



State-of-the-Art Irradiation Technology for Polymeric Hydrogel Fabrication and Application in Drug Release System

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Chronic and debilitating diseases can be marginally cured by anti-inflammatory, antiseptic, and antibiotic drugs, there is still need for more efficacious delivery approaches. Biodegradable and biocompatible polymeric hydrogels are essential requirements for drug release systems due to sustained or targeted drug delivery. Irradiation crosslinking of polymers is considered a safe route for the fabrication of hydrogels because crosslinking takes place without addition of unnecessary toxic reagents such as initiators or crosslinkers. This technology is a useful way to induce sterilization and crosslinking in a single step. Several natural and synthetic polymers in different combinations are crosslinked through high energy ionizing radiation such as electron beam and gamma ray irradiation. Polymeric hydrogels prepared using these techniques exhibit good gel fraction, swelling ratio, and mechanical properties. In addition, hydrogels possess drug loading and release characteristics, antimicrobial characteristics, and *in-vivo/in-vitro* cytocompatibility. The advantage of biodegradable and biocompatible drug release systems is the controlled release of drugs without deleterious effects on targeted sites. This mini review about irradiation crosslinked hydrogels will provide sufficient guidelines for new researchers to proceed further in this field.

Keywords: hydrogels, polymeric blends, irradiation crosslinking, biomedical applications, drug release systems

INTRODUCTION

The term “hydrogel” was first introduced and illustrated in 1894 with inorganic salt-based colloidal gels (Buwalda et al., 2014). Irradiation technology based hydrogels were introduced in 1958, when poly (vinyl alcohol) (PVA) was crosslinked using gamma ray irradiation (Buwalda et al., 2014). Lim and Wichterle pioneered the development of poly (HEMA) hydrogels, which exhibited swollen characteristics for contact lens applications (Wichterle and Lim, 1960). Hydrogels are hydrophilic crosslinked networks with three dimensional structures that can absorb large amounts of physiological fluids or water without being dissolution due to chemical or physical interactions; they can mimic soft tissue (Hoare and Kohane, 2008). Polymeric materials from natural, semi-synthetic, and synthetic origins can be utilized for hydrogel fabrication. The preparation of hydrogels includes crosslinking of linear chains or simultaneous crosslinking and polymerization of monomers with poly functional monomers (Nugent and Higginbotham, 2007).

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In polymeric hydrogels, crosslink density and hydrophilicity of the polymer are governing factors for the swelling capability and extent of swelling. Generally, mass fragments of water in the swollen state of the hydrogel are greater than mass fragments of polymer. Hydrogels can be further classified into two classes—permanent gels (chemical gels), which involve covalent linkages of chains, and pseudo gels (physical gels), which involve chain entanglements, electrostatic forces, hydrophobic interactions, or hydrogen bonds (physical gels are usually non-permanent and heating can convert them back to polymer solutions) (Benamer et al., 2006).

Currently, several crosslinking methods (chemical, physical, and irradiation) are being used (Syed K.H. Gulrez et al., 2010). Among the chemical methods, the most commonly used chemical additives are formaldehyde and glutaraldehyde. However, several studies have reported that chemical additives provoke cytotoxicity, which makes these method undesirable for pharmaceutical and biomedical applications (Yang et al., 2010). The irradiation crosslinking method is promising and clean process due to several advantages such as hydrogel fabrication and sterilization in a single step, simple process control, and absence of toxic reagents (crosslinkers and initiators), which could be difficult to remove (Benamer et al., 2006; Krklješ et al., 2007).

Stimuli responsive superabsorbents or hydrogels are triggered with even small external stimuli and undergo abrupt changes in network structure, growth, permeability, and mechanical strength due to the presence of so-called smart or environmentally sensitive hydrogels. Chemical stimuli comprising of chemical agents, ionic factors, and pH, alter the interaction at the molecular level between polymer chains, and interactions between solvents and polymer chains. On the other hand, physical stimuli include pressure, light, temperature, magnetic fields, electric fields, intensity of various energy sources, and mechanical stress, which alter interactions at the molecular level at critical onset points. Dual responsive hydrogels are another class that involves a combination of two stimuli responses in one hydrogel. Biochemical stimuli responsive hydrogels involve responses to enzyme, antigens, ligands, and several other biochemical entities. Hence, responsive hydrogels have huge potential for use as biomaterials for biotechnology, biomedical, and pharmaceutical applications (Zhang et al., 2015).

