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Asian Journal of Pharmaceutical Education and Research

Vol -2, Issue-2, February-April 2013

ISSN: 2278 – 7496

REVIEW ARTICLE

A REVIEW OF HYDROGEL AS A DRUG CARRIER

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Article Received on 12 January 2013.

Revised on 15 January 2013,

Accepted on 02 February 2013

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Abstract:
Hydrogels are three-dimensional networks formed from hydrophilic homopolymers, copolymers, or macromers (preformed macromolecular chains) crosslinked to form insoluble polymer matrices. These polymers, generally used above their glass transition temperature (Tg), are typically soft and elastic due to their thermodynamic compatibility with water and have found use in many biomedical applications. Synthetic hydrogels offer a possibly effective and convenient way to administer these compounds. Hydrogels are hydrophilic, three-dimensional networks, which are able to imbibe large amounts of water or biological fuids and thus resemble, to a large extent, a biological tissue. They are insoluble due to the presence of chemical (tie-points, junctions) and/or physical crosslinks such as entanglements and crystallites. These materials can be synthesized to respond to a number of physiological stimuli present in the body, such as pH, ionic strength and temperature. Though far from extensive, the aim of this review article is to study the various method of preparation of hydrogels and there application in pharmaceutical field.

Keywords: Hydrogel, Xerogels, crosslinled polymer.

Introduction

Hydrogels are three-dimensional networks formed from hydrophilic homopolymers, copolymers, or macromers (preformed macromolecular chains) crosslinked to form insoluble polymer matrices. These polymers, generally used above their glass transition temperature (Tg), are typically soft and elastic due to their thermodynamic compatibility with water and have found use in many biomedical applications[1]. Synthetic monomers used in tissue engineering include, among others, poly(ethylene glycol) (PEG), poly(vinyl alcohol) (PVA), and polyacrylates such as poly(2-hydroxyethyl methacrylate) (PHEMA). Biological hydrogels have been formed from agarose, alginate, chitosan, hyaluronan, fibrin, and collagen, as well as many others[2,3]. The hydrophilic/hydrophobic balance of the hydrogels, the degree of cross-linking, and especially, the degree of ionization and its interaction with counterions are the important parameters which control the equilibrium swelling, dimensional change and the release patterns of drugs from these carriers[4]. The water holding capacity of the hydrogels arise mainly due to the presence of hydrophilic groups, viz. amino, carboxyl and hydroxyl groups, in the polymer chains. According to Hoffmann, the amount of water present in a hydrogel may vary from 10% to thousands of times of the weight of the xerogel [5]. A xerogel is a solid formed from a gel by drying with unhindered shrinkage. Xerogels usually retain high porosity (15-50%) and enormous surface area (150–900 m^2/g), along with very small pore size (1-10 nm). When solvent removal occurs under hypercritical (supercritical) conditions, the network does not shrink and a highly porous, low-density material known as an *aerogel* is produced. Heat treatment of a xerogel at elevated temperature produces viscous sintering (shrinkage of the xerogel due to a small amount of viscous flow) and effectively transforms the porous gel into a dense glass.[6].

Hydrogels can be classified into two groups depending on the nature of the crosslinking reaction. If the crosslinking reaction involves formation of covalent bonds, then the hydrogels are termed as permanent hydrogel. The examples of permanent hydrogels include pMMA and pHEMA. If the hydrogels are formed due to the physical interactions, viz. molecular entanglement, ionic interaction and hydrogen bonding, among the polymeric chains then the hydrogels are termed as physical hydrogels [5,7]. The examples of physical hydrogels include polyvinyl alcohol-glycine hydrogels, gelatin gels and agar-agar gels. Hydrogels can also be categorized as conventional and stimuli responsive hydrogels [8]. Conventional hydrogels are the crosslinked polymer chains which absorb water when put in an aqueous media and there is no change in the equilibrium swelling with the change in the pH, temperature or electric field of the surrounding environment

while the stimuli responsive hydrogels are the polymeric networks which change their equilibrium swelling with the change of the surrounding environment. pH sensitive hydrogels have been used since long in the pharmaceutical industry as an enteric polymer. The enteric polymers/ hydrogels generally are used to either protect the stomach mucosa from the gastric irritant drugs (e.g. aspirin) or to protect the acid-labile drugs (e.g. penicillin G, erythromycin) from the harsh environment of the stomach [9]. pH sensitive hydrogels have also been used for the development of blood-glucose detection kit and insulin delivery [10]. Temperature sensitive hydrogels are being used in tissue culture. Electric field sensitive hydrogels have been used in artificial muscles, and controlled drug delivery systems [11].

