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Review

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Effect of Chemical Cross-linking on Properties of Polymer Microbeads: A Review

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Abstract: Cross-link property has been used to improve the insolubility, mechanical strength, stiffness, and rigidity of polymer microbeads having potential applications in solid-phase synthesis, solid-phase extraction, and biomedical fields. Therefore synthesis of polymer with desired cross-linker (hydrophilic/hydrophobic/rigid/flexible) and concentration of cross-linker (cross-link density) is an important. In the present review, chemical cross-linking by free-radical, condensation, UV radiation, and small-molecule cross-linking are discussed in details. Further, effects of cross-linker (type/concentration) on polymer properties like surface area, pore volume, pore size, particle size, thermal degradation, glass transition temperature, and polymer swelling are also discussed. Importantly, present review discusses the influences of rigidity, flexibility, hydrophilicity, and hydrophobicity of a cross-linker on polymer properties.

Keywords: Chemical cross-linking, Parameter designing, Polymer properties, Porosity, Surface area, Thermal properties

1. INTRODUCTION

In 1839, Charles Goodyear [1] invented that, rubber containing sulphur cross-linking has tough and long lived property. In other words, rubber containing sulphur cross-linking has much better properties than in the absence of sulphur. Cross-link polymer is an important engineering material due to their excellent stability than same polymer without cross-linking. Different types of solid-supports such as organic polymer, inorganic nanoparticle (silica, metal oxide, or mixed metal oxide nanoparticles), and organic-inorganic framework are available for immobilization of catalyst, reagent, substrate, enzyme, and protecting groups. However, each type of solid-support has own merits and demerits. Over the last two decades, cross-linked polymers are potentially used in different fields such as synthesis [2], extraction [3], tissue engineering [4], drug delivery [5], pharmaceutical [6], and in biomedical applications [7,8] because polymer properties can be significantly improved by cross-linking [9,10]. The properties such as mechanical strength, thermostability, glass transition temperature, swelling, permeability, rigidity, and stiffness can be improved to a remarkable extent [11].

Till now, three types of cross-linking methods are widely used. These methods are chemical, physical, and biological cross-linking [11]. Indeed, each cross-linking method has own merits and demerits. Chemical cross-linking is the cross-linking by free-radical, condensation (cationic/anionic), UV radiation, or small-molecule cross-linking. In free-radical, condensation, and small-molecule cross-linking, degree of cross-linking is controlled by an amount of cross-linker, reaction time, temperature, stirring speed, and an initiator/catalyst (type and concentration). In UV radiation cross-linking, degree of cross-linking is controlled by high-energy ionizing radiation, gamma, or x-ray [12] and their radiation dose. Physical cross-linking is a weak compared to chemical cross-linking since physical cross-linking forms by secondary forces. Biological cross-linking is also one of an emerging cross-linking method. Till date, this method is not developed for industrial scale like chemical cross-linking. Stability of cross-linking and improvement in polymer properties depends on the type and degree of cross-linking. Recently, we reported the cross-linking by free-radical polymerization. Monomer unit containing two or more functionality (double bond or functional group) called as a cross-linking agent or a cross-linker [12–14]. Cross-linker may contain two [13], three [14], or four [15], cross-linking sites. In 2006, Tang et al. [16] described the application of cross-linked β-cyclodextrin polymer for adsorption of aromatic amino acids where β-cyclodextrin was cross-linked by hexamethylene-diisocyanate (HMDC) to obtain cross-link polymer. This falls under the category of condensation cross-linking. In 2011, Harikrishna et al. [17] reported the cross-linking by UV radiation. These three (free-radical, condensation, and UV radiation) cross-linking methods are widely used to obtain cross-linked polymer.

