CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.3263862

Available online at: http://www.iajps.com *Review Article*

HYDROGELS: A REVIEW ON CLASSIFICATION, PREPARATION METHODS, PROPERTIES AND ITS APPLICATIONS

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Article Received: April 2019 **Accepted:** May 2019 **Published:** June 2019

Abstract:

Hydrogels are composed of three dimensional cross linked polymer network. The hydrogels shows excellent biocompatibility, when swelled and resemble the living tissue. High water content of hydrogels and physiochemical similarities to the native extracellular matrix, both compositionally and mechanically promotes biocompatibility. The evaluation of biocompatible properties consider more attention before the hydrogels are applied. Due to the higher water absorption capacity, long service life, and wide varieties of raw chemical resources natural hydrogels were gradually replaced by synthetic types. For hydrogel production, different technologies adopted with process design implications, block diagrams, and optimized conditions of the preparation process. Based on the different classification, hydrogels could be homo-polymeric, co-polymeric, semi-interpeneterating and interpeneterating polymer networks. These are categorized as natural, synthetic and semisynthetic and based upon polymer used they can be temperature triggered, pH triggered and ion activated and in this case these are known as smart gels. Hydrogels can be used as biosensors as well as drug delivery systems that are responsive to specific molecules, such as glucose or antigens,. Hydrogels are used in different biomedical fields such as cellular immobilization, specific site drug delivery, tissue reconstruction, tissue engineering, as biosensors, diagnostics and separation of molecules due to their unique properties and are also used in contact lenses. In this review article an attempt has been made to describe the available methods of hydrogel synthesis, classification of hydrogels, their properties, methods of preparation and its applications.

Keywords: *Hydrogels, Biocompatibility, Polymer, Immobilization, Chemical cross-linking.*

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QR code

Please cite this article in press Lalita Chauhan et al., ***Hydrogels: A Review On Classification, Preparation Methods, Properties And Its Applications.,*** *Indo Am. J. P. Sci, 2019; 06(06).*

INTRODUCTION:

Hydrogels are biomaterials that consist of a water-swollen network of crosslinked polymer chains. They can be made from chains of natural polymers such as collagen or alginate or from synthetic polymers such as Poly Vinyl Alcohol (PVA) or Poly Acrylic Acid (PAA). Their biocompatibility, ease of fabrication and viscoelastic properties makes them highly suitable for use as constructs to engineer tissues. The hydrogels are widely used in clinical practice and in experimental medicines in a very wide range e.g. diagnostics, cellular immobilization or separation of biomolecules or cells and barrier materials to regulate biological adhesion. Hydrogel is very significant for the drug delivery because of its unique physical properties. Tuning of highly porous structure can be done by controlling the density of crosslinks in the gel matrix and the affinity of the hydrogels for the aqueous environment in which they are swollen. Loading of drugs in the gel matrix is permitted by their porosity and subsequent drug release at a rate dependent on diffusion coefficient of the small molecule or macromolecule through the gel network (Peppas et al.,2000).

They can serve as scaffolds which provide structural integrity to tissue constructs, control drug and protein delivery to tissues and serve as adhesives or barriers between tissue and material surfaces. Hence, the properties of hydrogels are important for tissue engineering and other areas of biomedical field. Among these properties one must evaluate the swelling, mechanical and biocompatible properties before the hydrogel biomaterials are applied (Das, 2013).

Advantages of hydrogels:

1. Due to their significant water content they possess a degree of flexibility very similar to natural tissue.
2. Release of medicines or nutrients timely.
3. They are biocompatible, biodegradable and can be injected.
4. Hydrogels have the ability to sense changes of pH, temperature, or the concentration of metabolite and release their load as result of such a change.
5. Hydrogels also possess good transport properties and easy to modification.

Disadvantages of hydrogels:

1. High cost.
2. Can be hard to handle.
3. Low mechanical strength.
4. They are non-adherent and may need to be secured by secondary dressing and also cause sensation felt by movement of the maggots.
5. Difficult to load with drugs/nutrients (Singh et al., 2017 & Devi et al., 2014).

Classification of Hydrogels:

Classification of hydrogel products

The hydrogel products can be classified on different bases as detailed below:

1) On the basis of their occurrence and synthesis

Hydrogels are broadly classified into three types.

- Natural hydrogels
- Synthetic hydrogels
- Semisynthetic hydrogels

(a) Natural hydrogels

These are hydrogels that exist naturally in the environment and need not to be synthesized. Examples of naturally occurring hydrogels are mucus, vitreous humor of eye cartilage, tendons and blood clots.

(b) Synthetic hydrogels

These hydrogels are synthesized artificially and has similar properties to that of the natural hydrogels. Synthetic hydrogels have been considered as potential candidates for mimicking life.

(c) Semi synthetic hydrogels

These hydrogels are prepared by the partial chemical synthesis. Need of semi synthetic hydrogels arises when precursor molecule is too structurally complex or costly to be produced by total synthesis. It is also possible that the semi synthetic out-performs the original biomolecule itself with respect to potency, stability or safety. In such cases semi synthetic hydrogels can itself perform the task of natural hydrogels (Peppas et al.,2000).

2) Classification based on source

Hydrogels can be classified into two groups based on their natural or synthetic origins (Ahmed, 2015).

3) Classification according to polymeric composition

The method of preparation leads to formations of some important classes of hydrogels. These can be exemplified by the following:

(a) Homopolymeric hydrogels are referred to polymer network derived from a single species of monomer, which is a basic structural unit comprising of any polymer network (Takashi et al., 2007).

Homopolymers may have cross-linked skeletal structure depending on the nature of the monomer and polymerization technique.