Mechanism of network formation

Gelation refers to the linking of macromolecular chains together which initially leads to progressively larger branched yet soluble polymers depending on the structure and conformation of the starting material. The mixture of such polydisperse soluble branched polymer is called 'sol'. Continuation of the linking process results in increasing the size of the branched polymer with decreasing solubility. This 'infinite polymer' is called the 'gel' or 'network' and is permeated with finite branched polymers. The transition from a system with finite branched polymer to infinite molecules is called 'sol-gel transition' (or 'gelation') and the critical point where gel first appears is called the 'gel point' [12]. Different types of gelation mechanism are summarised in Figure 1. Gelation can take place either by physical linking (physical gelation) or by chemical linking (chemical gelation). Physical gels can be sub categorised as strong physical gels and weak gels. Strong physical gel has strong physical bonds between polymer chains and is effectively permanent at a given set of experimental conditions. Hence, strong physical gels are analogous to chemical gels. Examples of strong physical bonds are lamellar microcrystals, glassy nodules or double and triple helices. Weak physical gels have reversible links formed from temporary associations between chains. These associations have finite lifetimes, breaking and reforming continuously. Examples of weak physical bonds are hydrogen bond, block copolymer micelles, and ionic associations. On the other hand, chemical gelation involves formation of covalent bonds and always results in a strong gel. The three main chemical gelation processes include condensation, vulcanisation, and addition polymerisation.

