Hydrogels And Their Medical Applications

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Abstract: Biomaterials are essential for many biomedical applications, such as scaffolds that support guided tissue growth, therapeutic and diagnostic devices, drug delivery systems, and engineered tissue substitutes. Of the various classes of biomaterials, including metals, ceramics, natural tissues, and polymers, hydrogels are particularly promising because they are hydrophilic polymeric gels that are known for their biocompatibility and ability to interact with living tissues, particularly when synthesized using ionizing radiation.

Since the early 1950s, when pioneers in polymer radiation chemistry started investigating radiation crosslinking of hydrophilic polymers, radiation has been used to create hydrogels. Initial research primarily focused on understanding the underlying mechanisms of radiation synthesis, network topology, and the influence of radiation parameters. A. Chapiro's Radiation Chemistry of Polymeric Systems (Interscience, New York, 1962) and A. Charlesby's Atomic Radiation and Polymers (Pergamon Press, Oxford, 1960) are seminal publications in this topic. Due to the work of American and Japanese researchers, such as Hoffman in the US and Kaetsu in Japan, there was a noticeable increase in interest in the biomedical uses of radiation-processed hydrogels in the late 1960s. Through their efforts, hydrogels for the immobilization of physiologically active compounds, drug delivery systems, enzyme entrapment, and surface changes to improve antigen-antibody interactions and biocompatibility were developed.

The principles and dynamics of radiation-induced hydrogel formation are briefly reviewed in this article along with successful commercialization examples of hydrogel biomaterials.

Keywords: Hydrogels; Ionizing radiation; Biomaterials; Polymers.

1. INTRODUCTION

Any substance, with the exception of pharmaceuticals, or a blend of natural or synthetic materials that can be utilized either permanently or temporarily as a full or partial system to sustain, improve, or replace tissues, organs, or bodily functions is referred to as a biomaterial [1].

A medical device is defined as "any apparatus, implement, machine, contrivance, in vitro reagent, or any related component, part, or accessory that is intended for use in diagnosing diseases or other medical conditions, or in the cure, mitigation, treatment, or prevention of diseases in humans or animals" (FDA, 1976 amendment). Crucially, it does not rely on metabolism to work and does not accomplish its main intended impact through chemical action within or on the body.

When evaluating the safety and effectiveness of biomaterials, it's vital to consider them in the context of the specific device and its intended application. It is impossible to evaluate effectiveness without considering the instrument itself. Comparably, assessing safety necessitates balancing the possible advantages against the risks. Certain risks, such the potential for long-term failure, might be acceptable for devices that are essential to maintaining life. Devices intended to restore appearance or function, on the other hand, need to adhere to stricter safety regulations in order to be used. The biomaterials that are now in use are generally thought to be safe, with few problems relating to systemic toxicity or local tissue responses. The truth is that almost everyone will encounter biomaterials at some point in their lives.

Analysing the intended use and the precise placement of the biomaterial within the body, comprehending the physiology of the bodily fluids and tissues that will come into direct contact with the artificial material, choosing the right constituent materials and biomaterial's design entails a number of crucial processes, including determining the material's intended use and precise location within the body, comprehending the physiology of the bodily fluids and surrounding tissues that will come into direct contact with it, choosing appropriate constituent materials, and utilizing the right technologies to create the finished product. The creation of a prototype and a careful assessment of its mechanical, chemical, and physical characteristics come next.

In vitro cell culture research and in vivo animal testing are used to evaluate biocompatibility and functionality in later stages, which are followed by clinical trials and regulatory evaluation. Experts from a variety of scientific fields must work closely together during this extensive procedure. The requirements for any substance used in or on the human body are often divided into four main categories: biocompatibility, functioning, sterilizability, and non-toxicity [1,2].