The major concern of cross-link polymer is the less reactivity because large number of functional groups buried into the polymer matrix. However, this concern can be eliminated to a remarkable extent using core-shell polymer [18]. Thus, cross-link polymer with improved surface area, porosity, swelling, and thermal properties is the demand of solid-phase chemistry. The main objective of the present review is to compare the effect of cross-linker and cross-link density on polymer properties. Synthesis of an engineering material need to be trial and error experiments for obtaining the desired properties. Present review provides the information for designing the controlling parameters without any trial and error. In the present review, effects of type of cross-linking, cross-linker (rigid/flexible or hydrophobic/hydrophilic), and cross-link density are discussed in details.

2. CROSS-LINKED POLYMERS

Over the last two decades, natural and synthetic polymers were potentially used for various applications [19–21]. Both types of polymers have their own merits and demerits. Natural polymers have more solubility, no strength, and low thermal stability. Therefore, to improve these properties is an essential for wide polymer applicability. Undoubtedly, synthetic cross-link polymers improve these polymer [22,23]. Based on synthesis method, cross-linking are classifieds into *in-situ* cross-linking and post-cross-linking polymer. *In-situ* cross-linking is a process of direct cross-linking of functional monomer with cross-linker to obtain macromolecular chain of polymer whereas post-cross-linking is a process of cross-linking after polymerization. Polymer cross-linking may be reversible or irreversible depending upon the nature of the cross-linking. Three main types of cross-linking methods are widely studied [24–26]. These cross-linking methods are chemical, physical, and biological [27]. Chemical cross-linking is irreversible and cannot be reversed whereas physical and biological cross-linking can be

reversed by applying temperature, pressure, light, electricity, magnetic field, stress, or by changing pH.

Chemical cross-linking is a function of primary forces like covalent bond formation whereas physical cross-linking is a function of secondary forces [28], such as ionic [29], hydrophobic [30], hydrogen bonding (intermolecular/intramolecular) interaction [31], stereocomplexation [32], supramolecular chemistry [33], and these are well-known cross-linking methods. Ionic interaction is the powerful interaction of the physical cross-linking compared to rest of the physical methods. Chemical cross-linking is much stronger and stable towards heat, mechanical, or any other action. Gulrez et al. [34] discussed the chemical and physical cross-linking methods to obtain cross-linked polymer. Conventional polymerization techniques such as free-radical and condensation polymerization are widely used for the chemical (covalent) cross-linking of the polymer [35]. Free-radical and condensation polymerization technique offers degradable or non-degradable polymer depending upon the bond formation. Polymers obtained by these techniques could not create any problem during application due to strong cross-linking by primary forces whereas polymers obtained by physical cross-linking may interfere during application due to weak cross-linking by secondary forces. As a result, chemical cross-linking is preferred widely.

Biological cross-linking is also an emerging cross-linking method wherein biomolecules such as complementary oligonucleotides [36], oppositely charged peptide [37], and heparin growth factor are used to obtain biological cross-linking [38]. The oligonucleotides such as oligo(cholesteryl) methacrylaten-PEG-oligo(cholesteryl)methacrylate)n-(OC_5ma-PEO-C_5MA) and oligo(10-cholesteryloxy decyl methacrylate)n-PEG-oligo(10-cholesteryloxy decyl methacrylate)n-OC_{10}MA-PEO-OC_{10}MA) were used [36]. Further, peptide containing opposite charge can be used to obtain biological cross-linked polymers [38]. Oppositely charged peptide and polymer has attractive interaction which attributes to form biological cross-linking. This process could not allow dissolving the polymer into the aqueous medium or organic solvent. Nevertheless, this type of cross-linking is not stronger like chemical cross-linking. This review is mainly focused on the discussion of the effect of chemical cross-linking on polymer properties. Different *in-situ* polymer cross-linking methods are described below.