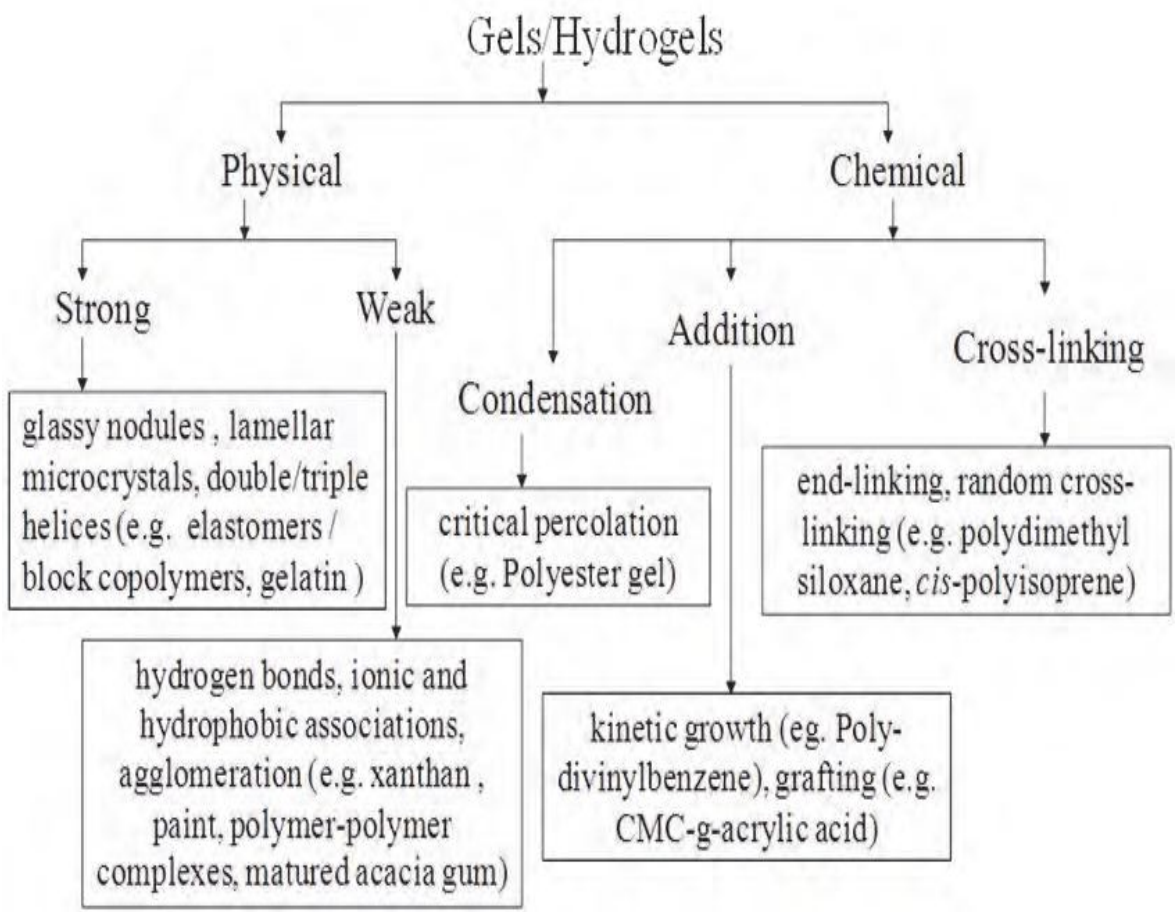

Fig. 1. Classification of gelation mechanism and relevant examples.

CHARACTERIZATION OF HYDROGELS

Generally hydrogels are characterized for their morphology, swelling property and elasticity. Morphology is indicative of their porous structure. Swelling determines the release mechanism of the drug from the swollen polymeric mass while elasticity affects the mechanical strength of the network and determines the stability of these drug carriers [13]. Some of the important features for characterization of hydrogels are as follows:

Morphological characterization

Hydrogels are characterized for morphology which is analyzed by equipment like stereomicroscope. Also the texture of these biomaterials is analyzed by SEM to ensure that hydrogels, especially of starch, retain their granular structures [14].

Light scattering

Gel permeation chromatography coupled on line to a multi angle laser light scattering (GPC-MALLS) is a widely used technique to determine the molecular distribution and parameters of a polymeric system. Hydrogel in a polymeric system can be quantified using this technique [15]. This technique is widely used in quantifying the hydrogels of several hydrocolloids such as gum arabic, gelatin and pullulan [16,17] It can be demonstrated how mass recovery data obtained from GPC-MALLS correlate with actual amount of hydrogel obtained for dextran radiation in solid state [16] (Figure 2).

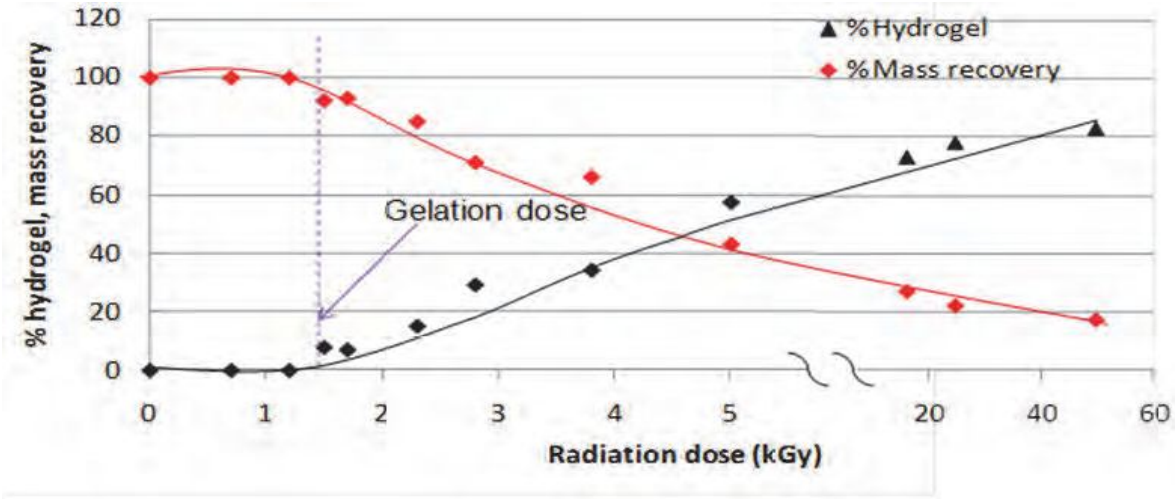

Fig. 2. Correlation between mass recovery data obtained from GPC-MALLS for dextran and amount of hydrogel formed as a function of radiation dose.

