

CURRENT SCENARIO OF CHALLENGES AND OPPORTUNITIES IN HYDROGELS SYNTHESIS FOR BIOMEDICAL APPLICATIONS

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Abstract

Hydrogels are networks of hydrophilic polymers that are three-dimensional and have a great capacity to contain water and biological fluids. Hydrogel's unique structure and swelling behavior have a significant impact on its biological and water-holding capabilities. These polymer networks are formed through physical crosslinking such as heating/cooling of polymer solution, hydrogen bonding, hydrophobic interactions, crystallization, ionic interactions and chemical crosslinking such as free radical polymerization, click reactions, grafting, enzymatic crosslinking. Physically crosslinked hydrogels are formed by weak secondary forces while chemical hydrogels are formed by covalent forces. Due to swelling behavior, mechanical properties and other biological properties hydrogels are used in various biomedical applications such as contact lenses, drug delivery system, wound dressings, and tissue engineering. The primary objective of this article is to review the literature regarding the structure of hydrogels, classification of hydrogels on different basis and challenges and opportunities for synthesis and their biomedical applications.

INTRODUCTION

Hydrogels are three-dimensional networks of water-based polymers that can be composed of natural or synthetic materials with great elasticity. These kinds of structures can hold different amounts of water depending on the type of polymer used and the density and type of the network joints. When a hydrogel is in swollen state, the mass fraction of water is usually much higher than the mass fraction of polymer (Rosiak & Ulański, 1999). Hydrogels are ideal for a wide range of applications because of their soft, elastic

texture, which is similar to that of living tissues, and their capacity to hold onto huge volumes of water or biological fluids under physiological conditions (Ullah *et al.*, 2015). Hydrogels are incapable of being dissolved because polymer chains are linked together, but they can absorb water because they have hydrophilic functional groups connected to the polymer backbone. Hydrogels include a wide range of both man-made and natural materials (Ahmed, 2015). The desired properties of a hydrogel include high viscoelasticity, flexibility, biocompatibility, and

permeability (Ahsan *et al.*, 2021).

The word 'hydrogel' was first used in 1894 to describe a colloidal gel, while the first documented application of hydrogels in the biomedical field was presented by Wichterle and Lim in 1960 (Thakur *et al.*, 2018). The first time a hydrogel was used in biomedical implants was in 1949, when poly(vinyl alcohol) was cross-linked with formaldehyde and sold under the name Ivalon. Wichterle and Lim created poly(2-hydroxyethyl methacrylate) (pHEMA) gels for use in contact lenses in 1960. This was the beginning of modern hydrogel technology (Rizwan *et al.*, 2017). Since then, "hydrogel" has been used to characterize the three-dimensional structure of hydrophilic polymers (Dodda *et al.*, 2023). The literature that is now available details polymeric hydrogels with novel chemical structures, improved physical characteristics, and creative uses dating back to the 1970s (Mishra *et al.*, 2018).

When polymer chains cross-link, they make three-dimensional networks that make up hydrogels. This cross-linking can happen in a number of ways, such as covalent bonding, by van der Waals forces, hydrogen bonding, or other physical interactions. When hydrogen bonds, hydrophobic effects, ionic interactions, or chain entanglements happen, they make transient connections in physically cross-linked hydrogels. Chemically cross-linked hydrogels, however, have permanent junctions because of stable covalent connections (Ahmed, 2015).

There are many hydrophilic groups or moieties in the crosslinked network of hydrogels. The chemical residues that make this hydrophilic include mostly carboxylic, sulfonic, amide, hydroxyl, primary amide groups, and others that are located on the polymer backbone or as side chains. These chemical groups join the polymer backbones in a chemical or physical manner. These hydrogel swells as water molecules get into the polymer network, but it may go back to its previous structure (Khan *et al.*, 2016). Hydrogels may vary and adapt to several environmental changes, like variations in pH, electric fields, ionic strength, temperature, and the presence of enzymes (Zaman *et al.*, 2015).

1. Hydrogel structure

The chemical composition, structure, and equilibrium swelling of a hydrogel influence their mechanical strength and the movement of chemicals into and out of cells (Chamkouri & Chamkouri, 2021). Because of their flexible physical features, adjustable degradability, and capacity to protect unstable medications from breaking down, hydrogels are a great way to study different physical and chemical interactions with encapsulated drugs for controlled release (Khan *et al.*, 2022). Hydrogels display varying properties based on their crosslinking ratio, influencing their swelling behaviour. An increased crosslinking ratio produces a denser network with diminished swelling, while a decreased crosslinking ratio yields softer polymeric structures with enhanced swelling capacity. Recent advancements in various methodologies enable precise modulation of hydrogel rigidity and pliability through the adjustment of crosslinking density. These property changes frequently determine their appropriateness for particular pharmaceutical and biological uses (Kaith *et al.*, 2021).

The crosslinking process has an impact on mechanical strength, heat and solvent resistance, and molecular mass. When the hydrogel is crosslinked chemically or physically, it forms a three-dimensional structure that traps and releases therapeutic substances, such as medications and biomolecules. The characteristics of hydrogels and how they are used in different medical domains are examined, for instance Drug delivery could be accomplished with hydrogels of various sizes, shapes, and functions (Figure 1) (Chamkouri & Chamkouri, 2021).