One of the most promising categories of biomaterials is hydrogels. These networks of hydrophilic polymers can absorb water up to ten percent of their dry weight, or thousands of times more. They are known as "permanent" or "chemical" gels when their polymer chains are covalently crosslinked. Depending on variables like the density of crosslinking and the interaction between the polymer and water, these gels eventually attain an equilibrium swelling state. Conversely, non-covalent interactions such as molecular entanglements, hydrogen bonds, ionic forces, or hydrophobic contacts create "reversible" or "physical" gels. Changes in temperature, pH, or mechanical stress can modify these interactions, which are not permanent. Additionally, hydrogels can be divided into two primary groups according to their function or place of origin:

- Traditional hydrogels are hydrophilic polymers with a weak crosslinking that absorb a lot of water without disintegrating. Usually uncharged, they continue to expand at a constant rate despite variations in light, electric fields, pH, temperature, and other environmental factors.
- Stimuli-responsive hydrogels – Similar to conventional hydrogels in structure, these materials differ in that they can undergo significant volume changes in response to slight variations in environmental conditions such as pH, temperature, electric fields, or light. They typically include a notable hydrophobic component and may be either charged or uncharged. When charged, they often contain ionic groups that are sensitive to pH changes.

Hydrogels are generally heterogeneous, with areas of high crosslink density and low water uptake (called "clusters") scattered across areas with lower crosslink density and higher swelling capacity.

Water-filled 'voids' or'macropores' may emerge as a result of phase separation in some situations, contingent on the solvent content and composition during gel formation. Furthermore, the network frequently has structural "defects" such loose chain ends that don't add to the gel's flexibility. It is also possible for crosslinking agents to aggregate and form clusters with a very high crosslink density. Additionally, entanglements and chain loops can develop, which also reduces the network's long-term flexibility.

The water molecules initially hydrate the most polar, hydrophilic groups—usually ionic (if present) and hydrogen-bonding functional groups—when a dry hydrogel starts to take water. A common term for this first hydration is "primary bound water." The polymer chains start to swell when these groups are moistened. When hydrophobic segments come into contact with water, they connect with one another through hydrophobic interactions, creating a coating of water that envelops these areas. This layer is known as "secondary bound water." It's common to combine these two types under the umbrella of "bound water."

The network can absorb more water once all short-range interactions between the water molecules and the polymer backbone have been resolved. This will cause the network to swell even more until equilibrium is achieved. Some people call this extra water "free water" or "bulk water." It is further separated by some researchers into "intermediate water," which is situated between the bound water and the "truly free" water that fills the hydrogel's larger pores and voids.

The network's elastic retraction forces oppose the osmotic forces, which are mainly responsible for this continuous swelling. Osmotic forces include both electrostatic interactions and configurational entropy. The hydrogel eventually achieves an equilibrium swelling state as a result of these opposing pressures balancing.

How solutes are absorbed and diffuse through hydrogels is greatly influenced by the type and quantity of water that is absorbed by the polymer. The average pore size, the distribution of pore sizes, and the level of interconnectivity between pores are important variables that affect solute transport. These structural characteristics are primarily governed by the hydrogel’s composition and the density of crosslinking within the network. Furthermore, the solute's size, shape, and hydrophilia or hydrophobia have a big impact on how well it penetrates the hydrogel.

The availability of water molecules to hydrate solute molecules is another key factor influencing solute transport through a hydrogel. Although there are a number of methods for producing persistent hydrogels, radiation-based synthesis is frequently thought to be the most appropriate for use in medical settings.

In the end, the particular polymerization and crosslinking techniques employed during network development greatly influence the hydrogels' solute transport, swelling behavior, and other functional traits.

2.RADIATION-INDUCED HYDROGEL SYNTHESIS

1. Techniques

There are several methods for creating hydrogels with radiation techniques. Pure polymers, monomers, or their solutions—whether in bulk, solution, or emulsion form—can be exposed to radiation. One popular method for this is to irradiate dry hydrophilic polymers. This approach does have certain drawbacks, though. For example, it frequently calls for particular sample preparation techniques, like melting or pressing, and it could be difficult to generate homogeneous macroscopic gels. Furthermore, compared to solution-based irradiation, gelation in the dry state usually requires much greater radiation doses. The challenge of totally eliminating oxygen, which may result in unfavourable side effects, is partially to blame for this [4,5]. In comparison to aquatic conditions, the higher gelation dosage needs in the dry state are also associated with a decreased radiation-chemical yield of radicals. Furthermore, the efficacy of crosslinking is further diminished by the restricted mobility of chains carrying radicals in the dry state.