FTIR

FTIR (Fourier Transform Infrared Spectroscopy) is a useful technique for identifying chemical structure of a substance. It is based on the principle that the basic components of a substance, i.e. chemical bonds, usually can be excited and absorb infrared light at frequencies that are typical of the types of the chemical bonds. The resulting IR absorption spectrum represents a fingerprint of measured sample. This technique is widely used to investigate the structural arrangement in hydrogel by comparison with the starting materials. [18,19]

Swelling measurement

The swelling measurement of hydrogel was carried out as follows. Pieces of xerogel were immersed into 250 ml distilled water. The samples of swollen hydrogel were weighed after removal of surface water using filter paper at designed time intervals. Data presented in this experiment were the mean values of triplicate measurements. Results were calculated according to the following equation:

$$Q = \frac{W_s}{W_d}$$

Where Ws is the mass of the hydrogel in the swollen state, Wd is the mass of the hydrogel in the dried state and Q is equilibrium swelling ratio.

Scanning Electron Microscopy (SEM)

SEM can be used to provide information about the sample's surface topography, composition, and other properties such as electrical conductivity. Magnification in SEM can be controlled over a range of up to 6 orders of magnitude from about 10 to 500,000 times. This is a powerful technique widely used to capture the characteristic 'network' structure in hydrogels [20-22].

PREPARATION METHODS OF HYDROGELS

Hydrogels are polymeric networks. This implies that crosslinks have to be present in order to avoid dissolution of the hydrophilic polymer chain in aqueous solution. The various methods for crosslinking are as follows:

Crosslinking of Polymers: - In this method chemically crosslinked gels are formed by radical polymerization of low molecular weight monomers, or branched homopolymers, or copolymers in the presence of crosslinking agent. This reaction is mostly carried out in solution for biomedical applications [23].

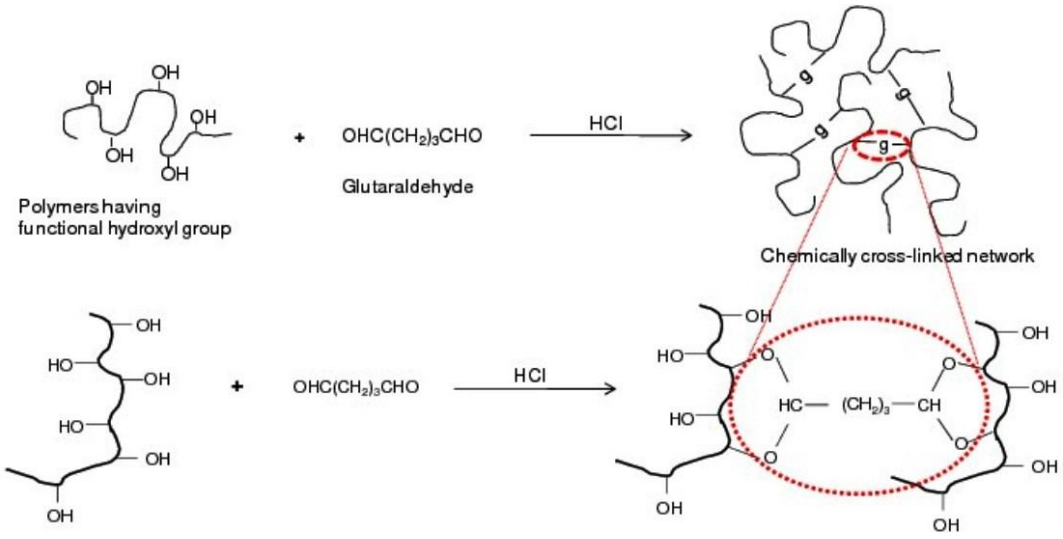

Fig. 3. Schematic illustration of using chemical cross-linker to obtain cross-linked hydrogel network.