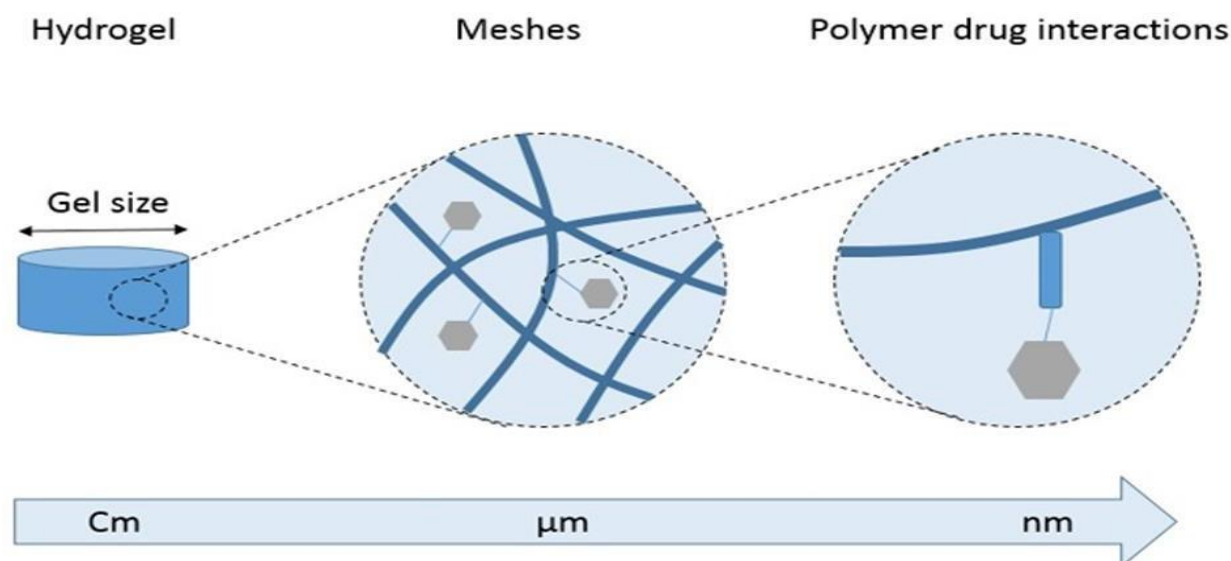


Figure 1. Multiscale properties of hydrogels (Chamkouri & Chamkouri, 2021)

Hydrogels are made up of three-dimensional networks of polymer chains that are randomly crosslinked. These networks establish a structural framework comprising three distinct phases. The initial phase consists of a robust polymer matrix, while the second phase is either biological fluid or interstitial water. The solid part is made up of crosslinked polymer chains that form a mesh-like structure with spaces between them that are filled with fluid. These polymer meshes not only hold the fluid, but they also offer elastic forces like rubber that keep the hydrogel from swelling or shrinking, which keeps its dimensions stable. The fluid that fills the holes in the network makes hydrogels squishy and wet, which is comparable to how real tissues work (Singhal & Gupta, 2016). Hydrogels can absorb water from 10–20% of their dry weight, regarded as a modest quantity, to several thousand times their dry weight. The characteristics of the water in a hydrogel

significantly influence the infiltration of nutrients and the expulsion of cellular wastes (Chirani *et al.*, 2015). Figure 2 illustrates the molecular structure of hydrogels and the various types of water they encompass. Water in a hydrogel network manifests in four distinct forms: (i) free or bulk water, which is loosely retained outside the network and can be readily extracted under standard conditions; (ii) interstitial water, physically confined within the voids of the hydrated polymer network but not chemically bonded; (iii) bound water, which is chemically linked to the polymer chains via hydrating functional groups or ions and can only be removed under particular conditions, as it is an essential component of the hydrogel; and (iv) semi-bound water, which displays properties intermediate between bound and free water (Singhal & Gupta, 2016).

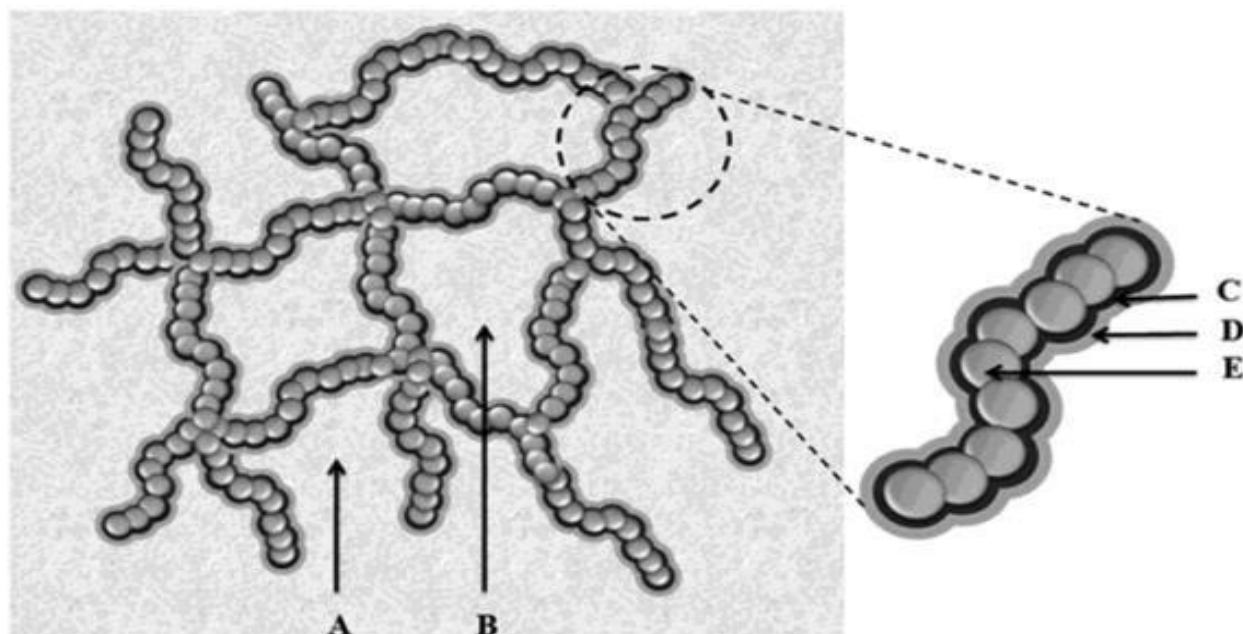


Figure 2. Molecular framework of hydrogel network. A: Free water, B: Interstitial water, C: Bound water, D: Semi-bound water, E: Monomer (Singhal & Gupta, 2016)

Despite all of its advantages, hydrogels have certain limitations (Garg *et al.*, 2016). Among the disadvantages of hydrogels is their low mechanical strength, which is particularly problematic when they are utilized as scaffolds for tissue engineering or in any application that requires strong mechanical strength with great elasticity and compression tolerance (such as cartilage tissues). Because of their poor mechanical qualities, they are challenging to load and manage in various body areas (Rafieian *et al.*, 2019).

