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Novel Crosslinking Methods to Design Hydrogels

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Abstract

Hydrogels are presently under consideration as matrices for the controlled bioactive molecules delivery particularly proteins and for living cells encapsulation. For these applications, gels must undergo degradation under physiological conditions. This overview summarized and discussed the various physical and chemical crosslinking methods to design hydrogels that are biodegradable. Highly versatile method to prepare hydrogels with good mechanical stability is chemical crosslinking. However, the crosslinker employed can give undesirable reactions with the bioactive substances present in the hydrogel matrix and are often toxic. So, it required to be removed from the gels before application. Physically crosslinked gels can be developed to overcome these adverse effects. Distortion due to variations in environmental conditions like presence of solute particles, ionic strength, pH, temperature and stress are the major disadvantages of reversible gels.

Key Words: Smoking, Addiction, Bahawalpur community

Introduction

Hydrogels are polymeric network assimilating large amount of water but do not diffuse in water. Cross linking of hydrogels can be achieved via physical or chemical means. Hydrogels retain their configurations during swelling mechanism [1-3]. Hydrogels possess hydrophilic functional groups through which they interact with biological fluids or water. Hydrogels have soft or rubbery nature that looks like living tissue. Swelling properties of hydrogels are attributed to hydrophilic functional groups and they exhibit insolubility in aqueous media due to presence of covalent bonds [1].

Hydrogels have gained considerable significance as controlled drug delivery system due to its desirable properties [4]. Problems related to conventional drug delivery system such as variation in plasma drug level and not able to maintain therapeutic window are overcome by novel drug delivery system (NDDS)[5]. NDDS includes hydrogels, liposomes, noisome, Nano particles, vesicles, micro particles, micelle, dendritic polymers. For controlled drug delivery system, hydrogels fit best to attain the pharmaceutical needs [6].

Now a days, hydrogels have various applications in bio medical fields such as ophthalmological devices, bio sensors and bio medical devices [6]. In order to design system with advanced features of drug delivery, hydrogel properties like loading capability, biodegradability, safety and control in drug release needs to be optimized [7]. Hydrogels also possess variety of biomedical applications in various fields of hygienic industry, tissue engineering, agricultural, diagnostics, cellular immobilization, and biomolecules separation. Sensitive nature and sensitivity to environment makes their used best for controlled drug delivery [8].

Hydrogels must have crosslinks in network to prevent polymer chains dissolution in an aqueous environment due to hydrophilic nature. Various crosslinking methods have been established to prepare hydrogels. These bonds can be either in the crosslinks used to fabricate gel or in polymer backbone. Bonds that are labile can undergo degradation either chemically or enzymatically, in most of the cases by hydrolysis under environmental conditions [9].

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It is definitely of great concern to control the degradation kinetics and developed hydrogels have a low toxicity and a good biocompatibility. The nature of the products formed as a result of degradation can be tailored by a proper selection of the hydrogel precursors [10–13].

In this contribution, various crosslinking methods to fabricate hydrogels are discussed and described. Features along with some applications of the hydrogels are discussed conferred to their method of synthesis. This overview summarized and discussed the various physical and chemical crosslinking methods to design hydrogels that are biodegradable. Highly versatile method to prepare hydrogels with good mechanical stability is chemical crosslinking. However, the crosslinker employed can give undesirable reactions with the bioactive substances present in the hydrogel matrix and are often toxic Hydrogels resulted from physical means of crosslinking shows various problems in loading and drug release because of defected networking while hydrogels synthesized by chemical means are stable in nature that is attributed to covalent bonds present in different chains. Stable hydrogels do not degrade and retain their shape under ordinary pressure [9].

Cross-linking in Hydrogels

Various polymer chains possessed by hydrogel are interconnected by a cross link which act as a bond. In polymer chemistry, crosslinking is taken as a stabilization procedure which causes the polymer chains to form crosslinked network. Physical characteristics of hydrogel are affected by crosslinks' additions between polymer chains [10].

Different polymerization techniques are developed to prepare hydrogel by physical and chemical means [10]. polymerization techniques and involved reactions result in hydrogels with improved chemical, thermal, physical and mechanical properties of prepared hydrogel [11]. Different polymerization techniques are used to fabricate hydrogel are illustrated in figure 1 [3].