Copolymerization/Crosslinking Reactions: -

Copolymerization reactions are used to produce polymer gels, many hydrogels are produced in this fashion, for example poly (hydroxyalkyl methylacrylates).

Crosslinking by High Energy Radiation: - High energy radiation, such as gamma and electron beam radiation can be used to polymerize unsaturated compounds. Water soluble polymers derivatized with vinyl groups can be converted into hydrogels

using high energy radiation.[24]

Complex coacervation

Complex coacervate gels can be formed by mixing of a polyanion with a polycation. 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 (Figure 4). One such example is coacervating polyanionic xanthan with polycationic chitosan (Esteban & Severian, 2000; 2001; 1999). Proteins below its isoelectric point are positively charged and likely to associate with anionic hydrocolloids and form polyion complex hydrogel (complex coacervate) [25]

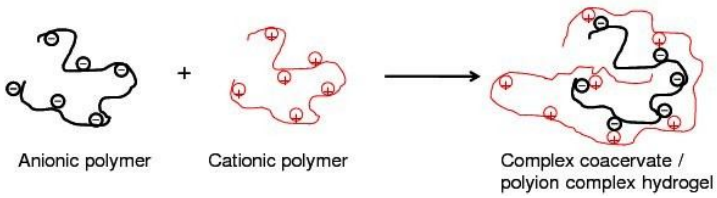

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Fig. 4. Complex coacervation between a polyanion and a polycation.

Crosslinking Using Enzymes: - Recently a new method was published using an enzyme to synthesize PEG-based hydrogels. A tetrahydroxy PEG was functionalized with addition of glutaminyl groups and networks were formed by addition of transglutaminase into solution of PEG and poly (lysine-cophenylalanine) [26].

Several techniques have been reported for the synthesis of hydrogels A chromia alumina hydrogel was prepared as in the preceding example except that ammonium nitrate was substituted as ammonium sulfate as base exchange solution. A portion of washed hydrogel was impregnated in 13 liters of an aqueous solution maintaining 775 g of copper acetate and 223 g of potassium acetate. The impregnated hydrogel was dried in 100% steam at 260-270o F. and tempered 4 hours at 1100o F. in a hydrogen atmosphere [27]

- Hydrogel sheets based on poly(vinyl alcohol) (PVA) and poly(vinyl acetate) (PVAc) have been prepared by the technique of acetalization of PVA using formaldehyde and grafting of acrylic acid onto PVAc by gamma irradiation. PVA hydrogel (PVAB) sheets have been prepared in geometrically stable shapes by compression moulding process.[28].
- Semicrystalline crosslinked poly (vinyl alcohol) hydrogels in the form of films were prepared by electron beam irradiation and a subsequent slow dehydration process at 25 ± 1°, using various drying agents [29].As a result, hydrogels synthesized contain weakly acidic groups like carboxylic acids, or a weakly basic group like substituted amines, or a strong acidic and basic group like sulfonic acids, and quaternary ammonium compounds.
- The synthesis of hydrogel in industry is Consist of solution and reversed suspension and reversed emulsion polymerizations. Figure: 5 shows a block diagram of a generic solution polymerization process. This figure represents the major procedure of super absorbent polymer manufacturing in the laboratory and industrial scales [30].