2. Classification of hydrogels

Hydrogels can be classified based on various criteria, as outlined below:

2.1. Classification based on source

According to their source, hydrogels are

categorized as either natural (alginate, collagen, dextran, agar-agar, chitosan, gelatin, etc.) or synthetic (poly(vinyl alcohol) (PVA) or poly(ethylene glycol)-poly(lactone)-poly(ethylene glycol) (PEG-PL-PEG)) (Subramanian & Vijayakumar, 2015) and hybrid hydrogels.

2.1.1. Natural hydrogels

In addition to having outstanding biocompatibility and biodegradability, natural hydrogels have significant cell adhesion characteristics. The two main natural polymer kinds that they are composed of are proteins and polysaccharides. Proteins include lysozyme, collagen and gelatin, while polysaccharides like chitosan and alginate are employed (Ahmad *et al.*, 2022).

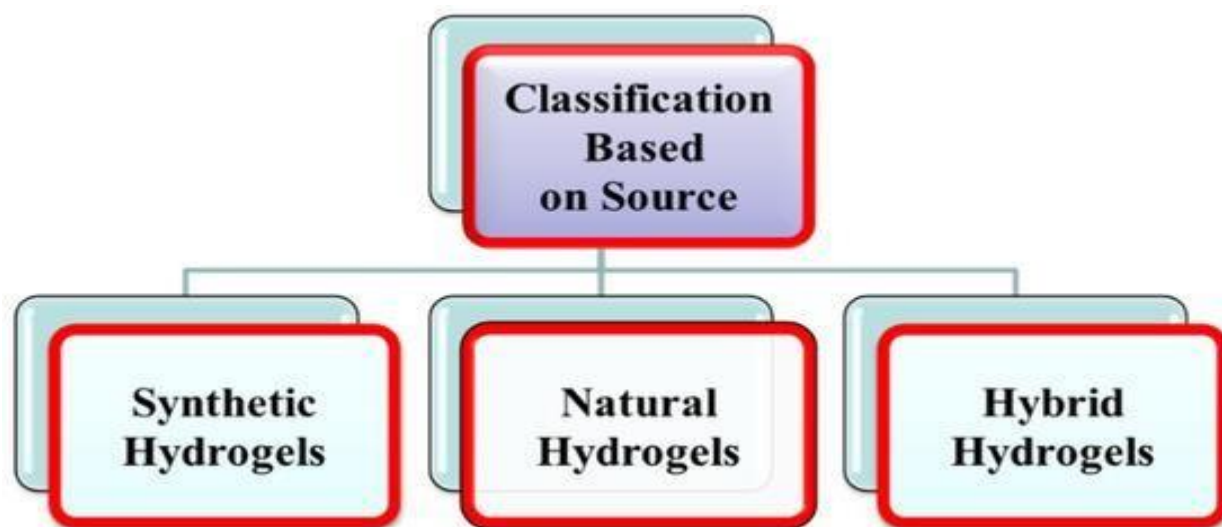


Figure 3. Classification of hydrogels according to their origin (Ahmad *et al.*, 2022)

2.1.2. Synthetic hydrogels

Synthetic hydrogels are usually less reactive than natural hydrogels made from biomaterials since they are made of artificial polymers. Compared to natural hydrogels, they hold water better, last longer, and are easier to change (Khansari *et al.*, 2017). For the past few years both natural and synthetic hydrogels are becoming more and more prevalent. The main benefits of synthetic hydrogels are their high product purity, more consistent lot-to-lot consistency, and lack of immunogenicity problems. (Mehta *et al.*, 2023). Applications requiring a material that is both non-soluble and has strong compatibility with aqueous solvents can benefit from synthetic hydrogel networks. These applications include electrophoresis gels, chromatographic packings, controlled-release devices, and biomaterials. Synthetic hydrogels have a number of advantages that make them suitable for biomedical uses that need to interact with biological tissues (Mathur *et al.*, 1996).

2.1.3. Hybrid hydrogels

Hybrid hydrogels are formed by integrating natural and synthetic polymer hydrogels. These systems amalgamate the advantages of both material types, yielding improved characteristics and functionality. Hybrid hydrogels, through the amalgamation of various components, can

demonstrate enhanced performance, rendering them ideal for a range of biomedical applications (Maleki *et al.*, 2025).

2.2. Classification Based On Polymeric Composition

2.2.1. Homopolymeric hydrogels

These materials are produced from a singular type of monomer. Depending on the polymerisation method and the characteristics of the monomer, they may display skeletal cross-linking. The resultant polymer chains may be organized in random, block, or alternating configurations. (Chelu & Musuc, 2023).

2.2.2. Co-polymeric hydrogels

Copolymeric hydrogels consist of two distinct types of monomers, with a minimum of one being water-soluble. These hydrogels are often sourced from natural origins. An example is the triblock polycaprolactone-polyethylene glycol copolymer (PECE), which has been developed as a hydrogel matrix for pharmaceutical delivery applications. (Chuang *et al.*, 2018). Copolymers can be divided into three groups based on the order of their monomer units: block copolymers (with groups of the same monomer), alternating copolymers (with monomer units that switch places frequently), and random copolymers (with

monomers that are mixed up without a set order) (Figure 4) (Ho *et al.*, 2022).

2.2.3. Semi-Interpenetrating polymeric hydrogels (Semi-IPN)

When a linear polymer gets physically tangled up in another cross-linked polymer network without making any covalent bonds between the two polymer systems, it produces a semi-interpenetrating network (semi-IPN). (Waqar *et al.*, 2024).

2.2.4. Interpenetrating polymeric hydrogels

IPNs are formed by two distinct kinds of polymer chains which are cross-linked with each other (Madduma-Bandarage & Madihally, 2021). The most significant is interpenetrating network hydrogel (IPN), which is a network-like mixture of crosslinked polymers. One polymer is created or crosslinked in IPN when another polymer network is present. Because of IPN's mechanical qualities, particularly its hardness, researchers are becoming more interested in it (Aswathy *et al.*, 2020).