(b) Copolymeric hydrogels are comprised of two or more different monomer species with at least one hydrophilic component, arranged in a random, block or alternating configuration along the chain of the polymer network (Yang et al., 2002).

(c) Semi- Inter Penetrating Network (Semi-IPN)

If one polymer is linear and penetrates another cross-linked network without any other chemical bonds between them, it is called a semi-inter penetrating network. Semi-IPNs can more effectively preserve rapid kinetic response rates to pH or temperature due to the absence of restricting interpenetrating elastic network, while still providing the benefits like modified pore size & slow drug release etc. (Das, 2013).

(d) Multipolymer Interpenetrating polymeric hydrogel (IPN), an important class of hydrogels, is made of two independent cross-linked synthetic and/or natural polymer component, contained in a network form. In semi-IPN hydrogel, one component is a cross-linked polymer and other component is a non-cross-linked polymer (Maolin et al., 2000 & Hacker and Mickos, 2011).

4) Classification based on configuration

The classification of hydrogels depends on their physical structure and chemical composition can be classified as follows:

(a) Amorphous (non-crystalline)
(b) Semicrystalline: A complex mixture of amorphous and crystalline phases
(c) Crystalline

5) Classification based on type of cross-linking

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

(a) Chemically cross-linked networks have permanent junctions
(b) While physical networks have transient junctions that arise from either polymer chain entanglements or physical interactions such as ionic interactions, hydrogen bonds, or hydrophobic interactions.

6) Classification based on physical appearance

Hydrogels appearance as matrix, film, or microsphere depends on the technique of polymerization involved in the preparation process.

7) Classification according to network electrical charge

Hydrogels may be categorized into four groups on the basis of presence or absence of electrical charge located on the cross-linked chains:

(a) Nonionic (neutral).
(b) Ionic (including anionic or cationic).
(c) Amphoteric electrolyte (ampholytic) containing both acidic and basic groups.
(d) Zwitterionic (polybetaines) containing both anionic and cationic groups in each structural repeating unit.

7) Classification according to mechanism controlling the drug release they are classified into:

a. Diffusion controlled release systems
b. Swelling controlled release systems
c. Chemically controlled release systems
d. Environment responsive systems (Ahmed, 2015).

Smart Hydrogels

Hydrogels may exhibit swelling behavior dependent on the external environment. Over the past 30 years there has been a significant interest in the development and analysis of environmentally or physiologically responsive hydrogels (Peppas, 1991). Environmentally responsive materials show drastic changes in their swelling ratio due to changes in their external pH, temperature, ionic strength, nature and composition of the swelling agent, enzymatic or chemical reaction, and electrical or magnetic stimuli (Peppas et al., 1993). In most responsive networks, a critical point exists at which this transition occurs. An interesting characteristic of numerous responsive gels is that the mechanism causing the network structural changes can be entirely reversible in nature. The ability of pH- or temperature-responsive gels to exhibit rapid changes in their swelling behavior and pore structure in response to changes in environmental conditions lend these materials favorable characteristics as carriers for bioactive agents, including peptides and proteins. This type of behavior may allow these materials to serve as self-regulated, pulsatile drug delivery systems.

1) pH-Sensitive Hydrogels

One of the most widely studied types of physiologically responsive hydrogels is pH-responsive hydrogels. These hydrogels are swollen ionic networks containing either acidic or basic pendant groups. In aqueous media of appropriate pH and ionic strength, the pendant groups can ionize developing fixed charges on the gel. All ionic materials exhibit a pH and ionic strength sensitivity. The swelling forces developed in these systems are increased over those of nonionic materials. This increase in swelling force is due to the localization of fixed charges on the pendant groups. As a result, the mesh size of the polymeric networks can change significantly with small pH change.

2) Complexing Hydrogels

Some hydrogels may exhibit environmental sensitivity due to the formation of polymer complexes. Polymer complexes are insoluble, macromolecular structures formed by the non

covalent association of polymers with affinity for one another. The complexes form as a result of the association of repeating units on different chains (interpolymer complexes) or on separate regions of the same chain (intrapolymer complexes). Polymer complexes are classified by the nature of the association as stereo complexes, polyelectrolyte complexes, or hydrogen-bonded complexes. The stability of the associations is dependent on such factors as the nature of the swelling agent, temperature, type of dissolution medium, pH and ionic strength, network composition and structure, and length of the interacting polymer chains. In this type of gel, complex formation results in the formation of physical cross-links in the gel. As the degree of effective cross-linking is increased, the network mesh size and degree of swelling is significantly reduced. As a result, if hydrogels are used as drug carriers, the rate of drug release will decrease dramatically upon the formation of interpolymer complexes.

3) Temperature-Sensitive Hydrogels

Another class of environmentally sensitive gels exhibits temperature-sensitive swelling behavior due to a change in the polymer compatibility over the temperature range of interest. Temperature-sensitive polymers typically exhibit a lower critical solution temperature (LCST), below which the polymer is soluble. Above this temperature, the polymers are typically hydrophobic and do not swell significantly in water (Kim et al., 1996). However, below the LCST, the crosslinked gel swells to significantly higher degrees because of the increased compatibility with water (Merril et al., 1987).