Recently, drug development has led to several controlled/targeted drug delivery approaches that consist of suitable polymer carriers containing encapsulated drugs and that deliver drugs in sustained fashion/novel route or both. Drugs can be made accessible at numerous locations within the body by choosing suitable biocompatible carriers. Targeted drug delivery to various tissues or organs can be simultaneously complemented with auxiliary benefits of obtaining both temporally and spatially controlled release, in accordance with the fundamental purpose of drug delivery. Controlled release of a drug and targeted drug delivery to diseased organs or tissues have several advantages compared to the oral (traditional) route, such as that higher drug concentration makes therapy more effective;

reduction in undesired side effects and duration of therapy; and drug release sustains improved pharmacokinetics over an extended time period. In the end, convenient and simplified dosage are attributed to the wellbeing of the patient because they reduce the necessity of potentially uncomfortable repeated dosing and shorten the chances of inappropriate dispensing (Ražem and Katušin-Ražem, 2008).

In this mini review, our focus is on discussing the fabrication of natural and synthetic polymers base hydrogels for drug release systems. We explicitly describe the utilization of gamma ray and electron beam irradiation techniques for hydrogel development, the mechanism of crosslinking, the impact of crosslinking, and applications of these methods in drug release systems.

BLENDING OF POLYMERS

Natural polymer-based hydrogels can be prepared through chemical or physical crosslinking mechanisms (Ullah et al., 2015; Lou et al., 2020). The chemical crosslinking procedure induces higher mechanical strength and durability due to interconnectivity fostered through covalent bonds. The irradiation fabrication of a hydrogel is preferable as it produces sterile and pure hydrogels quickly and in the absence of toxic chemical agents (Moghaddam et al., 2019). Nevertheless, natural polymer hydrogel fabrication in aqueous solution through high ionizing energy irradiation method produces low molecular weight products, instead of good hydrogel formation, due to chain cleavage reactions (Hafezi Moghaddam et al., 2019). To overcome this issue, a blend of natural polymer and vinyl reagent or synthetic polymer has been used instead of mere natural polymers (Prusty and Swain, 2018; Moghaddam et al., 2019).

In comparison to neat polymers, polymer blends are regarded as a dominant material in the fabrication of better performance low-cost products. Composites and blends are expanding the utilization of polymers from renewable resources to recently-developed valuable products (Yu et al., 2006). The main purpose of blend formation of two or more polymers is to optimize the blend performance and to not dramatically alter the individual properties (Matveev et al., 2000). Nowadays, it is common practice to use the polymer modification process to blend two or more polymers to acquire desired properties. Polymer blends produce rare and superior properties that homo-polymers do not exhibit. Generally, chemical, physical, and irradiation techniques are used for the synthesis of polymer blends. In particular, the irradiation method is very appropriate tool that involves modification or improvement of polymeric materials through degradation, grafting, or cross-linking. Numerous research studies have been carried out in this regard (Güven et al., 1999; Bhattacharya, 2000). Natural and synthetic polymer-based blends for biomedical applications have drawn attention for their biodegradable nature (Carenza, 1992; Crescenzi et al., 1997). These blends have different material properties and can be used as hydrogels in the fields of pharmacy and biomedicine (Rosiak, 1994; Crescenzi et al., 1997; Rosiak and Ulański, 1999; Rosiak and Yoshii, 1999).

IONIZING IRRADIATION OF POLYMERIC BLENDS FOR HYDROGEL FABRICATION

On the electromagnetic spectrum, gamma rays fall in the high ionizing energy region, which has the ability to penetrate most materials. Gamma rays are radiation-source dependent high-frequency waves. Usually, radioactive nuclides such as cesium-137 and cobalt-60, are the radioactive sources used in this technology. Electron beam involve beams of energetic electrons from electron accelerators. Industrial electron beam accelerators have been categorized with respect to energy range such as high energy (>5 MeV), medium energy (300 keV–5 MeV), and low energy (80–300 keV) (Shahidi, 2019).