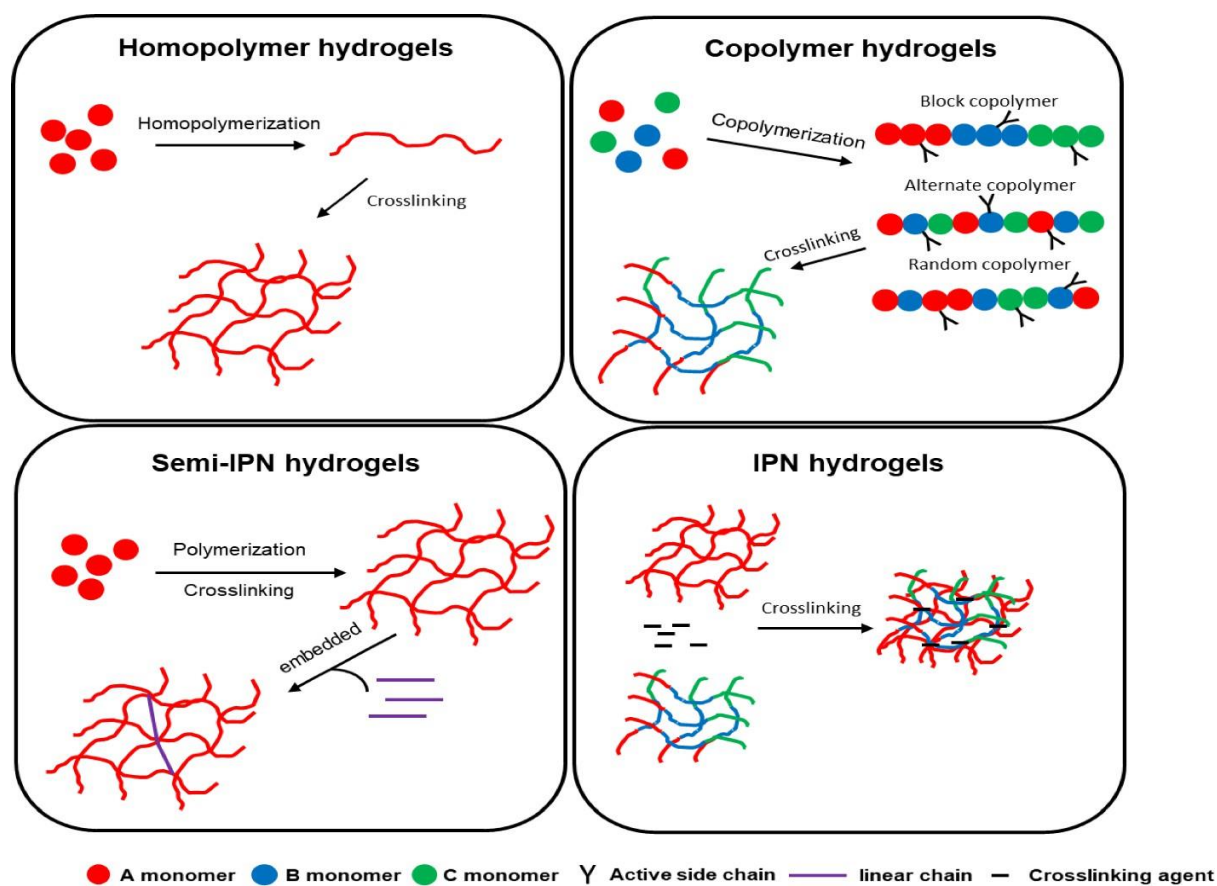


Figure 4. Classification based on polymeric composition (Ho *et al.*, 2022)

2.3. Classification based on cross-linking

Crosslinking is necessary to improve characteristics enhance surface properties, and increase hydrogel functionalization. The two primary methods of hydrogel crosslinking are physical crosslinking and chemical crosslinking (Su *et al.*, 2024).

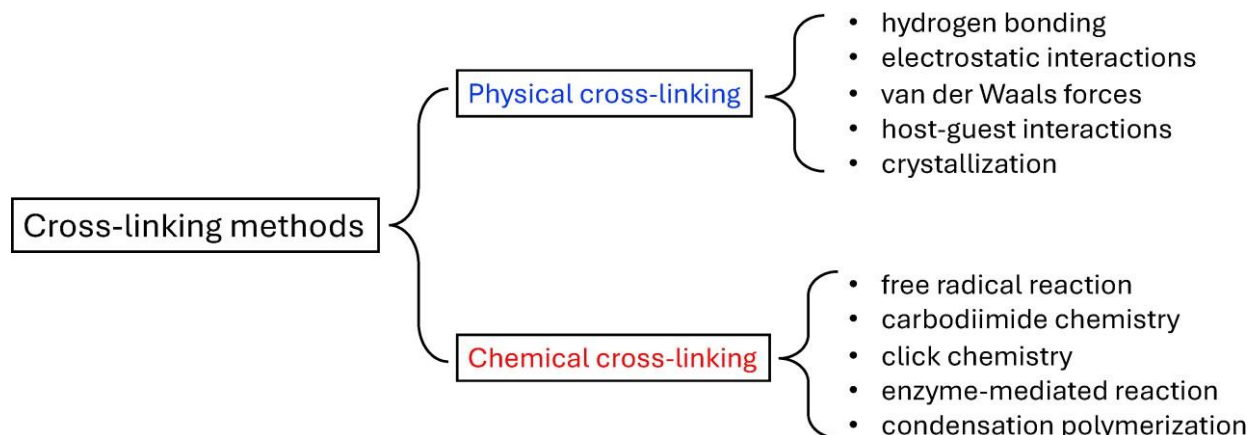


Figure 5. Classification of Hydrogels Based on the Methods of Cross-Linking Formation (Liu & Chen, 2024)