4) Ion-Sensitive Hydrogels

Ion-sensitive polymers belong to the mainly used *in situ* gelling materials for ocular drug delivery. Gelling of the instilled solution is also triggered by change in ionic strength. It is assumed that the rate at which electrolytes from the tear fluid is adsorbed by the polymer will depend on the osmotic gradient across the surface of the gel. It is therefore likely that the osmolality of the solution might have an influence on the rate of the sol gel transition occurring in the eye. One example is Gelrite®, an anionic extra cellular polysaccharide, secreted by *Pseudomonas elodea* .Gelrite® formulations in aqueous solutions form a clear gel in the presence of the mono or divalent cations typically found in the tear fluids. The electrolyte of the tear fluid and especially Na^+, Ca^{++} and Mg^{++} cations are particularly suited to initiate gelation of the polymer when instilled as a liquid solution in to the cul-de-sac. Gelrite® has been the most widely stsudied and seems to be preferred compared to the pH sensitive or temperature setting systems. The polymeric concentration is much lower compared to previously described systems. Slightly viscous gellan gum solutions in low concentrations (<1%) show markedly increase in apparent viscosity, when introduced into presence of a physiological level of cations, without requiring more ions than 10–25% of those in tear fluid. The precorneal contact times for drugs can thus be extended up to 20-h. Gellan containing formulations of pilocarpine HCl allowed reduction of drug concentration from 2% to 0.5% obtaining the same bioavailability.

Recently, some other natural polymers believed to be able to form *in situ* gels by interacting with the lachrymal fluid have been evaluated as potential adjuvant in ophthalmic formulation. This includes carageenans, xyloglucans and some alginates that are rich in guluronic acid residues. Kcarrageenan forms rigid, brittle gels in reply of small amount of K^+, I-carrageenan forms elastic gels mainly in the presence of Ca^{2+}. Gelation of the low-methoxy pectins can be caused by divalent cations, especially Ca^{2+}. Likewise, alginic acid undergoes gelation in presence of divalent/polyvalent cations e.g. Ca^{2+} due to the interaction with guluronic acid blocks in alginate chains. Sodium alginate consists chiefly of the sodium salt of alginic acid, a linear glycuronan polymer consisting of a mixture of β- (1, 4)-D-mannosyluronic acid and α- (1, 4)- L-Gulosyluronic acid residues (Nunjundsway et al., 2009).

5) H-bonding Hydrogel

H-bonded hydrogel can be obtained by lowering the pH of aqueous solution of polymers carrying carboxyl groups. An example of such hydrogel is a hydrogen-bound CMC (carboxy methyl cellulose) network formed by dispersing CMC into 0.1M HCl. The mechanism involves replacing the sodium in CMC with hydrogen in the acid solution to promote hydrogen bonding (Fig 1). The hydrogen bonds induce a decrease of CMC solubility in water and result in the formation of an elastic hydrogel. Carboxymethylated Chitosan (CM-Chitosan) hydrogels can also prepared by cross-linking in the presence of acids or polyfunctional monomers. Another example is Poly Acrylic Acid and Polyethylene Oxide (PEO-PAAc) based hydrogel prepared by lowering the pH to form H-bonded gel in their aqueous solution. In case of Xanthan-Alginate mixed system molecular interaction of Xanthan and Alginate causes the change in matrix structure due to intermolecular hydrogen bonding between them resulting in formation of insoluble hydrogel (Madolia and Sheo, 2013).

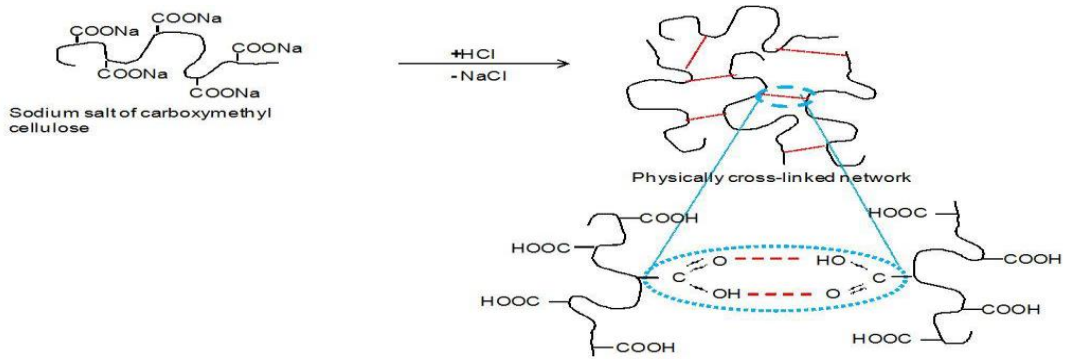

Fig 1: Hydrogel network formation due to intermolecular H-bonding in CMC at low pH. (Source:http://cdn.intechopen.com/pdfs/17237/InTech-Hydrogels_methods_of_preparation_characterisation_and_applications.pdf)

Technologies adopted in the preparation of hydrogels:

In general, hydrogels can be prepared from either synthetic polymers or natural polymers. The synthetic polymers are hydrophobic in nature and chemically stronger compared to natural polymers. Their mechanical strength results in slow degradation rate, but on the other hand mechanical strength provides the durability as well. These two opposite properties should be balanced through optimal design. Water-soluble linear polymers of both natural and synthetic origin are cross-linked to form hydrogels in a number of ways:

1. Linking polymer chains via chemical reaction.
2. Using ionizing radiation
3.Physical interactions such as entanglements, electrostatics, and crystallite formation. In general, the three integral parts of the hydrogels preparation are monomer, initiator, and cross-linker. To control the heat of polymerization and the final hydrogels properties, diluents can be used, such as water or other aqueous solutions. Hydrogels are usually prepared from polar monomers. According to their starting materials, they can be divided into natural polymer, synthetic polymer, and combinations of the two (Shetye et al., 2015 & Ahmed, 2015).

1) Bulk polymerization

Bulk hydrogels can be formed with one or more types of monomers mainly include vinyl monomers for the productions of hydrogels. Usually, a small amount of cross-linking agent is added in any hydrogel formulation. Radiation, ultraviolet, or chemical catalysts is used for the initiation of the polymerization reaction. The initiator is chosen which depends upon the type of monomers and solvents being used. The polymerized hydrogel may be produced in a wide variety of forms including rods, particles, films and membranes, and emulsions (Shetye et al., 2015 & Ahmed, 2015).