Monomer irradiation is becoming a more popular technique [6]. In this method, the resultant polymer chains undergo crosslinking after polymerization. When the monomer is easily accessible but the associated polymer is not, this approach is frequently chosen. However, unlike the generally safer polymers, many monomers are poisonous or dangerous, therefore they need to be handled carefully, particularly when making hydrogels for biomedical applications.

2.2. Macroradical Formation

Reactive species, often referred to as macroradicals, are produced inside the polymer chains of a polymer solution upon exposure to ionizing radiation. These radicals can be created directly by radiation striking the molecules of the polymer or indirectly by the polymer reacting with reactive intermediates created in the surrounding water.

Three main reactive species are produced when radiation strikes water: hydrogen atoms, hydroxyl radicals, and hydrated electrons. When it comes to neutral, hydrophilic polymers that are utilized to create hydrogels, hydrated electrons often exhibit little reactivity. Since low-molecular-weight analogs of these polymers usually lack functional groups that effectively scavenge hydrated electrons, this limited interaction is expected and has been seen even with these polymers. The pulse radiolysis method, which tracks variations in the lifetime of the hydrated electron as the concentration of the polymer rises, can be used to determine the reactivity. In these situations, the reaction rate constants are typically less than 1×10^7 dm³ mol^{-1} s^{-1} (see Table 1).

The main reactive species known to transfer radiation-induced reactivity from water to polymer chains are hydroxyl radicals. By removing hydrogen atoms from the macromolecules, they do this. This results in much quicker reactions involving OH radicals, where the rate constants frequently surpass 10^8 dm³ mol^{-1} s^{-1}, particularly in diluted water solutions with average molecular weights.

In general, rate constants tend to decrease with increasing chain length when they are computed using the molar concentration of monomer units rather than entire polymer chains. These rate constants are also influenced by the polymer's concentration. Polymers exist in solution as isolated coils at low concentrations. These coils start to overlap and interpenetrate as concentration increases, eventually uniformly filling the solution volume. The reaction rate constant rises as a result of this structural alteration, becoming nearly independent of molecular weight in concentrated solutions and approaching the values found for comparable low-molecular-weight compounds.

Studies on polymers in acidic environments (where hydrated electrons are transformed to hydrogen atoms) and data from small organic molecules structurally related to the polymers indicate that hydrogen atoms react with these polymers similarly to OH radicals, primarily through hydrogen abstraction. On the other hand, these reactions typically have somewhat smaller rate constants [13]. Since their overall contribution to macroradical generation is still rather small—typically under 20%, and roughly 10% in N_2O-saturated solutions—

unless irradiation takes place in an acidic environment, there aren't many detailed investigations on hydrogen atom interactions with polymers.

Table 1. Selected rate constants for the reactions of hydroxyl radicals (KOH) and hydrated electrons (Ke) with hydrophilic polymers in aqueous solution.
Polymer concentration: 1×10^{-2} mol·dm^{-3} (concentration based on monomer units).
Rate constants are given in dm^3·mol^{-1}·s^{-1}.
Weight-average molecular weights (Mw) are given in Daltons (Da).

Polymer	Molecular Weight (Mw)	KOH (dm^3·mol^{-1}·s^{-1})	Ke (dm^3·mol^{-1}·s^{-1})
PEO [8]	9.1×10^4	1.1×10^8	$< 5 \times 10^6$
PVAL [9]	1.1×10^4	1.5×10^8	$< 9 \times 10^6$
PVP [10]	2.2×10^4	2.0×10^8	Not determined
PVME [11]	$\sim 1 \times 10^5$	2.2×10^8	$< 1.1 \times 10^7$

In most cases, hydroxyl radicals' abstract hydrogen atoms from multiple, non-equivalent positions along a polymer chain, resulting in the formation of two or more structurally distinct macroradicals. An exception is poly (ethylene oxide), where all hydrogen atoms in the polymer are equivalent, allowing the formation of a single type of macroradical. For the neutral polymers studied, these radicals are typically carbon-centered. The structure of these carbon-centered radicals can influence processes such as crosslinking and hydrogel formation. Available data for PVAL, PVP, and PVME suggest that the hydroxyl radical attack on these polymers lacks high selectivity—meaning no single position on the polymer backbone is preferentially targeted [4].

