E.M., Taylor, M.M., Payne, G.F., 2003. Enzyme-catalyzed gel formation of gelatin and chitosan: potential for in situ applications. Biomaterials 24, 2831-2841.

Coviello, T., Palleschi, A., Grassi, M., Matricardi, P., Bocchinfuso, G., Alhaique, F., 2005. Scleroglucan: a versatile polysaccharide for modified drug delivery. Molecules 10, 6-33.

Das, N., 2013. Preparation methods and properties of hydrogel: a review. Int J Pharm Pharm Sci 5, 112-117.

Ganji, F., Vasheghani-Farahani, E., 2009. Hydrogels in controlled drug delivery systems. Iran Polym J 18, 63-88.

Gupta, P., Vermani, K., Garg, S., 2002. Hydrogels: from controlled release to pH-responsive drug delivery. Drug Discovery Today 7, 569-579.

Hoare, T.R., Kohane, D.S., 2008. Hydrogels in drug delivery: Progress and challenges. Polymer 49, 1993-2007.

Hoffman, A.S., 1991. Environmentally sensitive polymers and hydrogels. MRS Bulletin 16, 42-46.

Hoffman, A.S., 2002. Hydrogels for biomedical applications. Advanced Drug Delivery Reviews 54, 3-12.

Kim, S.W., Bae, Y.H., Okano, T., 1992. Hydrogels: swelling, drug loading, and release. Pharmaceutical Research 9, 283-290.

Kim, S.Y., Shin, H.S., Lee, Y.M., Jeong, C.N., 1999. Properties of electroresponsive poly (vinyl alcohol)/poly (acrylic acid) IPN hydrogels under an electric stimulus. Journal of Applied Polymer Science 73, 1675-1683.

Knipe, J.M., Peppas, N.A., 2014. Multi-responsive hydrogels for drug delivery and tissue engineering applications. Regenerative Biomaterials 1, 57-65.

Laftah, W.A., Hashim, S., Ibrahim, A.N., 2011. Polymer hydrogels: A review. Polymer-Plastics Technology and Engineering 50, 1475-1486.

Lee, W.F., Fu, Y.T., 2003. Effect of montmorillonite on the swelling behavior and drug-release behavior of nanocomposite hydrogels. Journal of Applied Polymer Science 89, 3652-3660.

Lin, C.-C., Metters, A.T., 2006. Hydrogels in controlled release formulations: network design and mathematical modeling. Advanced Drug Delivery Reviews 58, 1379-1408.

Maolin, Z., Jun, L., Min, Y., Hongfei, H., 2000. The swelling behavior of radiation prepared semi-interpenetrating polymer networks composed of polyNIPAAm and hydrophilic polymers. Radiation Physics and Chemistry 58, 397-400.

Mathur, A.M., Moorjani, S.K., Scranton, A.B., 1996. Methods for synthesis of hydrogel networks: A review. Journal of Macromolecular Science, Part C: Polymer Reviews 36, 405-430.

Miyata, T., Uragami, T., Nakamae, K., 2002. Biomolecule-sensitive hydrogels. Advanced Drug Delivery Reviews 54, 79-98.

Murdan, S., 2003. Electro-responsive drug delivery from hydrogels. Journal of Controlled Release 92, 1-17.

Omidian, H., Park, K., 2010. Introduction to hydrogels, Biomedical applications of hydrogels handbook. Springer, pp. 1-16.

Omidian, H., Park, K., 2012. Fundamentals and Applications of Controlled Release Drug Delivery, Juergen Siepmann, Ronald Siegel, and Michael Rathbone, Eds. Spinger, New York, NY, 2012, pp. 75-106. 75-106.

Peppas, N., Huang, Y., Torres-Lugo, M., Ward, J., Zhang, J., 2000a. Physicochemical foundations and structural design of hydrogels in medicine and biology. Annual Review of Biomedical Engineering 2, 9-29.

Peppas, N.A., Bures, P., Leobandung, W., Ichikawa, H., 2000b. Hydrogels in pharmaceutical formulations. European Journal of Pharmaceutics and Biopharmaceutics 50, 27-46.

Peppas, N.A., Hilt, J.Z., Khademhosseini, A., Langer, R., 2006. Hydrogels in biology and medicine: from molecular principles to bionanotechnology. Advanced Materials 18, 1345-1360.

Qiu, Y., Park, K., 2001. Environment-sensitive hydrogels for drug delivery. Advanced Drug Delivery Reviews 53, 321-339.

Ramanathan, S., Block, L.H., 2001. The use of chitosan gels as matrices for electrically-modulated drug delivery. Journal of Controlled Release 70, 109-123.

Rao, K.R., Devi, K.P., 1988. Swelling controlled-release systems: recent developments and applications. International Journal of Pharmaceutics 48, 1-13.

Siepmann, J., Peppas, N., 2001. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews 48, 139-157.

Sri, B., Ashok, V., Arkendu, C., 2012. As a review on hydrogels as drug delivery in the pharmaceutical field. Int J Pharm Chem Sci 1, 642-661.

Tabata, Y., 2009. Biomaterial technology for tissue engineering applications. J R Soc Interface 6, S311-324.

Zhang, J.-T., Bhat, R., Jandt, K.D., 2009. Temperature-sensitive PVA/PNIPAAm semi-IPN hydrogels with enhanced responsive properties. Acta Biomaterialia 5, 488-497.