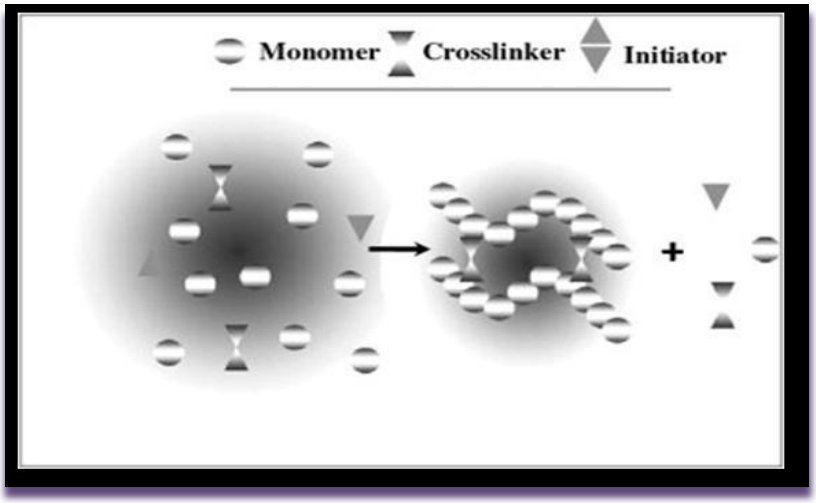

Fig.2. Schematic diagram of hydrogel preparation (Ahmed, 2015)

2) Free radical polymerization

The main monomers which are used in this method for the preparation of hydrogels are such as acrylates, vinyl lactams and amides. These polymers have suitable functional groups or have been functionalized with radically polymerizable groups. This method involves the chemistry of typical free-radical polymerizations, which includes propagation, chain transfer, initiation, and termination steps. For the radical generation in the initiation step a wide variety of thermal, ultraviolet, visible, and redox initiators can be utilized, the radicals react with the monomers which convert them into active forms (Shuanhong et al., 2016).

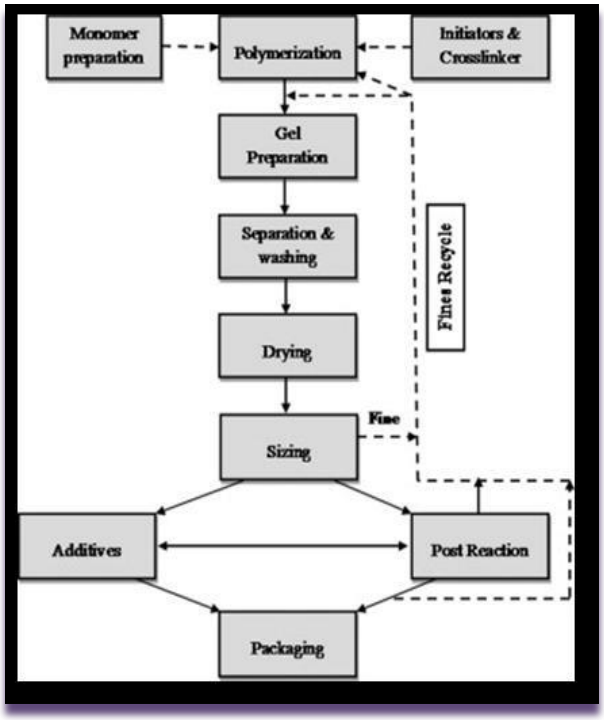

Fig.3. Hydrogel preparation block

3) Solution polymerization/cross-linking

In these ionic or neutral monomers are mixed with the multifunctional crosslinking agent. The polymerization is initiated thermally by UV-irradiation or by a redox initiator system. The major advantage of the solution polymerization over the bulk polymerization is the presence of solvent serving as a heat sink. The prepared hydrogels is washed with distilled water to remove the initiator, the soluble monomers, oligomers, cross-linking agent, and extractable polymer, and other impurities. Solvents used water–ethanol mixtures, water, ethanol, and benzyl alcohol.

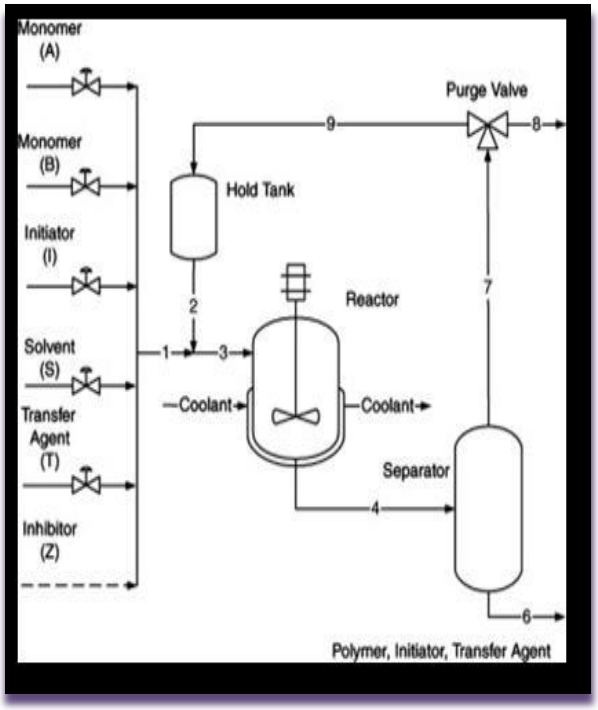

Fig.4. Solution polymerization with (solution polymerization/cross-linking procedure) recycle loop

4) Suspension polymerization or inverse-suspension polymerization

Dispersion polymerization is an advantageous method since the products are obtained as powder or microspheres (beads), and thus, grinding is not required. Since water-in-oil (W/O) process is chosen instead of the more common oil-in-water (O/W), the polymerization is referred to as “inverse-suspension” technique (Ahmed, 2015).