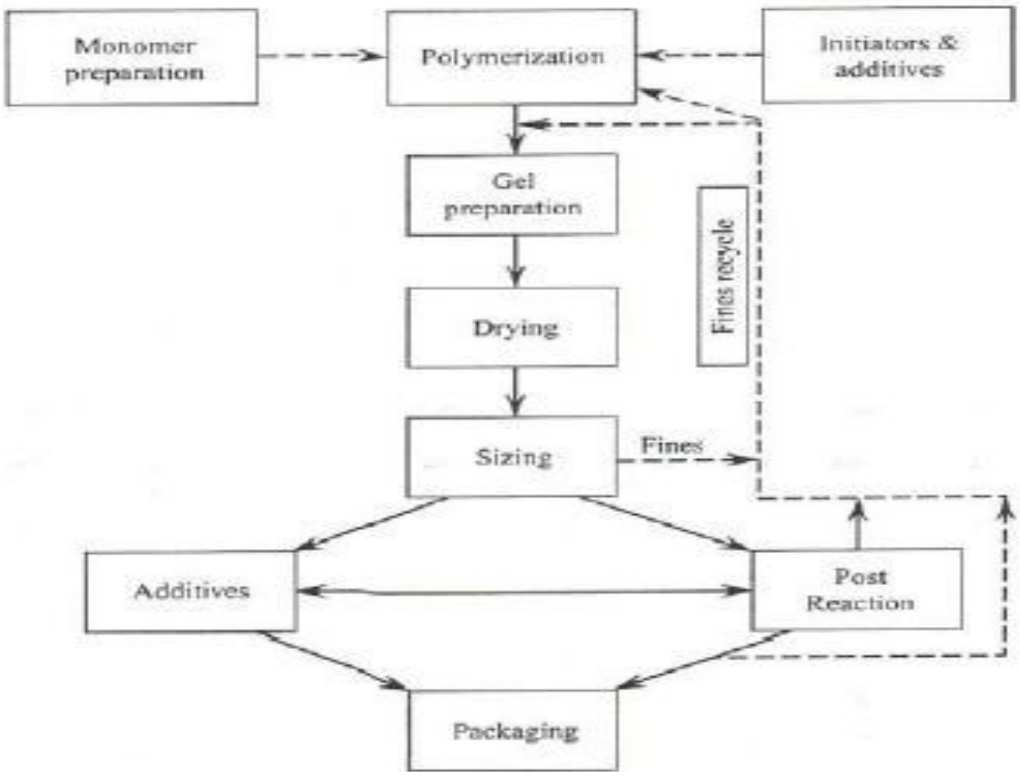

Fig. 5: Hydrogel preparation block diagram

(solution polymerization procedure) [30]

ADVANTAGES

- Entrapment of microbial cells within polyurethane hydrogel beads with the advantage of low toxicity.
- Hydrogel is more elastic and stronger than available hydrogels of similar softness. Poly (methyl acrylate-co-hydroxyethyl acrylate) hydrogel implant material of strength and softness.
- Hydrogel-based microvalves have a number of advantages over conventional microvalves, including relatively simple fabrication, no external power requirement, no integrated electronics, large displacement (185 μm), and large force generation (22 mN).
- Environmentally sensitive hydrogels. These 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.
- Natural hydrogel materials are being investigated for tissue engineering, these materials include agarose, methylcellulose, hylaronan, and other naturally derived polymers [31,32].

DISADVANTAGES

- The main disadvantages are the high cost and the sensation felt by movement of the maggots.
- Its disadvantage include thrombosis at anastomosis sites and the surgical risk associated with the device implantation and reterieval.
- Hydrogels are nonadherent; they may need to be secured by a secondary dressing.
- Disadvantages of hydrogel in contact lenses are lens deposition, hypoxia, dehydration and red eye reactions.

Application of Hydrogels [81]

- **Drug delivery in GI tract** - hydrogels delivers drugs to specific site in the GIT. In presence of micro flora drug loaded with colon specific hydrogels show tissue specificity and change in the pH or enzymatic action which causes degradation of drug.
- **Rectal Delivery** – hydrogels showing bioadhesive properties are used for recatal deug delivery.
- **Transdermal delivery –** hydrogels can be used as controlled release devices in the filed of wound dressing due to it swelling properties. Hydrogels based formulation are being explored for transdermak iontophoresis to obtain enhanced permeation of products.
- **Subcutaneous delivery –** anticancer drugs are mainly used for the subcutaneous delivery. Implantable vegetable are now leading towards the development of biodegradable system which don't require surgical removal once the drug administered.
- **Gene delivery –** change in composition of hydrogels leads to effective targeting and delivery of nuclei acids to specific cells for gene therapy. Hydrogels has more potential application in the treatment od many genetic or acquired disease and condition.
- **Cosmetology –** hydrogels when implanted into breast accentuate them for aesthethic reason. These implant hace silicon elastomer shell and are filled with hydroxyl propyl cellulose polysaccharide gels.
- **Wound healing –** modified polysaccharide found in cartilage is used in formation of hydrogels to treat cartilage defects. For example, the hydrogel of gelatin and polyvinyl alcohol together with blood coagulants are formulated.
- **Industrial application** - mainly used as absorbents for industrial effluents like methylene blue dye.