2.3. Macroradicals' Transformation

Practically speaking, intermolecular crosslinking, or the recombination of radicals on separate polymer chains, is the most important change of macroradicals, especially when it comes to hydrogel production. The yield of intermolecular crosslinks (G_x) should be half of the original production of OH and H radicals if this were the only reaction taking place in an irradiated aqueous polymer solution and if hydroxyl radical recombination were minimal. G_x would be roughly 1.6×10^{-7} mol·J^{-1} in deoxygenated solutions (saturated with Ar or However, observed G_x values are frequently much lower in practice. This disparity suggests that instead of engaging in beneficial crosslinking, a large number of the initially generated macroradicals engage in side reactions.

In addition to single-radical processes like hydrogen transfer and chain scission, these side processes also include radical–radical interactions including intramolecular crosslinking and intermolecular and intramolecular disproportionation. These processes do not aid in the creation of macroscopic gels because they do not cause covalent bonds to form between polymer chains.

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The structure of the radicals involved determines the balance between recombination and disproportionation processes, and this parameter is usually hard to control. Nonetheless, the rivalry between intramolecular and intermolecular crosslinking can be influenced. Two recombining radicals are more likely to be found on different chains when polymer chains start to interpenetrate at high concentrations, specifically above the critical hydrodynamic concentration, which varies according on molecular weight. Furthermore, if the chains are connected at two or more locations close to the entanglement site, physical entanglements between them may become permanently integrated into the network.

The outcome of radical reactions is significantly influenced by irradiation conditions, especially the dosage rate, in addition to concentration. For instance, when applied at low polymer

concentrations, high dose rates, like those obtained by pulse irradiation with an electron beam, can produce tens or even hundreds of radicals on a single polymer chain. The likelihood of intermolecular crosslinking is much reduced in these circumstances, which lowers the total yield of network creation.

Kinetic studies can be used to examine the rivalry between intramolecular and intermolecular recombination. While intramolecular recombination frequently shows notable departures from this straightforward kinetic behaviour, intermolecular processes generally follow standard second-order kinetics [14]. The average amount of radicals per polymer chain, as opposed to the overall radical concentration in the system, is more closely correlated with the reaction rate in the case of intramolecular recombination. These dynamics have been successfully described numerically using a non-homogeneous kinetic model.

Although they change the location of radical sites along the polymer backbone, hydrogen transfer reactions do not lower the overall number of radicals in a chain. Consequently, the quantity of radicals accessible for crosslinking is typically not reduced by their existence. These reactions may still have an effect on the final network's microstructure and overall crosslinking effectiveness, though. Since the chance of recombination varies among radical structurzes, this influence results from changes in the initial distribution of radical types. However, it should be mentioned that these effects only become important when there is a large yield from hydrogen transfer processes.

In this context, chain scission—basically the opposite of intermolecular crosslinking—is important. Gel formation does not occur when chain scission has a high yield (more than 4Gx). These scission reactions are thankfully quite slow in deoxygenated solutions, where the chain-breaking precursors are carbon-centered radicals on or near the polymer backbone. Thus, radicals usually recombine before chain scission reaches a detectable level in the neutral polymers considered here.

It is crucial to remember that a rise in molecular weight or even the development of a gel does not always mean that degradation has not taken place. Nonetheless, reliable estimations of scission yields can be obtained using sol–gel analysis and the characterization of irradiation products from model compounds. Under typical irradiation settings, these yields are almost zero for the majority of non-ionic polymers. When oxygen is present or ionic polymers are present, this is not the case.

In aqueous polymer solutions, additives have a major impact on the processes brought on by radiation. To improve crosslinking effectiveness, customize the gel structure, or start grafting reactions, crosslinking agents and monomers are frequently utilized. Complex factors must be taken into account while choosing these chemicals, as well as the underlying reaction mechanisms and ideal processing conditions. These subjects, in our opinion, are worthy of a separate investigation and won't be covered in depth here.

One ingredient that has the most influence is oxygen. Every piece of information that was previously addressed relates to deoxygenated systems. The first carbon-centered macroradicals quickly react with oxygen in oxygen-containing polymer solutions to yield peroxyl radicals. This reaction has a rate constant of about 10^9 dm^3 mol^{-1} s^{-1}, making it incredibly fast—basically diffusion-controlled [15].