2.1. Free-radical polymerization

Generally, suspension, emulsion, and dispersion polymerization techniques are used to obtain chemically cross-link polymers whereas suspension polymerization method is preferably used [39]. This type of polymer is much stable and falls in degradable or non-degradable type [40]. Free-radical polymerization is carried out in the presence of an initiator and heat. Mostly, acrylic acid and acrylate based monomers are polymerized by this method. In the past, poly(styrene-*co*-divinylbenzene) was widely used as a solid-support. Gupta et al. [41] reported the surface area of 79 m^2/g for a poly(styrene-*co*-divinylbenzene). Our published work reported much higher surface area which is above 500 m^2/g using 1,2-dichlorobenzene as a solvating porogen [14,42]. As a result, porogen selection is a need to obtain improved properties of the beaded polymer. Monomers and cross-linkers used for free-radical polymerization are reported in **Fig. 1**.

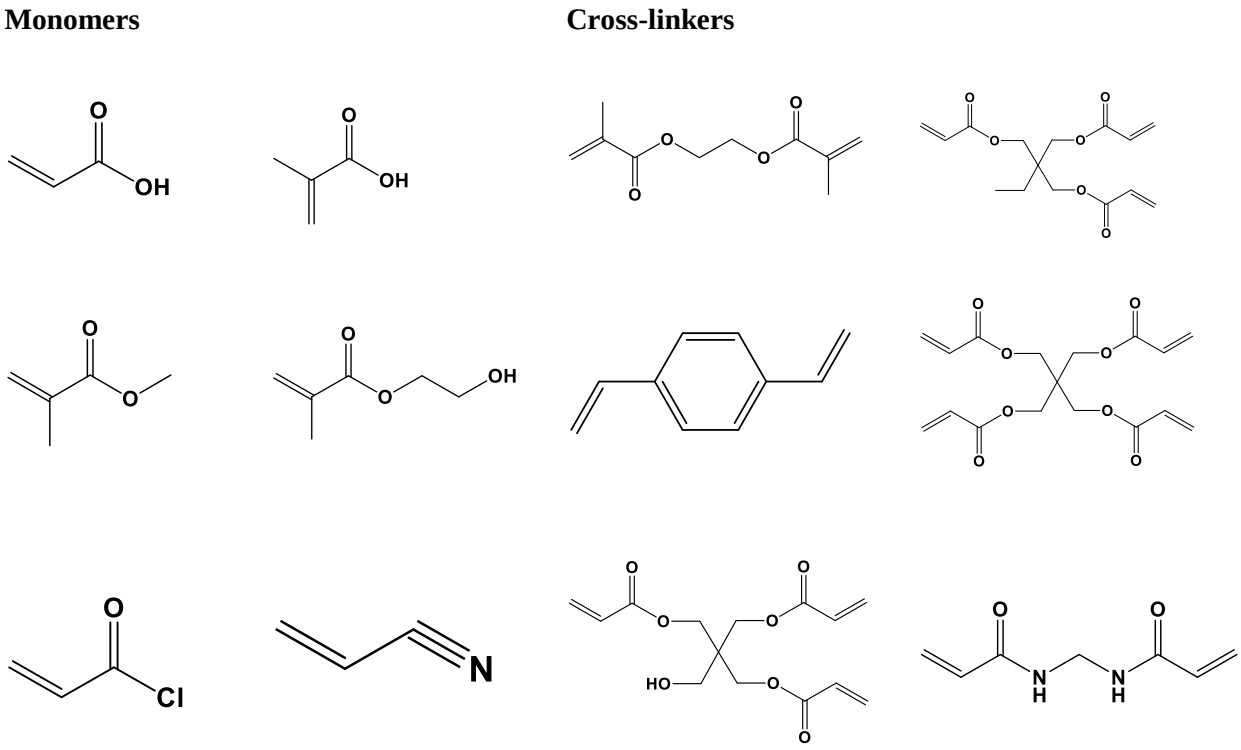
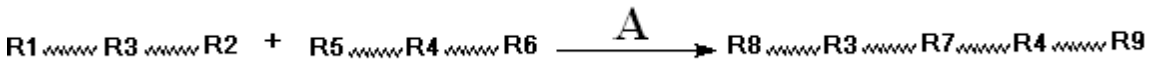


Figure 1. Monomers and cross-linkers used for free-radical polymerization.