In this technique, the monomers and initiators are dispersed in the hydrocarbon phase as ahomogenous mixture. The viscosity of the monomer solution, agitation speed, rotor design, and dispersant type mainly governs the resin particle size and shape. The dispersion is thermodynamically unstable and requires both continuous agitation and addition of a low hydrophilic–lipophilic-balance (HLB) agent (Ahmed, 2015).

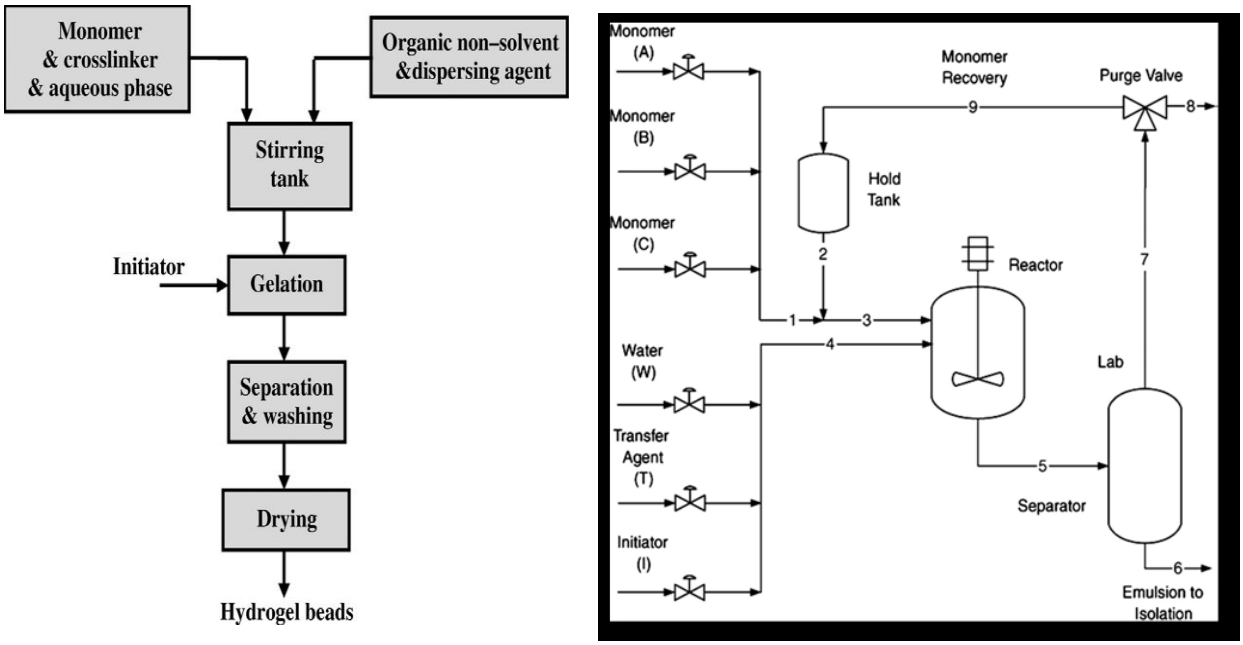

Fig.5. (A) (B)

Fig. 5. (A)Block diagram of suspension polymerization process. (B)Suspension polymerization process with recycle loop

5) Polymerization by Irradiation

Ionizing high energy radiations like gamma rays and electron beams have been used as an initiator to prepare the hydrogels of unsaturated compounds. The irradiation of aqueous polymer solution results in the formation of radicals on the polymer chains. Also, radiolysis of water molecules results in the formation of hydroxyl radicals, which also attack the polymer chains, resulting in the formation of macro-radicals. The major advantage of the radiation initiation over the chemical initiation is the production of relatively pure and initiator-free hydrogels (Ahmed, 2015).

6) Grafting to a support

Generally, hydrogels prepared by bulk polymerization have inherent weak structure. To improve the mechanical properties of a hydrogel, it can be grafted on surface coated onto a stronger support. This technique involves the generation of free radicals onto a stronger support surface and then polymerizing monomers directly onto it as a result a chain of monomers are covalently bonded to the support (Das, 2013).

7) Physical cross-linking

It is the most common and easy routes for hydrogel formation by cross linking of polymers through physical interactions. This physical cross linking includes interaction of ions such
as hydrogen bonding, polyelectrolyte complexation and hydrophobic association. The various methods used in physically cross-linked hydrogels preparation are:-

- **Heating/cooling a polymer solution**

It is prepared by cooling hot solutions of gelatin or carrageenan to form physically cross-linked gels. The gel formation is due to association of the helices, helix-formation, and forming junction zones. Some of the examples are polyethylene glycol-polylactic acid hydrogel and polyethylene oxide-polypropylene oxide (Flowerlet,2014).

- **Complex coacervation**

Formation of complex coacervate gels by mixing of polyanions with a polycations. The underlying principle of this method is that polymers with opposite charges stick together and form soluble and insoluble complexes depending on the concentration and pH of the respective solutions. One such example is coacervating polyanionic xanthan with polycationic chitosan (Madolia and Sheo, 2013).

- **Ionic interaction**

Addition of di- or trivalent counter ions in ionic polymer leads to cross linking between polymers. This method underlies the principle of gelling polyelectrolyte solution (e.g. Na^+ alginate-) with a multivalent ion of opposite charges (e.g. Ca^{2+} + $2Cl^-$). Some other examples are chitosan-polylysine,

chitosan-glycerol phosphate salt, and chitosan dextran hydrogels.