In this case, three important points are pertinent. First, when recombining, neither oxyl nor peroxyl radicals create stable crosslinks. Low efficiency oxyl radical recombination results in a peroxide bond that is not regarded as a stable crosslink. Second, chain scission is the outcome of one of the main reaction routes involving these radicals. Lastly, peroxyl radicals may participate in a chain reaction involving hydrogen abstraction when termination processes are delayed. This is followed by the newly produced alkyl radical reacting with oxygen, thereby perpetuating the cycle.

The information above does not necessarily imply that irradiating oxygen-saturated polymer solutions or exposing them to air cannot result in the formation of hydrogels. First, there may be an initial induction period where deterioration is predominant when irradiation is done in sealed containers. But after the oxygen has been used up, more radiation may cause crosslinking and gel formation. If the rate of oxygen diffusion from the surface into the bulk is slower than the rate of oxygen consumption, which can be facilitated by employing a high dosage rate, a similar situation might arise when the solution is exposed to radiation in open vessels.

Hydrogel production is still possible during irradiation even when oxygen is present. The recombination of carbon-centered radicals

efficiently competes with their reaction with oxygen when oxygen-saturated PVP solutions are exposed to pulsed electron beam irradiation at high doses per pulse (400 Gy or higher), as shown by Rosiak et al. [17]. A state where crosslinking overcame chain scission was achieved by raising the concentration of the polymer to encourage intermolecular crosslinking. However, the basic idea that hydrogel production is more effective in oxygen-free settings is not refuted by these results.

3. HYDROGELS MADE COMMERCIALLY USING RADIATION METHODS

Nowadays, hydrogels made via radiation techniques are extensively employed as biomaterials in a number of industries, such as:
artificial coverings for wounds;
transdermal applications and drug delivery systems;
dental supplies;
implants;
systems of injectable polymers;
eye care items;
artificial organs that are hybrids and include living cells.

The radiation synthesis of hydrogels is still a vibrant and expanding area of study and application, even with the substantial amount of literature and multiple patents on the subject.

Only a small number of radiation-synthesized hydrogels have been marketed, despite a large number of studies and suggestions from researchers to use them in biomedical applications. All of the commercial products that are currently on the market are classified as synthetic wound dressings.

Thin films, hydrocolloid/hydrogel dressings, alginate-based dressings, biological or biosynthetic healing materials, and polyurethane absorbent dressings are some of the main categories into which contemporary synthetic wound care treatments can be divided. Sales of synthetic wound care products and associated services were over US$341 million in the U.S. market alone. This accounts for roughly 16.6% of the worldwide wound care market, which is worth over US$2 billion and comprises both conventional and modern bandages and dressings, for US-based businesses who compete in this industry.

Total sales of synthetic wound dressings were predicted to reach US$680 million by the year 2000, essentially double the 1995 levels, with an expected average annual growth rate of 14–15% through the end of the decade (see Table 2). Given the numerous cutting-edge wound care technologies, novel therapy strategies, and sophisticated treatment items that have recently been developed as well as those anticipated to hit the market soon, these estimates are regarded as cautious.

Among hydrocolloid and hydrogel dressings—which dominate this market segment and account for the highest sales volume—continued demand is expected, barring significant shifts in healthcare trends. Leading products in this category on the U.S. market include ConvaTec's DuoDERM®, Coloplast's Comfeel®, Hollister's Restore®, and Smith & Nephew's IntraSite® and Replicare® [18]. Radiation-produced hydrogel dressings make up a very modest portion of the global hydrocolloid/hydrogel market. These dressings belong to the class of "true" hydrogels, where covalent connections permanently crosslink the polymer chains. They have a number of advantageous qualities as wound coverings, including the ability to absorb wound exudate, the inability to stick to freshly created tissue, the ability to let oxygen to the wound site, the ability to reduce pain, and the ability to generally speed up healing.

Table 2. Global and Japanese Markets for Synthetic Wound Dressings – Historical and Projected Data
The table below presents the market performance and forecast for various categories of synthetic wound dressings in both global and Japanese markets for the years 1995, 1997, and 2000. The figures are shown in total market value (US$ million) and Japanese market value (in thousands of yen), along with the percentage share of each category.