2.2. Condensation polymerization

The polymers obtained by this technique may be degradable [26] or non-degradable depending upon the bridging groups formed during polymerization. This type of polymerization is carried out in the presence of catalyst, heat, or both. In 2015, Wei et al. [43] reported the silsesquioxane-based polymer containing hydroxyl functionality which was obtained by condensation polymerization. Besides ester, ether, amide, and imine [44] based polymer can be obtained by condensation polymerization. General reaction scheme of a chemically cross-linked polymer synthesis by condensation polymerization is depicted in **Fig. 2** whereas functional end group and aromatic/aliphatic composition used for condensation polymerization is reported in **Table 1.**



A = acidic/basic catalysts, or heat, or both

Figure 2. Chemically cross-linked polymer synthesis by condensation polymerization.

Table 1. Monomer and cross-linker functional end group of aromatic/aliphatic composition used for condensation polymerization

R1,R2 (monomers)	R3,R4	R5,R6 (cross-linkers)	R7,R8,R9
Diol, diamine, and dithiol based functional compound	Aliphatic and aromatic based bifunctional compound	Tri or multi-functional based compounds	Ester, amide, imide, and imine based linkages

2.3. Ultra-violet radiation

Compared to free-radical and condensation polymerization, UV radiation is an inexpensive route to obtain cross-linked polymer and generally carried out at an ambient temperature. Polymerization using UV radiation is the safest and clean way of polymerization since it can not deteriorate the polymer properties. Any chemical additives like an initiator, solvent, protective colloid, or surfactant are not needed for this type of polymerization. As a result, polymer retains their biocompatibility. Recently, Kurecic et al. [45] used the UV radiation technique for the polymerization of poly(N-isopropylacrylamide) to obtain a hydrogel. In another, Polavka et al. [46] reported the polymerization of poly(vinyl alcohol) using UV radiation in the presence of terephthalic aldehyde. The time required for photopolymerization is considerably low which is in the range of few second to few minute, while thermal polymerization can take several hours. Moreover, Fechine et al. [47] reported the preparation of poly(N-vinyl-2-pyrrolidone) and they were discussed the new methods to accelerate the UV radiation for cross-linking. Recently, Harikrishna et al. [48] studied the photopolymerization using UV radiation to evaluate the extent of polymerization by a gas chromatography. They demonstrated that, the extent of photopolymerization of ethyl hexyl acrylate, ethyl hexyl methyacrylate, and ethylene dimethacrylate which was 94, 95.3, and 98.7%, respectively using a phenyl bis(2,4,6-thimethyl benzoyl) phosphine oxide (IRGACURE 819) as a photo initiator. Further, radiation dose and radiation time are also an important issue which affects degree of cross-linking of polymer. However, use of radiation dose depends upon the application area of the cross-linked polymer. The monomers and cross-linkers reported in **Fig. 1** can be polymerized by UV radiation method.

2.4. Small-molecule cross-linking

In addition to multifunctional (bi, tri, or tetra) cross-linking agent, some small-molecule also acts as a cross-linker. Small-molecules like glutaraldehyde, formaldehyde, osmium tetroxide, potassium dichromate, and potassium permanganate were potentially used to obtain cross-linked polymer [49,50]. This type of method is generally used for the polymers containing hydroxyl, carboxylic acid, and amine based functionality. This is also widely used technique like addition or condensation polymerization. The