- **Hydrogen Bonding**

A hydrogen bond is formed through the association of electron deficient hydrogen atom and a functional group of high electron density. Example, a hydrogel can result from hydrogen bond formation between PA and PNVP. The factors which affect the hydrogels are the molar ratio of each polymer, polymer concentration, the type of solvent, the solution temperature, and the polymer structure.

- **Chemical cross-linking**

In this process the use of a crosslinking agent to link two polymer chains and grafting of monomers on the backbone of the polymers takes place. The cross-linking of natural and synthetic polymers can be achieved through the reaction of their functional groups (such as OH, COOH, and NH_2) with cross-linkers such as aldehyde (e.g. glutaraldehyde, adipic acid dihydrazide). IPN is a polymerize monomer within another solid polymer to form interpenetrating network structure (Chauhan et al., 2012).

Desired features of hydrogel material

The functional features of an ideal hydrogel material can be listed as follows.

- Must have highest absorption capacity (maximum equilibrium swelling) in saline.
- Must show desired rate of absorption (preferred particle size and porosity) depending on the application requirement.
- Must exhibit the highest absorbency under load (AUL).
- Should show lowest soluble content and residual monomer.
- Have lowest price.
- Must have highest durability and stability in the swelling environment and during the storage.
- Must have highest biodegradability without formation of toxic species following the degradation.
- pH-neutrality after swelling in water.
- Colorless, odorless, and absolutely non-toxic.
- Must have good photo stability.
- Re-wetting capability (if required) the hydrogel has to be able to give back the imbibed solution or to maintain it; depending on the application requirement (e.g., in agricultural or hygienic applications) (Chien, 2009).

Properties of Hydrogels

The multitude of hydrogels available leaves numerous choices for polymeric formulations. The best approach for developing a hydrogel with the desired characteristics for biomedical application is to correlate the macromolecular structures of the polymers available with the swelling and mechanical characteristics desired. The swelling mechanical, diffusional, and biomedical characteristics of PHEMA (Polyhydroxyethylmethylacrylate) gels have been studied extensively. The properties of these hydrogels are dependent upon their method of preparation, polymer volume fraction, degree of cross-linking, temperature, and swelling agent. The most widely used hydrogel is water swollen, crosslinked PHEMA, which was introduced as a biological material. The hydrogel is inert to normal biological processes, shows resistance to degradation, is permeable to metabolites, is not absorbed by the body, is biocompatible, with stands heat sterilization without damage, and can be prepared in a variety of shapes and forms (Peppas, 2001).

1) Swelling properties

All polymer chains in hydrogels are crosslinked to each other either physically or chemically and thus, considered as one molecule regardless of its size. For this reason, there is no concept of molecular weight of hydrogels and therefore, sometimes called infinitely large molecules or super macromolecules. A small change in environmental condition may trigger fast and reversible changes in hydrogel. The alteration in environmental parameters like pH, temperature, electric signal, presence of enzyme or other ionic species may lead to a change in physical texture of the hydrogel. These changes may occur at macroscopic level as precipitate formation, changes in size and water content of hydrogels. The difference in concentration of mobile ions in the hydrogel interior relative to external solution (osmotic pressure), changes in solvent pH, drives the volume change. Hydrogels with acidic or basic functional groups respond to the fluctuations in the external environmental pH. Degree of ionization of the functional groups dictates its swelling profile and hence the volume change. Polyacrylic acid is such type of pH sensitive hydrogel where swelling ratio changes due to the ionization of carboxyl groups on the polymer chain (Das, 2013).

2) Biocompatible properties

It is important for the hydrogels to be biocompatible and nontoxic in order to make it applicable in biomedical field. Most polymers used for this purpose must pass cytotoxicity and in-vivo toxicity tests. Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application. Biocompatibility consists basically of two elements:

(a) bio-safety i.e. appropriate host response not only

systemic but also local (the surrounding tissue), the absence of cytotoxicity, mutagenesis, and/or carcinogenesis.
(b) bio-functionality i.e. the ability of material to perform the specific task for which it is intended.
This definition is particularly relevant in tissue engineering since the nature of tissue construct is to continuously interact with the body through the healing and cellular regeneration process as well as during scaffold degradation. If this requirement is not met, the hydrogel can be fouled or there may be damage and scarring to connected tissues, whether those tissues are immediately adjacent or linked by vasculature. Toxic chemicals that may be used in the polymerization of synthetic hydrogels present a challenge for in vivo biocompatibility if conversion is not 100%. Furthermore, initiators, organic solvents, stabilizers, emulsifiers, unreacted monomers and cross-linkers used in polymerization and hydrogel synthesis may be toxic to host cells if they seep out to tissues or encapsulated cells.[2] Though natural polymers are frequently regarded to have superior biocompatibility over synthetic one, yet the presence of synthetic crosslinkers and initiators used in the polymerization of naturally derived monomers and pre-polymers are subject to the same toxicity concerns as purely synthetic hydrogel (Yin et al., 2010).

Evaluation of biocompatibility

1) In vitro cell culture tests are often used to screen the tissue compatibility of implantable devices. The cell culture methods are also known as cytotoxicity tests. Three primary cell culture assays are used to evaluate biocompatibility of the hydrogels:
a) Elution (extract dilution)
b) Direct contact
c) Agar diffusion
These assays are described in the US Pharmacopeia and in standards published by the International Standards Organization. The in vivo assessment of tissue compatibility of a hydrogel is the knowledge of chemical composition of the biomaterial and the conditions of tissue exposure (including nature, degree, frequency and duration of exposure). Principles generally applied to the biological evaluation of hydrogels are described as follows:
The material(s) of manufacture; Intended additives, process contaminants, and residues; Leachable substances; Degradation products; other components and their interactions in the final product determine the properties and characteristics of the final product. Most of the problems associated with hydrogel regarding toxicity, are the unreacted monomers, oligomers and initiators that leach out during application (Das, 2013 & Shetye et al., 2015).