2.3.1. Physical crosslink hydrogels

Physical hydrogels are formed from low-molecular-weight chemicals or polymers by non-covalent interactions, including electrostatic forces, hydrogen bonds, van der Waals forces, and specialised host-guest interactions. The reversible bonds permit physical gels to demonstrate flexibility and responsiveness, facilitating their transition between gel and sol states in response to environmental alterations such as pH, temperature, or ionic strength. (Liu & Chen, 2024). In physiological conditions, these kinds of hydrogels usually don't last for a long time, from a few days to a month at most. Physical hydrogels therefore benefit from this and are employed in situations when a brief release of the medicine is required (Bashir *et al.*, 2020). Chemical crosslink

hydrogels Chemical hydrogels, as opposed to physical hydrogels, are created by covalently crosslinking biopolymers at particular locations. During the crosslinking process, crosslinkers unite polymer chains to make a stable and even network. You can regulate the production and properties of chemical hydrogels more precisely by changing the crosslinking conditions instead of only depending on pH. Important hydrogel properties, including mechanical strength, biodegradability, and swelling behaviour, can be altered by chemical crosslinking. There are many ways to make covalent crosslinks, such as using small molecules, ionizing radiation, and free radical polymerisation processes. Because of their increased stability and durability, chemically crosslinked hydrogels are appropriate for longer-term uses (Said *et al.*, 2023).

2.4. Classification based on configuration

There are different types of hydrogels based on their chemical composition and how their structures are organized: Amorphous (having no clear crystalline structure), Semicrystalline (which have both amorphous and crystalline areas), Crystalline (which have a well-organized, ordered molecular structure) (Mohite & Adhav, 2017). In 1994, scientists used chemical crosslinking methods to make semicrystalline hydrogels, which have both crystalline and amorphous areas. It is also possible to make physically crosslinked

semicrystalline hydrogels utilizing micellar and bulk polymerisation processes. Unlike chemically crosslinked semicrystalline hydrogels, physically crosslinked semicrystalline hydrogels can change from solid to liquid and back again. This characteristic makes them useful as shape-memory and injectable hydrogels (Aswathy *et al.*, 2020).

2.5. Classification based on ionic charge

Hydrogels are classified into three groups on the basis of nature of electric charge on the cross-linked chains.

2.5.1. Neutral (Non-Ionic) hydrogels

Neutral hydrogels don't possess any electrical charge on their primary polymer backbone or their side chains, therefore they don't act like ions in water.

2.5.2. Ionic hydrogels

There are two kinds of ionic hydrogels: cationic and anionic. Cationic hydrogels have functional groups that are positively charged, like amines, and they tend to swell more in acidic (low pH) environments. Anionic hydrogels, on the other hand, have negatively charged groups like carboxylic or sulfonic acids and swell more in basic (high pH) environments.

2.5.3. Ampholytic hydrogels

Ampholytic hydrogels have groups that are both positively and negatively charged along the same polymer backbone. These hydrogels achieve a point of balance called the isoelectric point, where the overall charge is neutral since there are equal amounts of both sorts of charges (Thakur *et al.*, 2018).

3. Synthesis of hydrogels

Hydrogels comprise polymer networks. Consequently, the characteristics of the polymer

constrain the attributes of the hydrogel (Madduma-Bandarage & Madihally, 2021). Polymers made from carbohydrates are commonly used to generate both physical and chemical hydrogels because they are readily available, have a wide range of functional groups, are biocompatible, and have other useful features (Chamkouri & Chamkouri, 2021). Stable polymer networks are mostly crosslinked to generate hydrogels. Physical and chemical crosslinking procedures are the two main ways to accomplish this crosslinking (Hu *et al.*, 2019). Covalent linkages connect more than one polymer chain in chemically crosslinked gels. On the other hand, physically crosslinked gels don't dissolve since the polymer chains interact with each other through physical interactions (Hennink & van Nostrum, 2002). Theoretically, many uses of hydrogels can be achieved by optimizing their properties, which are influenced by the degree of crosslinking (Sikdar *et al.*, 2021).). Glutaraldehyde is one of the compounds used to crosslink hydrogels. Dialdehyde, formaldehyde and epoxy compounds are further crosslinking agents (Maitra & Shukla, 2014).