polymers obtained by this method have the non-degradable property and this type of cross-linking cannot be reversed by heat, light, acid, or base. Fugueiredo et al. [51] explored the poly(vinyl alcohol) cross-linking using glutaraldehyde. In another, Alemzadeh et al. [52] used the glutaraldehyde cross-linked polymer for the application in controlled release of paraquat. Over the last decade, potential work is published on the use of formaldehyde as a cross-linking agent [53]. Recently, Mulani et al. [54] published the tannin-aniline-formaldehyde resin for arsenic removal from contaminated water. The same author published the coffee polyphenol-formaldehyde/acetaldehyde resins for adsorption of chromium from an aqueous solution [55]. Another widely used small-molecule cross-linking agent is osmium tetroxide. Hopwood was used the osmium tetroxide, potassium dichromate, and potassium permanganate for the fixation of proteins, bovine serum albumin, and tissue blocks [50,56]**.** Chemically cross-linked polymer synthesis by small-molecules such as glutaraldehyde, formaldehyde, or osmium tetroxide is represented in **Fig. 3 (a), (b), and (c),** respectively.

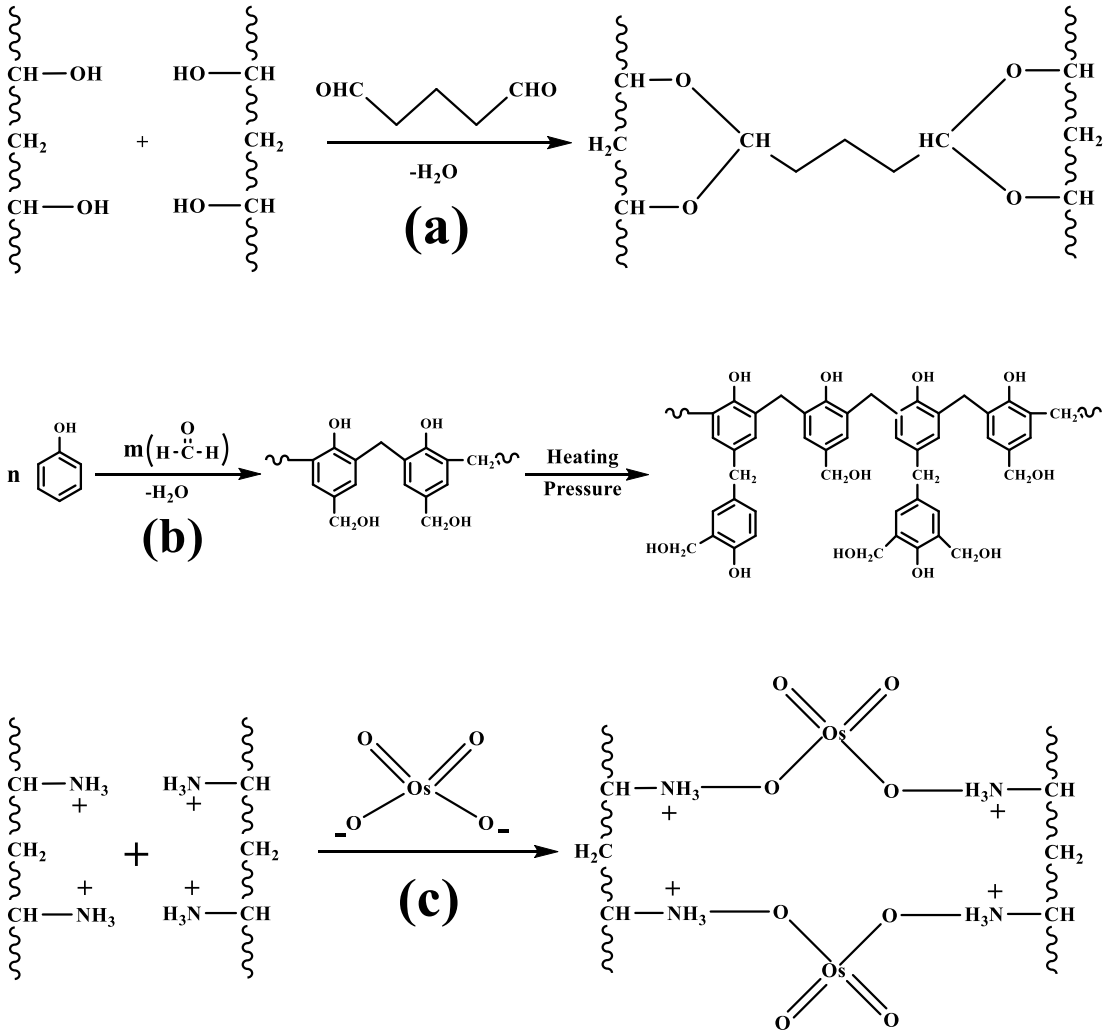


Figure 3. Chemically cross-linked polymer synthesis by small-molecule cross-linking **(a)** glutaraldehyde, **(b)** formaldehyde, and **(c)** osmium tetroxide.

2.5. Effect of chemical cross-linking on different physical properties

On the basis of degree of cross-linking, polymers are broadly classifieds into hypo or hyper cross-linking. Without cross-linking, polymers have the limited applications whereas cross-linked (hypo/hyper) polymers have the potential applications. The degree of cross-linking may vary depending upon the application of polymers. Both types of polymers have their own merits and demerits from the view of reactivity and recovery. Generally, homopolymer is soluble in most of the solvents and synthesizes by the polymerization of a single monomer unit. Homopolymer has more reactivity which relates to the merit whereas higher solubility relates to the demerit. On the other hand, cross-linked polymer has insolubility and less reactivity which relates to the merit and demerit of the cross-linked polymer, respectively in solid-phase chemistry. As a result, to balance these properties is a need of the solid-phase synthesis, solid-phase extraction, and biomedical applications. Polymer hypo-cross-linking consists of lower cross-linking of polymer which is widely used as a solid-support to immobilize the catalyst, reagent, or substrate by covalent modification [57–59]. On the other hand, hyper-cross-linked polymers were potentially used for an enzyme or cell immobilization by entrapment or adsorption method [60].

2.5.1. Surface area