Modifying the kinetics of polymerization and extensive washing of the resulting hydrogel can reduce the toxicity.

The formation of hydrogels without any initiators and using alternate path like radiation may eliminate the problem of the residual initiator (Das, 2013 & Shetye et al., 2015).

3) Mechanical properties

Mechanical properties of hydrogels are very important from the pharmaceutical and biomedical point of view. The evaluation of mechanical property is essential in various biomedical applications viz. ligament and tendon repair, wound dressing material, matrix for drug delivery, tissue engineering and as cartilage replacement material. The mechanical properties of hydrogels should be such that it can maintain its physical texture during the delivery of therapeutic moieties for the predetermined period of time. Changing the degree of cross linking the desired mechanical property of the hydrogel could be achieved. Increasing the degree of cross linking a stronger hydrogel could be achieved though the higher degree of cross linking decreases the % elongation of the hydrogels creates a more brittle structure. Hence there is an optimum degree of cross linking to achieve a relatively strong and yet elastic hydrogel. Copolymerization with co-monomer, may result into hydrogen bonding within the hydrogel which has also been utilized by many researchers to achieve desired mechanical properties (Grassi et al., 2009).

Table 1: Hydrogel-based products on the market

Product	Hydrogel composition	Indication	Product Manufactured by/Marketed by	Review	References
Cervidil® vaginal (PGE2)	Poly(ethylene oxide) and urethane	Initiation and/or continuation of cervical ripening (at or near term	Controlled Therapeutics, UK; marketed by insert Forest Pharmaceuticals St Louis, MO, USA)	Product contains 10 mg Dinoprostone and exhibits in vivo release rate of ~0.3 mg h–1	http://www btgplc.com
SQZ Gel oral release system	Chitosan and polyethylene glycol	Hypertension	Macromed (Sandy, UT, USA)	pH-Sensitive, once a-day tablet of Dilteazem Hydrochloride	http://www. macromed.com
Aquamere™	Interpolymers of PVPand PVPgrafted copolymers with urethane	Skincare, topical and oral drug delivery	Hydromer (Somerville, NJ, USA) Inte		http://www. hydromer.com
Hycore-V™ and Hycore-R™		Vaginal and rectal infections, respectively	™ CeNeS Drug (Irvine, UK) Delivery	Localized delivery of Metronidazole	http://www. cenes.com
Smart C Hydrogel	Liquid Poly(acrylic acid) (oxypropylene-, co-oxyethylene) glycol.	Used for development of ophthalmic, buccal, nasal, vaginal and transdermal.	MedLogi Global™ (Plymouth, UK)	Mucoadhesive composition that undergoes sol–gel transformation at body temperature,	http://www medlogic.com. Aqua

Applications:

1) Hydrogels have extensive application in regenerative medicine, because of its structural similarity to that of extracellular matrix As a result they can be effectively applied in the body. Some of the other properties which support their wide application are its biocompatibility, mechanical strength, swelling properties, muco adhesivity, haemocompatibility etc. Some of its applications are:
2) They are used as scaffolds in tissue engineering.
3) Environmentally sensitive hydrogels which are known as smart gels or intelligent gels. These hydrogels have the ability to sense pH, temperature or the concentration of metabolite and release their load as a result of such a change.
4) Those which are responsive to specific molecules such as glucose or antigens can be used as biosensors (Peppas et al., 1999).
5) They can also be used as contact lenses e.g. silicone hydrogels, polyacrylamide.
6) 6. EEG uses hydrogels composed of cross linked polymers (Satish et al., 2006).

Several applications of hydrogels

7. Biomedical applications of hydrogels

i. Contact lenses and ocular implants

Soft contact lenses are one of the most widely used applications of hydrogels. One of the main characteristics is the comfort since the hydrogel perfectly adapts to the global ocular curvature. Also they allow atmospheric oxygen to reach the cornea by dissolving in the water of lens. The PHEMA-based hydrogels are extensively used as soft contact lenses due to their excellent biocompatibility and mechanical properties. Several companies subsequently developed a range of hydrogel contact lens materials containing various monomers such as N-VP, MAA, MMA and glyceryl methacrylate among others which are incorporated to increase the water content of hydrogel contact lens, in the attempt to obtain materials with suitable mechanical properties, which allow them to resist the force of the eyelid along with an elevated permeability to oxygen. Medicated contact lenses are attracting keen interest for ophthalmic drug delivery, as they significantly increase residence time of the drug in the precorneal area because of the geometric barrier provided by the contact lenses to the drug when it diffuses out from the gel matrix into the tear film (Swarbrick, 2013).

ii. Tissue regeneration and tissue engineering

Hydrogels have a micro-architecture similar to that of natural extracellular matrix (ECM hence these have been utilized to support and assist restoration of range of tissues such as bones, cartilage, nerves, vessels and skin (Shuanhong et al., 2016).[16]

Scaffolds act as three-dimensional artificial templates in which the tissue targeted for reconstruction is cultured to grow onto. The high porosity of hydrogel allows for the diffusion of cells during migration, as well as the transfer of nutrients and waste products away from cellular membranes (Shuanhong et al., 2016).