Group of Dressings	Year	Global Market (US$ million)	% Share	Japan Market (¥ thousands)	% Share
Polymer Thin Films	1995	49.5	14.5%	340,684	7.28%
	1997	57.7	13.2%	367,938	6.89%
	2000	72.7	10.7%	397,373	6.44%
Hydrocolloids / Hydrogels	1995	126.7	37.1%	3,136,787	67.00%
	1997	167.6	38.3%	3,607,305	67.60%

Group of Dressings	Year	Global Market (US$ million)	% Share	Japan Market (¥ thousands)	% Share
	2000	268.4	39.5%	4,184,473	67.78%
Polymer Absorbent Dressings	1995	47.8	14.0%	749,006	16.00%
	1997	60.5	13.8%	842,631	15.79%
	2000	86.1	12.6%	977,451	15.83%
Alginate Dressings	1995	22.5	6.6%	100,000	2.14%
	1997	30.3	6.9%	116,000	2.17%
	2000	52.3	7.7%	139,200	2.25%
Other Biological / Biosynthetic	1995	94.7	27.8%	754,769	7.58%
	1997	122.0	27.8%	402,662	7.55%
	2000	200.4	29.5%	475,141	7.70%
Total Market	1995	341.2	100%	4,681,246	100%
	1997	438.1	128.4% (vs. 1995)	5,336,536	114.0%
	2000	679.9	199.3% (vs. 1995)	6,173,638	131.9%

Three hydrogel dressing items made with radiation technology are now on the market worldwide. Among these are AQUAGEL®, which is made in Poland by KIK-Gel Company [19], NuGel®, which is made by Johnson & Johnson Medical [20], and a wound dressing created in Japan by Nichiban Corporation, which does not yet have a registered trade name because it is pending official approval for release on the domestic market [21]. The overall technological approach seems to be quite constant across all three products, despite minor differences in the additives and manufacturing processes.

- An aqueous mixture comprising one or more hydrophilic polymers that can undergo radiation-induced crosslinking and crosslinking inhibitors (additives) in amounts adequate to regulate the degree of crosslinking during exposure to ionizing radiation is prepared to create a sterile adhesive hydrogel dressing. After shaping the mixture into a specific shape and sealing it in sterile packaging, it is exposed to radiation at a dose high enough to accomplish both crosslinking and sterilizing at the same time. Poly (ethylene oxide), poly (vinyl alcohol), and poly (vinyl pyrrolidone) are common hydrophilic polymers utilized in this method. A variety of materials can be included as useful additives, including:
- Antioxidant compounds, particularly food-grade antioxidants such as ascorbic acid and polysaccharides, which help stabilize the formulation;
- Biocompatible humectants, including substances like poly (ethylene glycol), poly (propylene glycol), and ethyl lactate, which help retain moisture and enhance skin compatibility;
- Crosslinking promoters, such as ethylene glycol dimethacrylate, triethylene glycol dimethacrylate, and N,N'-methylenebisacrylamide, which facilitate the formation of the hydrogel network during irradiation.

To improve the hydrogel dressing's structural integrity, reinforcing materials such films, release liners, foils, fibers, mats, linen, or non-woven polyethylene scrim can be used if desired. Both gamma rays and electron beams are acceptable types of ionizing radiation, and the usual radiation dose used during production is between 20 and 40 kGy. The manufacture of hydrogel dressings can be done continuously or in batches.

The final hydrogels may differ in electrical conductivity, adhesiveness, mechanical strength (including tensile strength and elasticity), and absorption capacity based on the manufacturer's particular formulation. However, their therapeutic qualities and medical efficacy are often similar.

4. CONCLUSION

Even with the widely acknowledged benefits of employing ionizing radiation to create and alter hydrogels and other biological materials, there is still a big disconnect between scholarly study and

large-scale manufacturing. For radiation chemists, closing this gap remains a challenge. Nonetheless, this area of study and technology advancement has a lot of potential because healthcare will continue to be a top priority on the international political, social, and economic agenda for the foreseeable future. Technological developments in radiation processing are probably going to become more and more important in addressing the changing needs of contemporary medicine.

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