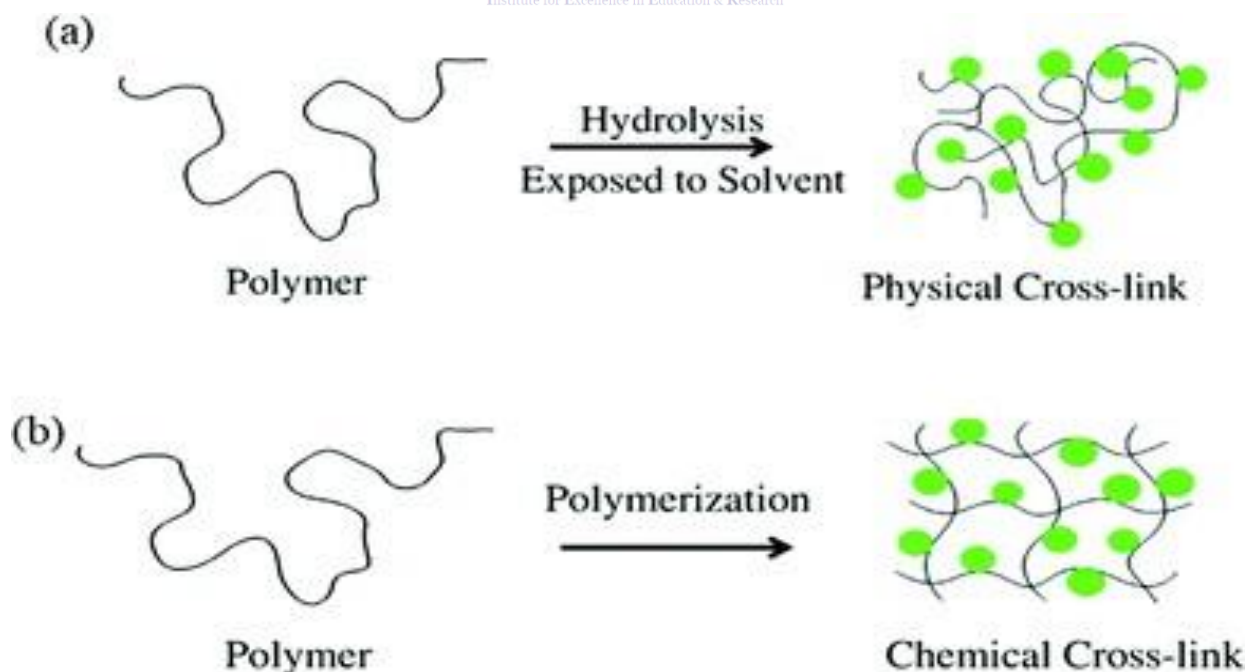


Figure 6. Polymeric composition-based classification (Maitra & Shukla, 2014)

3.1. Physical crosslinking

For the formation of hydrogels, polymer networks need to meet two primary requirements: (a) strong connections between the chains to create a stable molecular framework, and (b) the network must be able to let water soak into and retention in the gel. Non-covalent approaches like hydrophobic interactions, hydrogen bonding, and electrostatic forces between polymer chains can be used to meet these criteria. These kinds of interactions make hydrogels that are very sensitive to water and vary their behaviour when the temperature changes (Bashir *et al.*, 2020). Compared to chemical crosslinking procedures, physical crosslinking methods are gentler, easier to use, and offer better

biocompatibility and reduced toxicity because they don't require external chemical agents. High temperatures, however, can cause hydrogels made via physical crosslinking to lose their three-dimensional structure or deteriorate (Song *et al.*, 2022). Scientists have become more interested in physically crosslinked hydrogels in the last few years because they have special features that let the network mend itself and handle mechanical stress. By dissipating energy through sacrificial links that break under stress and help prevent permanent damage, these hydrogels can improve their mechanical performance and robustness (Li *et al.*, 2020).

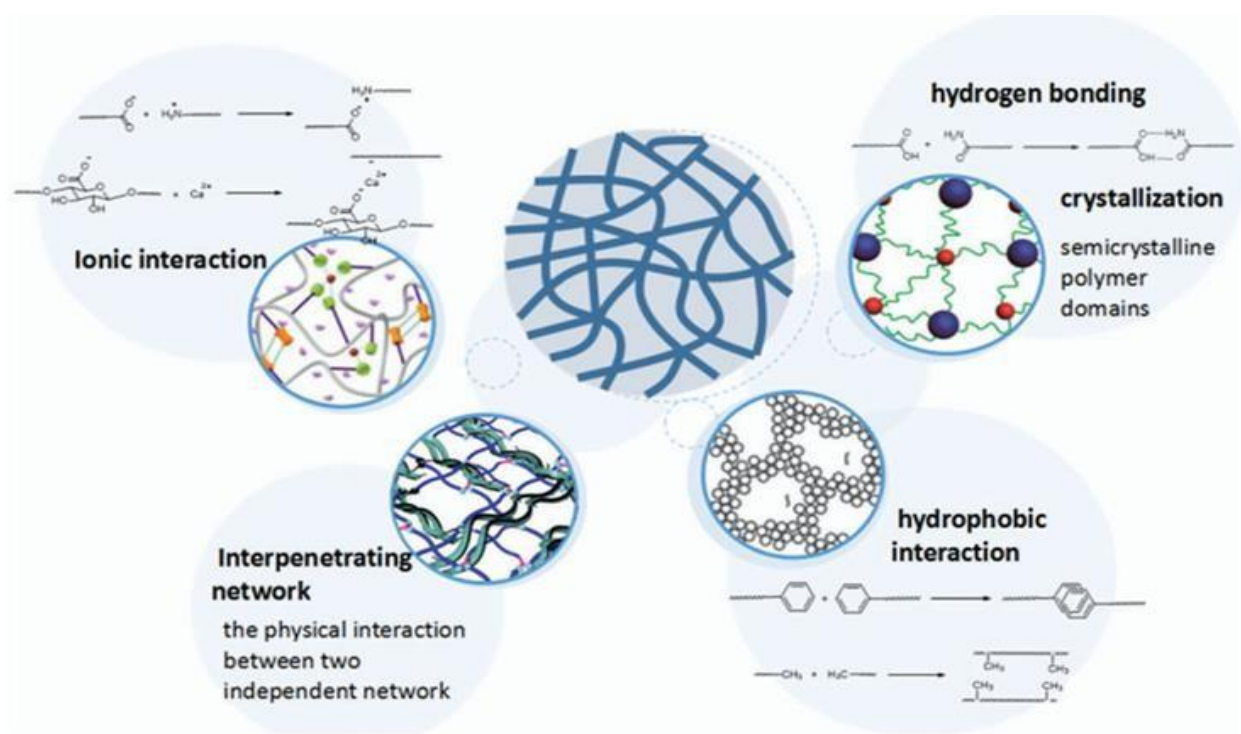


Figure 7. An illustration of the non-covalent bonding mechanism for hydrogel production (Huang *et al.*, 2017).

3.1.1. Heating/Cooling of a polymer solution

Cooling heated polymer solutions, like those of gelatin or carrageenan, can make physically cross-linked hydrogels. In these systems, gelation happens when helical structures form and stick together, which creates junction zones. When carrageenan cools down, for instance, it turns into

stiff helical rods. In some situations, heating polymer solutions can cause block copolymerisation to happen, which makes hydrogels. Polyethylene oxide-polypropylene oxide and polyethylene glycol-poly(lactic acid) block copolymers are two notable examples of hydrogels (Gulrez *et al.*, 2011).