Unsaturated compounds are polymerized through high ionizing energy irradiation, particularly using gamma rays and electron beams. Water soluble polymers containing vinyl groups undergo hydrogel formation when exposed to high ionizing energy irradiation (Giammona et al., 1999). These irradiations generate free radicals on the polymeric chains of the water-soluble polymers through C-H bond homolytic scission. In addition, water molecules undergo radiolysis, which creates hydroxyl radicals that further interact with polymeric chains to form macroradicals (Peppas and Mikos, 1986). Then, macroradicals generate intra- and inter-molecular interactions to form covalent bonded hydrogel networks. The irradiation crosslinked hydrogel fabrication process is usually carried out in inert atmosphere (argon or nitrogen) to avoid oxygen interaction with macroradicals in the propagation stage of polymerization. Recently, poly (acrylic acid) (Jabbari and Nozari, 2000), poly (ethylene glycol) (Kofinas et al., 1996), and poly (vinyl alcohol) (Peppas and Merrill, 1977) based hydrogels were crosslinked using high ionizing energy irradiation. Also, poly (methyl vinyl ether) was synthesized using irradiation crosslinking to form a thermosensitive hydrogel (Arndt et al., 2001). The advantage of irradiation technology for hydrogel formation is that this method can be performed in aqueous phase under mild conditions (physiological pH and room temperature).

Recently, hydrogel fabrication through gamma ray irradiation has gained enormous interest. This irradiation technique is suitable for the modification of the physical and chemical properties of polymers (Jha et al., 2010; Raza and Park, 2020). Furthermore, gamma ray irradiation has several advantages as compare to the thermal activation process such as polymerization in the absence of any extra reagent and crosslinking (Park et al., 2013). Exploiting these benefits, hydrogels prepared through gamma ray irradiation are useful for medical applications, for which even minor contamination is prohibited; these materials are employed to sterilize biomedical devices for veterinary and medical applications (Gad, 2008; Juby et al., 2012). During gamma ray irradiation, the polymers crosslink such that the backbone chains of polysaccharide polymers form chemical bonds and form a three-dimensional network structure. The irradiation method of polymers promotes quantitative changes and reproducibility in the absence of chemical additives and simultaneously allows sterilization of products (Eid et al., 2009).

Similar to free radical polymerization, electron beam and gamma polymerizations also undergo initiation, propagation, and termination steps (Hennink and Nostrum, 2002). The hydrogel formation occurs when the network achieves the critical gelation point. Hydrogel fabrication and sterilization through electron beam technology in single step is a rapid and convenient method because the crosslinking process completes in a short time at ambient temperature, there is no production of radioactive waste, and process control is easy (Rosiak, 1994; Raza et al., 2021).

MECHANISM OF CROSSLINKING AND APPLICATIONS IN VARIOUS DRUG RELEASE SYSTEMS

In irradiation technology, chemical reactions initiate in aqueous mediums which starts generating series of reactive species due to radiolysis of water. Molecular products and radical species with different reactivities such as e_{aq}^- , H^\bullet , HO^\bullet , H_2O_2 , H_2 , and H_3O^+ are produced as given below in equation. In argon saturated or deoxygenated polymer solutions, e_{aq}^- and HO^\bullet (hydroxyl radical) govern the highest yield (Spinks and Woods, 1990). The H^\bullet and HO^\bullet radicals interacts quickly with polymeric chains via hydrogen removal which give rise to series of macroradicals formation depending upon polymer concentration. These macroradicals undergoes inter or intra-molecular free radical recombination reactions and produce interconnected polymer networks having permanent and stable structure (Treloar, 1975).