Surface area is very important parameter from polymer efficiency point of view. Here, we discussed the effect of cross-link density and type of cross-linker on surface area. In general, as cross-link density of polymer increases, surface area also increases [39]. Nevertheless, surface area decreases after certain extent of cross-link density which depends on type of monomer, cross-linker, porogen (solvating/non-solvating), and their concentration. Hydrophilic cross-linker has more affinity toward aqueous phase inversely hydrophobic cross-linker has more affinity toward organic phase resulting into smaller and greater surface area of polymer obtained from hydrophilic and hydrophobic cross-linker, respectively [39]. This is the general trend of the surface area with respect to cross-link density and type of cross-linker.

2.5.2. Pore volume and pore size

Pore volume and pore size of the solid-support are the most important properties which can be controlled by varying physico-chemical parameters. Cross-link density and porogen are the most influencing factors to the pore volume and pore size. Generally, surface area and pore volume increases whereas pore size decreases with increase in cross-link density [39,61]. Porosity may be unimodal or bimodal depending upon the porogen or mixture of porogens. However, type of porosity (unimodal or bimodal) is not depending on the type of cross-linker and their concentration. The unimodal porosity may be micro, meso, or macro whereas bimodal porosity may be micro-meso, meso-macro, or micro-macro [62].

2.5.3. Particle size

Particle size is also one of the crucial properties of the polymer beads. Particle size may be nano or micron depending upon polymerization method, stirring speed, type of cross-linker (hydrophilic/hydrophobic), and porogen (solvating/non-solvating). Generally, suspension polymerization method offers particle size in the range of 5–200 μm [39]. Some published work reports the particle size of the beads in the range of 10–1000 μm [63,64]. Indeed, stirring speed of polymer composition significantly affects the particle size of the polymer. Stirring speed and particle size are inversely related to one another. High stirring speed allows decreasing particle size and vice-versa for slow stirring speed [65]. In another effect, hydrophilic cross-linker has greater affinity toward aqueous phase which allow decreasing polymer particle size and vice-versa for polymer containing hydrophobic cross-linker. Further, solvating porogen has less affinity toward aqueous phase which allow an increasing of interfacial tension between aqueous and organic phase resulting into smaller particle size [66]. On the other hand, non-solvating porogen has more affinity toward aqueous phase which decreases the interfacial tension resulting into larger particles size [67]. Overall, particle size is the outcome of the stirring speed and interfacial tension between aqueous phase containing protective colloid and organic phase containing monomer, cross-linker, initiator, and porogen.