Physical Cross-linking

In physical cross-linking, non-covalent interactions are responsible for linking of polymeric chains. Resulting crosslinked network is termed as 'physical gel' or 'reversible gel'.

Due to ease in preparation physical gels have gained enhanced fame in recent years. Secondly, cross-linker which may possess toxic effects is not required for their synthesis. Moreover, these cross-linking agents may also interfere with integrity of various entrapped substances like some proteins and cells. So, they should be eradicated before application [3, 12]. Distortion due to changes in environment like ionic strength, temperature, pH, solute particles present, and stress are the major disadvantages of reversible gels [13]. Methods employed to fabricate physically crosslinked gels are summarized below.

Heating/Cooling Polymer Solution

The most basic method to fabricate physically crosslinked gels is through cooling hot polymers' solution. Examples of employed polymers includes Gelatin, Carrageenan. Synthesis of helix and junction zones as well as alliance of helices is responsible for gel formation. Salts like K+, Na+ etc. cause the aggregation of helices to form a stable gel.

However, block copolymerization achieved via warming a polymer solution can also cause gel synthesis. Examples include Polyethylene glycol-poly lactic acid hydrogel, Polyethylene oxide-polypropylene oxide hydrogels [14].

Cross-linking via Ionic Interaction

Low molecular weight ions are used for the formation of ionic cross-linked polymer matrix. The ions commonly employed are monovalent, divalent or multivalent. Examples include A low molecular multivalent ion citrate at specific pH in aqueous media.

In aqueous solution, the union of chitosan and tri-sodium citrate causes gel beads formation. Coating of complex film of methacrylic acid over beads helps to hinder disintegration in gastric fluids [15]. For ionic crosslinking, polymeric network is not required to have ionic groups. For example: In dextran, there is no ionic binding sites for cations but still potassium ions cause the formation of hydrogels. As the ionic radius of K+ ions completely fix in network made via six oxygen atoms of glucose units in three polymeric chains. Resultantly, a microstructure was fabricated. However, owing to the fact that resulting gel is not stable in water, so it is not applicable for drug delivery [16].

Complex Coacervation

Coacervate gels are fabricated by the association of polyanions with polycations. Basic principle involves the attraction of opposite charged polymers towards each other and binding to form complex. The complexes may be regarded as soluble and insoluble,

on the basis of pH and concentration of respective solutions. Examples include chitosan (Polycationic), xanthan (Polyanionic) [14].

Cross-linking via Hydrogen Bonding

Hydrogen bonding is also used for cross-linking. Hydrogen bonding is employed as one of the best methods to enhance the mechanical characteristics of gels and thus administering more tensile and compressive strength with wider application range [17]. The examples include Poly methacrylic acid and poly acrylic acid are joined via hydrogen bonding to polyethylene glycol. Hydrogen bonding also causes the union of carboxylic group of polys methacylic acid and oxygen of PEG [18].

Physically Cross-linked Hydrogels by Graft and Block Copolymer

Multi-block and graft copolymers form physically cross-linked hydrogels [3]. Blocks and sequences of chemically distinct monomers constitute large block copolymer. Di and tri block copolymers are synthesized by polymerization of two or three different repeating units [19]. Example of block copolymer is PEG and PLGA unite to form tri block copolymer (PEG-PLGA-PEG) [3]. Arrangement of distinct alternating units implanted on polymer backbone synthesize graft copolymer [20]. An example of graft copolymer include In PLGA and poly lactic acid (PLA) [3].

Freeze-Thawing Method

Physically cross-linked hydrogels are synthesized by freeze-thaw cycles. The formation of microcrystals in structure is the basic mechanism underlying this process [14]. The example of this method is: When xanthan solution is passed through freeze-thaw cycles cohesive networks are fabricated with massive strength [21].

Chemical Cross-linking

In chemical cross-linking, the polymers are joined through covalent bonds. As compared to physical gels, the chemically cross-linked gels are more stable and depict excellent mechanical strength [12]. They are also known as ‘chemical’ or ‘permanent’ hydrogels. Their synthesis involves the use of cross-linkers like EGDMA and glutaraldehyde. In order to design hydrogels, the methods employed are described below:

Cross-linking through Radical Polymerization

Chemically crosslinked gels are fabricated by low molecular weight monomers. For example: Polymerization of HEMA and employing EGDMA as a cross-linking agent to form poly (2-hydroxyethyl methacrylate). Presence and content of cross-linking agent can modify the properties of hydrogels. Hydrogels are synthesized using above method employ water soluble polymers which are derivatives of polarizable groups [3].