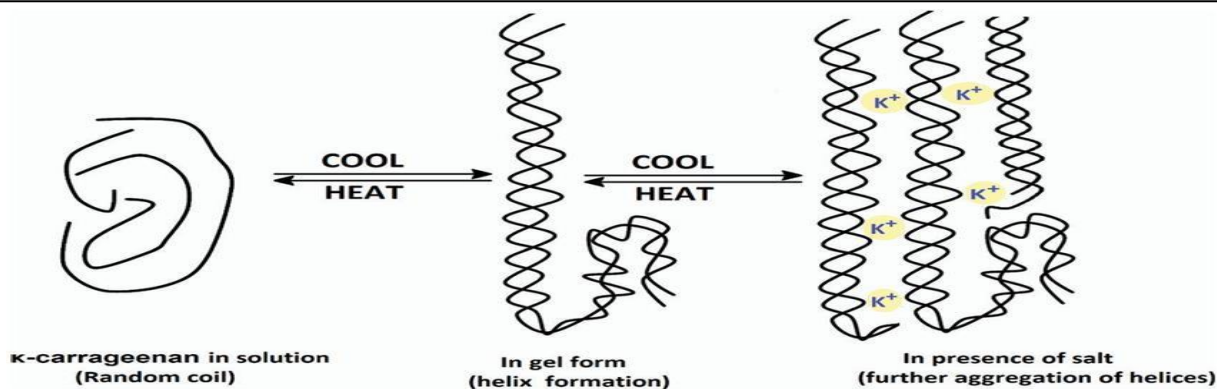


Figure 8. Formation of a carrageenan hydrogel (Khan *et al.*, 2022)

3.1.2. Hydrogen bonding

Self-assembled crosslinking by non-covalent interactions is based on hydrogen bonding, electrostatic interactions, and their combinations. These interactions can create hydrogels that are very elastic and shear-thinning, which makes them great for things like 3D bioprinting. (Song *et al.*, 2022). Polyacrylic acid and polymethacrylic acid can form complexes with polyethylene glycol by hydrogen bonding. In this process, the oxygen atoms in polyethylene glycol engage with the carboxylic acid groups in the other polymers. It is also possible to find this kind of hydrogen bonding in poly(methacrylic acid-g-ethylene glycol) systems. These interactions only happen when the carboxylic acid groups are protonated, which means that the gel's expansion depends on the pH (Akhtar *et al.*, 2016). However, water molecules can readily break the hydrogen bonds in a hydrogel, which can impair the stability of the network and lessen the efficiency of crosslinking in aquatic settings. Consequently, the development of functional hydrogels utilizing hydrogen bonding remains a formidable challenge. Diverse ways have been investigated to create highly efficient hydrogen bond crosslinking systems (Yu *et al.*, 2022).

Hydrogen bonds are a suitable choice for physical crosslinking in hydrogels due to their robust physical interaction, which plays a crucial function in biological systems, exemplified by the stabilization of the DNA double helix through the cohesion of its two strands. Despite this, the production of polymer hydrogels still faces

difficulties in creating strong and long-lasting hydrogen bonds because water molecules frequently obstruct or totally destroy these connections. In order to get over this restriction, Hu *et al.* proposed using clay nanosheets as "bridging" agents to join synthetic polymer chains together. Furthermore, studies have emphasised the application of specific natural macromolecules, like celluloses and polysaccharides, as well as artificial polymers, like polyvinyl alcohol, which are recognized for their ability to create intramolecular and intermolecular hydrogen bonds (Li *et al.*, 2020).

3.1.3. Crystallization

The technique involves freezing and thawing. This approach involves freezing and thawing a polymer solution several times, which causes a hydrogel to form with a coiled shape (Khan *et al.*, 2022). Polyvinyl alcohol is a naturally hydrophilic polymer that forms a weak gel when mixed with water at room temperature. But when the polyvinyl alcohol solution goes through cycles of freezing and thawing, it makes a gel that is very strong and stretchy (Akhtar *et al.*, 2016).

3.1.4. Ionic interactions

Ionic interactions are often used to connect natural polysaccharides like chitosan and alginate together in a physical way to make hydrogels. For this purpose, alginate has been investigated extensively. It usually makes ionic gels by swapping out sodium ions in its guluronic acid units for divalent cations including calcium (Ca^{2+}),

strontium (Sr^{2+}), and barium (Ba^{2+}) (Huang *et al.*, 2017). Hydrogels that form through ionic interactions have great ionic conductivity, resistance to fatigue, responsiveness to the environment, and the ability to heal themselves. But their potential in many areas is limited because they don't have enough mechanical strength and the production process is excessively complicated. Researchers are focusing more and more on making new hydrogels to get around these problems. For example, the PAAC/HACC hydrogel has a strong structure because it has a lot of dynamic ionic interactions between the negatively charged acrylic acid (AAC) and the positively charged 2-hydroxypropyl trimethylammonium chloride chitosan (HACC) (Su *et al.*, 2021).

3.1.5. Hydrophobic interaction

Amphiphilic polymers autonomously generate hydrogels in aqueous environments owing to the contrasting characteristics of their hydrophilic and hydrophobic segments, propelled by hydrophobic interactions. (Liao *et al.*, 2018). Hydrophobic interactions provide an innovative approach for the development of biomedical hydrogels. Two principal mechanisms exist for the formation of hydrogels via hydrophobic interactions. The initial technique employs micelles as cross-linking agents (Gong *et al.*, 2013). Pharmaceuticals can be included into these copolymers for wound management. The second method involves attaching hydrophobic groups to a hydrophilic precursor

(Zubik *et al.*, 2017). incorporating hydrophobic groups to hydrophilic polysaccharide structures gives amphiphilic polymers a wide range of versatile characteristics.

Hydrophobic interactions are often employed to make thermosensitive dressings. The manner in which hydrogels respond to temperature changes in water depends on the right balance of hydrophilic and hydrophobic parts within a

certain temperature range (Moon *et al.*, 2012). In biological applications, hydrogels that can change from a sol to a gel state within the physiological temperature range of 10–40 °C have gotten a lot of interest. Poly(ethylene glycol) (PEG) and poly(N-isopropyl acrylamide) (PNIPAM) are two well-known examples that show how these materials could be used to make biological gels that respond to heat (Yan *et al.*, 2019). Hydrogels that are cross-linked by hydrophobic interactions typically demonstrate superior adhesive properties to tissues, particularly live tissues in moist environments, such as lungs and blood vessels (Du *et al.*, 2019). This characteristic is advantageous for hemostasis and facilitating wound repair (Pan *et al.*, 2021).