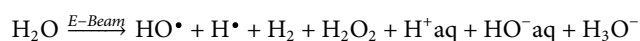


Figure 1 depicts applications of hydrogels in different areas. Research on the preparation of various hydrogels (ion and electrical conductive materials, and oral patches) for effective drug release using radiation crosslinking technology has been steadily undertaken. When a hydrophilic polymer is dissolved in water and irradiated with radiation, radicals are formed on the water molecules of H and OH by the radiation to attack with low bonding strength of the hydrophilic polymer. Since this is a very unstable state, radical recombination occurs between chains in which radicals are formed and crosslinking proceeds (Park et al., 2018; Jeong et al., 2020).

Table 1 shows natural and synthetic polymer based irradiation crosslinked hydrogels with irradiation types and different irradiation doses, and release of drugs. Herein, hydrogels crosslinked with both types of irradiation (electron beam and gamma ray irradiation) are discussed. Electron beam irradiation involves beam energies (usually 2.5 or 10 MeV), and parameters such as beam power, beam current and cart speed need to be adjusted for optimum crosslinking. Hafezi et al. used electron beam irradiation for the fabrication of hydrogels for drug release applications. In case of CA-O-CMCh/PAAM, irradiation dose (10–35 kGy) was used for crosslinking and doxycycline drug was loaded for

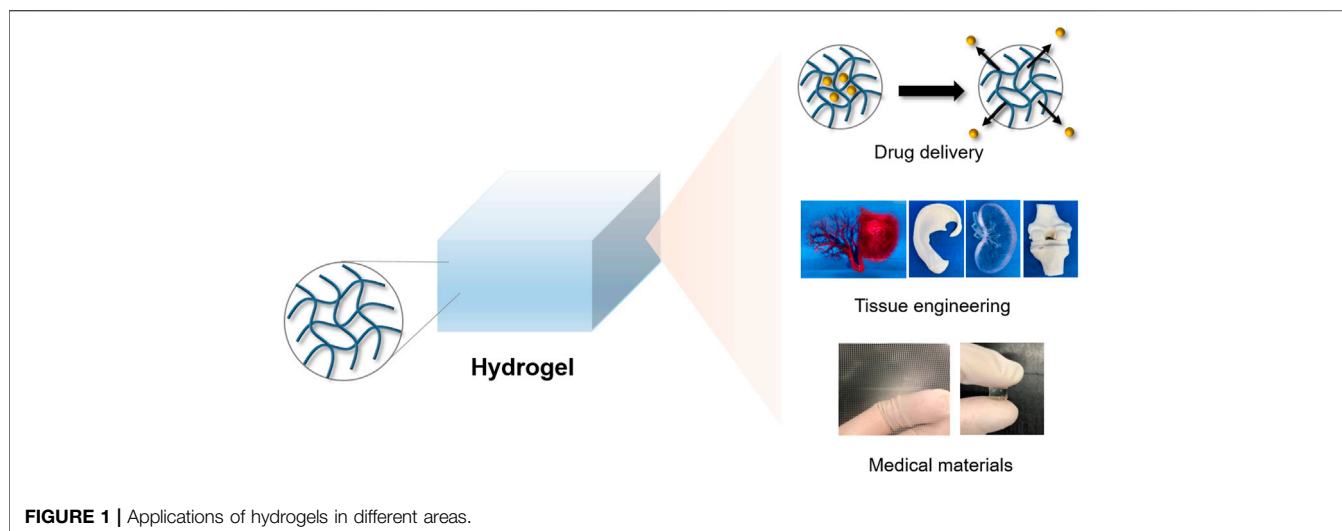


FIGURE 1 | Applications of hydrogels in different areas.

TABLE 1 | Depicting irradiation crosslinked polymers, irradiation types and dose, and used drugs.