Cross-linking by Irradiation

In this method hydrogels are synthesized when subjected to high energy radiations like electron beam and gamma rays. The use of cross-linker is not essential as there is formation of free radicals by radiation induced polymerization. Examples of hydrogels that are synthesized using this method are: Poly acrylic acid, PEG, Polyvinyl alcohol [22].

Cross-linking via Chemical Reaction

This technique of making hydrogels through chemical reaction is explained by few examples given below: Glutaraldehyde as cross linker is employed when hydroxyl group bearing water soluble polymer is chemically linked. However, alternative of glutaraldehyde is used as it possesses toxicity. Furthermore, cross-linking of gelatin is reported by the use of poly aldehyde obtained by partial oxidation of dextran [6, 23, 24]. Addition reaction employed to react cross-linker with various functional groups in water soluble polymers. Condensation reaction is used for cross-linking of PEG diamines and alginate with N, N-(3-dimethylaminopropyl)-N-ethyl carbodiimide (EDC) as cross-linking agent [22].

Cross-linking using Enzymes

Hydrogels can be formed by use of enzymes. For example: Cross-linking between functionalized PEG and lysine-containing polypeptide is obtained by using trans glutaminase as an enzyme and the resultant gel can swell up to 90% [25].

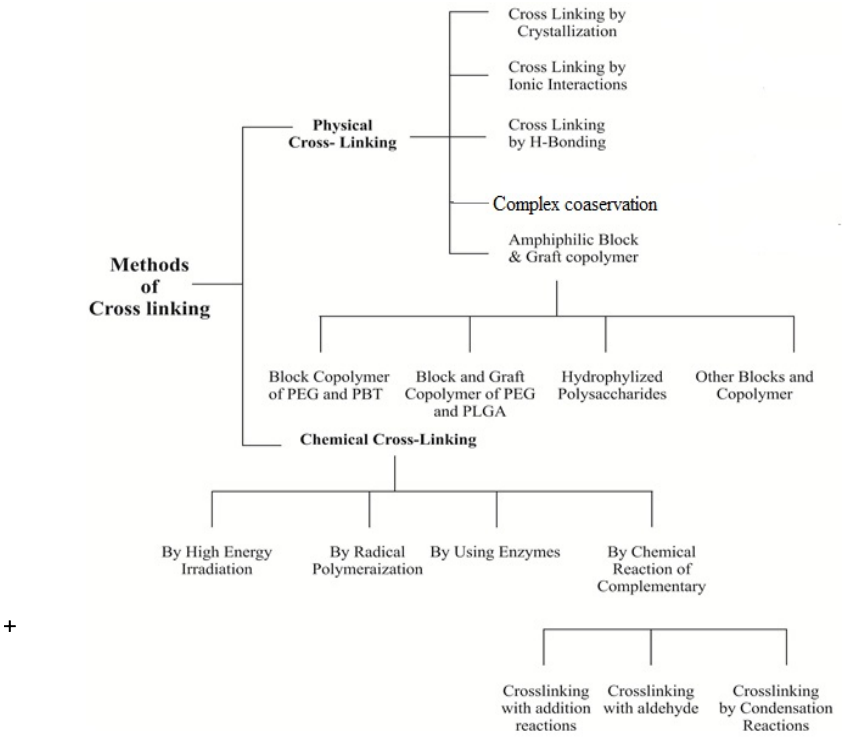

Figure 1: Novel Cross-Linking Methods

Conclusions

In recent years, many novel hydrogel systems have been developed. Fundamental studies greatly contributed to our present understanding of this unique class of materials. Various methods of crosslinking have been designed and are now available to fabricate hydrogels. Although several physical methods are presently available, there is definitely a necessity for other methods. It is expected that ideologies from the growing research area of supra-molecular chemistry will be useful to design novel type of hydrogels with tailored characteristics which can preferably be synthesized in an aqueous environment. Finally, it can be expected systems in which induction of gel formation by a specific trigger (pH, temperature or a specific compound) will be designed further and applied for biomedical and pharmaceutical purposes.

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