2.5.4. Thermal properties (thermal degradation/glass transition temperature)

In reality, thermal stability and glass transition temperature of a purely organic polymer can be increased upto a certain extent. Above this, it is not possible to increase these properties due to their organic composition. In copolymer composition, functional monomer attributes to reactivity whereas cross-linker attributes to hydrophilic/hydrophobic as well as thermal properties of the polymer. Thermal properties can be controlled by changing the type and concentration of cross-linker. Type of cross-linker consists of rigidity, flexibility, elemental composition, and aromatic/aliphatic properties of the cross-linker. In most of the cases, rigidity and aromatic ring containing polymer are stable toward thermal action whereas aliphatic and flexibile cross-linker containing polymer is less stable toward thermal action. In concentration effect, higher concentration of rigid cross-linker or lower concentration of flexible cross-linker in a copolymer matrix generates thermostable polymer. Our recent publication demonstrated that, rigid cross-linker (divinylbenzene) containing polymer revealed the high degradation (Tmax) and glass transition (Tg) temperature compared to polymer containing flexible cross-linker (ethylene dimethacrylate) [39]. Another interesting observation was that, higher concentration (cross-link density) of rigid cross-linker or lower concentration (cross-link density) of flexible cross-linker also improved the Tmax and Tg. This indicates that, cross-linker is the crucial parameter which substantially influences thermal properties of the beaded polymer.

2.5.5. Polymer swelling

Polymer swelling is an important parameter in deciding the polymer-solvent compatibility during polymer applications. Polymer swelling is a function of degree of cross-linking, surface area, and porosity. Higher the polymer cross-linking, lower is the polymer swelling and vice-versa for lower cross-link polymer. This is mainly because of lower cross-link polymers have longer chain length and easy to

expand. In contrast, in higher cross-link polymer, chain length is smaller and difficult to swell. Surface area and porosity of a polymer are tunable by changing physico-chemical parameters. High surface area and porosity also encourages the polymer swelling.

2.5.6. Polymer strength

Before polymer applications, to improve some of the properties are essential. In these properties, polymer strength is one of the crucial properties. Polymer strength is depending upon the porosity, cross-link density, and type of cross-linker (rigidity/flexibility). Suspension polymerization is the method which generates less porous and high mechanical strength polymer compared to emulsion polymerization. Therefore, balancing of these two properties in a single polymer is an important from application point of view. Higher cross-linker concentration (CLD) increases polymer strength and vice-versa for low CLD polymer. Rigid cross-linker is capable to generate high strength polymer than flexible cross-linker for same cross-link density.

3. CONCLUSION

In the present review, effects of chemical cross-linking on properties of polymer microbeads were discussed. Moreover, present review helps to design the controlling parameters according to the desired polymer properties. Higher cross-link density increases the surface area and pore volume whereas decreases the pore size of polymer beads and vice-versa for lower cross-link density polymer. Further, rigid cross-linker increases whereas flexible cross-linker decreases thermostability and glass transition temperature. On the other hand, greater concentration of rigid cross-linker and lower concentration of flexible cross-linker improves the aforementioned thermal properties. Lower cross-link density polymer has the tendency of greater swelling whereas high surface area and pore volume encourage the polymer swelling. Cross-link polymer provides insolubility, rigidity, and stiffness to the polymer which offer potential applications in solid-phase synthesis, solid-phase extraction, and biomedical applications. The cross-link polymer also offers an ease of recovery, recycle, and reuse properties which make them industrially economical and environmentally benign.

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The authors declare no conflict of interest

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