The micronized hydrogels (microgels) have been used to deliver macromolecules like phagosomes into cytoplasm of antigen-presenting cells. The release is because of acidic conditions. Such hydrogels mold themselves to the pattern of membranes of the tissues and have sufficient mechanical strength. This property of hydrogels is also used in cartilage repairing (Bindu et al.,. 2012)

Examples of various tissue engineering employing various hydrogels have been provided below: Collagen-coated tissue culture inserts are used for growing three- dimensional corneal implant, tracheal gland cells etc. Poly (lactic-co-glycolic acid) (PLGA) polymer foams are seeded with preadipocytes for the epithelial cell culture of the breast. Porous scaffolding (e.g. filter, swatch of

nylon, transwell, biodegradable microcarrier) coated with fibrillar collagen, ideally type III collagen mixed with fibronectin or with Matrigel are used for the culture of the normal mature liver cells (polyploidy liver cells) (Pal et al., 2012).

iii. Biosensors

Hydrogels are used in the preparation of biosensors, acting as supports for immobilization of enzymes. The microenvironment that surround the immobilized enzyme can act as a barrier for the free diffusion of molecules but it also may attract or repel the substrate or product to its surface thus concentrating or depleting the immediate vicinity of the enzyme. The Verones group has prepared diverse biosensors for enzyme immobilization, one of them being an amperometric sensor constructed by using PEG modified glucose oxidase immobilized in a PVA cryogel membrane, obtained by a freezing-thawing cyclic process. This sensor allows for determination of glucose electrochemically by measuring the hydrogen peroxide production as a result of the enzymatic reaction, which can be used in the determination of serum glucose. In view of the importance of sugar in foods and beverage industries, it is rather important to have e a detection method that is simple, sensitive and fast. Thus a biosensoric method of fructose determination has been developed based on polymer matrix of Polyethyleneimine (PEI) and Polycarbamoylsulphonate hydrogel used for immobilization of the enzyme D-fructose dehydrogenase (Swarbrick, 2013).

iv. Wound dressings

Hydrogel dressings are available in several forms including amorphous hydrogels (that can take up the shape of the wound), saturated gauzes or hydrogel sheets. Hydrogels that are shapeless or amorphous are composed of insoluble non-crosslinked hydrophilic polymers such as polyvinyl pyrrolidine or polyacrylamide in the form of a gel containing 70-95% water. Amorphous hydrogels may be packaged in tubes, spray bottles or foil packs. The gel is applied directly to the wound and is usually covered with a secondary dressing (for example foam or gauze). Exudate is absorbed into the gel whilst moisture evaporates through the secondary dressing. Saturated gauzes, obtained when gauze is impregnated with amorphous hydrogel, are sometimes used to fill the dead space in deeper wounds. Hydrogel sheets do not need a secondary dressing as a semi-permeable polymer film backing which may or may not have adhesive borders, controls the amount of water vapour transmitted through the dressing. (Aulton, 2001)

They are nonadherent dressings that through semipermeable film allow a high rate of evaporation (and cooling) without compromising wound hydration. This makes them useful in burn treatment. Hydrogels are also very useful in hairy are where entrapment of hair into the dressing would not be traumatic (Remington).

v. Oral

The oral administration of drugs through hydrogels is one of the routes that have aroused the highest interest among researchers, which have tackled this form of administration, mainly through two strategies. One of these strategies is the development of mucoadhesive hydrogels that interact with mucous as a result of physical entanglement and secondary bonding, mainly through hydrogen bonding and Van der Waals forces, due to the presence of hydroxyl, carboxyl, amine, and amide groups on the surface of polymeric matrix, thus prolonging the residence time of the dosage form on the absorption site. The use of buccal cavity for placing devices of controlled drug release allows it to avoid the first pass metabolism and prevents degradation of the drug in the GIT (Swarbrick, 2103).

Another area of the GI tract being considered for hydrogel drug delivery is the colon. One advantage that the colon has is that there is less proteolytic activity there compared to the small intestine. Various hydrogels, particularly enzyme-sensitive hydrogels, are currently being considered and developed for use in colon-specific drug delivery (Chien, 2009).

Rectal Delivery has been used to deliver many types of drugs for treatment of diseases associated with the rectum, such as hemorrhoids. This route is an ideal way to administer drugs suffering heavy first-pass metabolism (Ahmed, 2015).

vi. Super porous hydrogel systems

These swellable systems differ sufficiently from the conventional types to warrant separate classification. In this approach to improve gastric retention time

(GRT) super porous hydrogels of average pore size >100 micro miter, swell to equilibrium size within a minute due to rapid water uptake by capillary wetting through numerous interconnected open pores. They swell to a large size (swelling ratio: 100 or more) and are intended to have sufficient mechanical strength to withstand pressure by gastric contraction. This is advised by co-formulation of hydrophilic particulate material (Nayak et al., 2010).

vii. Sealant

Research into the use of self-healing hydrogels has revealed an effective method for mitigating acid spills through the ability to selectively crosslink under acidic conditions. Research carried out by the University of California San Diego, various surfaces were coated with self-healing hydrogels and then mechanically damaged with 300 micrometer wide cracks with the coatings healing the crack within seconds upon exposure to low pH buffers. The hydrogels also can adhere to various plastics due to hydrophobic interactions. Both findings suggest the use of these hydrogels as a sealant for vessels containing corrosive acids (Phadke et al., 2012).

CONCLUSION:

Hydrogels are hydrophilic polymeric networks and they are widely used in the medical industry as dressings and even in tissue regeneration and tissue engineering because they are capable of absorbing large amounts of water or biological liquids. For the formulation of hydrogel-based drug products, the major considerations are their mechanical strength and response-time in a physiological environment. The success of hydrogels as delivery systems can be judged by several marketed preparations (Table 1). The more appreciated delivery systems are the fast responding hydrogels which release maximum drug in less time while maintaining the structural integrity. The delivery of drugs would significantly improve the Progress and success in such aspects through hydrogels to certain desired locations in the body.

ACKNOWLEDGEMENT:

The authors wish to thank the Dr. Tilak Raj Bhardwaj, Dean of School of Pharmacy and Emerging Sciences, Baddi University for their support and encouragement.

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