- **Tissue Enginerring –** micronized hydrogels are used to deliver macromolecus into cytoplasm of antigen presenting cells. Natural hydogles material is used for tissue engineering include agaraose, methylcellulose and other naturally derived products.
- **Potein drug delivery –** hydrogels which show better complicance and form in situ polymeric network and release protein slowly.
- **Tropical drug delivery –** instead of conventional creams, hydrogels formulation are employed to deliver active components like desonide, a synthetic corticosteroids used as an anti – inflammatory for better patient compliance.

Pharmaceutical application of hydrogels

Hydrogels have been attempted extensively to achieve ideal drug delivery systems with desirable therapeutic features [33]. The unique attractive physicochemical and biological characteristics of hydrogels, along with their huge diversity, collectively, have led to considerable attention to these polymeric materials as excellent candidates for delivery systems of therapeutic agents [34-37]. Pharmaceutical hydrogels have been categorized according to a variety of criteria mainly including, rout of administration [38–42], type of material being delivered [43-46], release kinetics [47–50], etc. Therefore, a common classification system for the therapeutic hydrogel formulations might not be found within the literature. Nonetheless, a classification based on the route of administration of the hydrogel drug delivery systems, seems to include the vast area of these therapeutic materials. Accordingly, the pharmaceutical hydrogels can be classified as: i) oral hydrogel systems [51-55], ii) transdermal and implantable hydrogel systems [55-58] iii) topical and transdermal hydrogel systems [59-63], iv) hydrogel devices for gastrointestinal (GI) drug delivery [64-70], and v) hydrogel-based ocular delivery systems [71-73]. Furthermore, hydrogel-based formulations applied via other routs are also noteworthy. In this regard, novel approaches to improve bioavailability through nasal [74,75] and vaginal [76,77] routes using hydrogels have been presented

RECENT TRENDS OF HYDROGEL

Microparticles of Poly methacrylic acid and novel semi-interpenetrating network composed of Poly methacrylic acid-alginate (PMAA) were prepared and their application in oral insulin delivery was evaluated. The release kinetics at pH 7.4 exhibited sustained release of insulin for more than 5 hrs in case of PMAA microparticles whereas burst release of insulin (90% of total insulin loaded) within 1 hr of study was observed in the case of PMAAalginate microparticles [78].The new type of hydrogel system *HYPAN* (which is known under the trademark HYPANTM)

is described in some detail here, emphasizing its grades and those properties potentially useful in controlled drug delivery systems. A physical network of crystalline clusters, which fully replace the covalent network typical of other hydrogels, distinguishes *HYPAN* hydrogels. As a result, *HYPAN* hydrogels can be processed by a number of methods unusual for hydrogels, such as extrusion and injection molding[79]. Recent developments in the field of polymer science and technology has led to the development of various stimuli sensitive hydrogels like pH, temperature sensitive, which are used for the targeted delivery of proteins to colon, and chemotherapeutic agents to tumors. Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature sensitive hydrogels can be used for site-specific controlled drug delivery. Hydrogels that are responsive to specific molecules, such as glucose or antigens, can be used as biosensors as well as drug delivery systems. The liposomal drug delivery system developed here enables controlled release of vasodilator and would allow an appropriate time for beginning irradiation treatment to be defined. [80]

CONCLUSION

There are enough scientific evidences for the potentiality of hydrogels in delivery of drug molecules to a desired site by triggering the release through an external stimulus such as temperature, pH, glucose or light. These hydrogels being biocompatible and biodegradable in nature have been used in the development of nano biotechnology products and have marvelous applications in the field of controlled drug delivery as well. That is why these turn-able biomedical drug delivery devices are gaining attention as intelligent drug carriers.

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