Polymers	Irradiation types	Irradiation dose	Used drug	References
CA-O-CMCh/PAAm	E beam	10–35 kGy	doxycycline	Hafezi et al. (2020)
5-HTP/Pec	E beam	10–50 kGy	tetracycline	Hafezi et al. (2019)
Agarose	E beam	0–30 kGy	–	Krömmelbein et al. (2021)
CMSP/chitosan	E beam	25 kGy	diclofenac sodium	Tan et al. (2021)
TA-HMGT	E beam	5–90 kGy	–	Tavakol et al. (2016)
BC/AA	E beam	35 or 50 kGy	bovine serum albumin	Mohd Amin et al. (2012)
CMSP	E beam	10–20 kGy	ciprofloxacin	Lam et al. (2015)
p (HEMA/IA)	γ irradiation	25 kGy	theophylline and fenethylline hydrochloride	Tomić et al. (2007)
HA/CS/PVA	γ irradiation	5–25 kGy	Cefazoline and theophylline	Zhao et al. (2014)
HA/CS/HAP	γ irradiation	25 kGy	5-FU	Taşdelen et al. (2018)
Dextran/PNIPAAm	γ irradiation	5 kGy	ondansetron™	Almeida et al. (2013)
Cellulose/gelatin and CNCs/gelatin	γ irradiation	30 kGy	riboflavin	Ishak et al. (2018)
CS/PVA	γ irradiation	40 and 60 kGy	catechins	Sabaghi et al. (2020)
Gelatin	γ irradiation	16–20 kGy	methylene blue	Kojima et al. (2004)

release analysis. While in case of 5-HTP/Pectin, 10–50 kGy irradiation dose is utilized for tetracycline drug release. CMSP and CMSP/chitosan based hydrogels were prepared with different irradiation doses for the release of ciprofloxacin HCL and diclofenac sodium. Bacterial cellulose/acrylic acid crosslinked hydrogels were prepared at 35 or 50 kGy for the bovine serum albumin encapsulation and release. Also, Agarose and tyramine–high methoxyl content gum tragacanth based electron beam crosslinked hydrogels are prepared without involving drug loading and release.

Gamma ray irradiation involves gradual increase in dose with respect to time (k or Gy/h) to attain desired dose. Zhao et al. and Taşdelen et al. prepared different combinations of natural and synthetic polymers (HA/CS/PVA and HA/CS/HAP) using gamma irradiation for the release of cefazoline and theophylline, and 5-FU, respectively. While, Sabaghi et al. fabricated chitosan nanoparticles containing catechins and mixed with CS/PVA and crosslinked at 0, 40 and 60 kGy for drug release of catechins in different low fat and high fat simulant and studied modeling of release.

Gelatin and combination with cellulose in different forms were incorporated at lower irradiation doses and applied for methylene blue and riboflavin release analysis. Dextran/Poly (N-isopropylacrylamide) based thermo-sensitive hydrogels were irradiation crosslinked at 5 kGy and studied release pattern of ondansetron. Also, 2-hydroxyethyl methacrylate/itaconic acid copolymeric hydrogels were polymerized at 25 kGy for the drug delivery of theophylline and fenethylline hydrochloride, measured drug release kinetics and predicted drug release follows Fickian diffusion mechanism.

CURRENT CHALLENGES AND FUTURE PROSPECTIVE

Advances in the preparation of hydrogels for drug release using blending of various polymers with useful properties and radiation technology are indicating future aspects of technology. However, there are still many technical problems that need to be solved. In particular, further study on crosslinking properties related to

various polymers and/or polymer blending by irradiation are needed. Since radiation is a high energy state, it can induce various reactions such as crosslinking, degradation, polymerization, and grafting, depending on the characteristics of polymers. Therefore, to prepare a hydrogel for drug delivery, it is necessary to study the radiation crosslinking properties according to the radiation device type and radiation dose, and the type of polymer. However, it is difficult to optimize the conditions when preparing a hydrogel using radiation and time consuming due to the absence of basic research. From this point of view, research on the preparation of hydrogels for drug release after blending of polymers and drugs, and the preparation of hydrogels through irradiation (such as gamma ray and electron beam) and various polymers, all of which have been recently studied, could be said to be very noteworthy. The study of superior polymer crosslinking properties induced by irradiation

is directly related to the preparation of hydrogels for drug release and could play a promising role in the development of effective drug-releasing hydrogels.

AUTHOR CONTRIBUTIONS

MR and J-OJ performed the literature survey and prepared the manuscript. SP supervised, reviewed, and revised the draft. All authors read and agreed on the final version.

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