3.2. Chemical crosslinking

Chemical crosslinking is a means of joining monomers along the polymer backbone by interactions between their functional groups (such OH, COOH, and NH_2) and crosslinking agents like aldehydes, such as glutaraldehyde and adipic acid dihydrazide. Numerous methods documented in the literature exist for the acquisition of chemically crosslinked persistent hydrogels. (Merati *et al.*, 2018).

There are three main parts that comprise hydrogels: the monomer, the initiator, and the cross-linker. To adjust the polymerisation temperature and change the final properties of the hydrogels, people commonly utilise diluents like water or other aqueous solutions. After making the hydrogel mass, it needs to be properly washed to get rid of any impurities, like unreacted monomers, initiators, cross-linkers, and other undesired byproducts that may have produced during side reactions (Ahmed, 2015). Moreover, the incorporation of degradable linkers into the covalent crosslinks enables the creation of precisely specified network topologies with customizable features over time (Lin & Anseth, 2009).

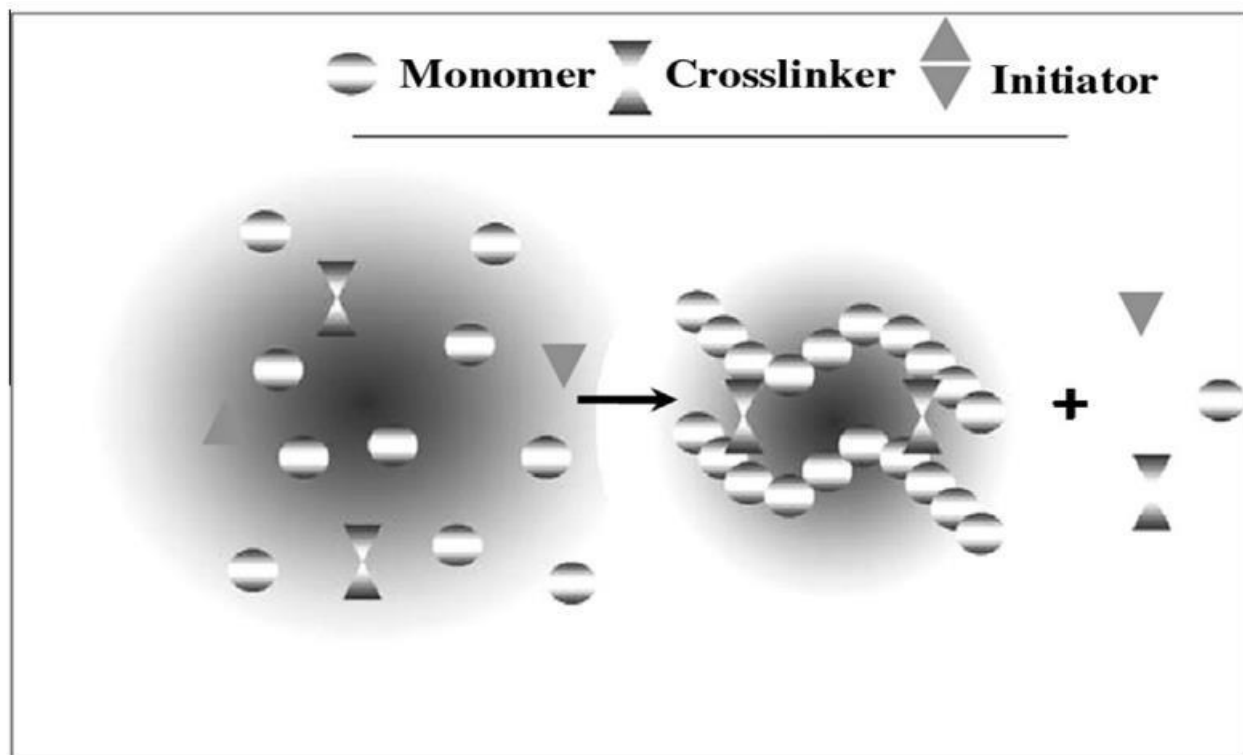


Figure 9. The polymerization technique controls the functionality and properties of the resultant polymer (Madduma-Bandarage & Madihally, 2021)

3.2.1. Free radical polymerization

Radical polymerisation of low molecular weight monomers in the presence of crosslinking agents can make chemically crosslinked hydrogels. Poly(2-hydroxyethyl methacrylate) (pHEMA), which was first made by Wichterle and Lim, is a well-known example. It is made by polymerising HEMA with crosslinkers such as ethylene glycol dimethacrylate. A lot of different hydrogel systems have been made using similar procedures. You can change the properties of these hydrogels, including how they swell, by changing the amount of crosslinker you use. Also, you can make hydrogels that respond to stimuli by adding functional monomers like methacrylic acid (for pH sensitivity) or N-isopropylacrylamide (for temperature sensitivity). Some of the free-radical polymerisation methods that are used are solution-based graft copolymerisation, photopolymerization, and radiation-induced polymerisation, which can be done with gamma rays or microwaves. These approaches depend on the generation of free radicals in the solution, which establish active

sites on the monomers during the initiation phase. After that, bifunctional crosslinkers like poly(ethylene glycol) diacrylate (PEGDA), N,N'-methylenebisacrylamide (NMBA), or glutaraldehyde connect active sites on two different monomers to make the crosslinked network structure (Duquette & Dumont, 2019). Visible or ultraviolet light can engage with light-sensitive chemicals known as photoinitiators to generate free radicals that initiate polymerization, resulting in crosslinked hydrogels (Nguyen & West, 2002). In order to figure out how these reaction conditions affect the hydrogel's swelling behaviour, phase transition temperature, and overall shape, you can change the polymerisation parameters. These include the temperature (for example, 7°C or 40°C, which are below or above the phase transition temperature in pure water), the type of solvent used (water or a 50/50 water/ethanol mixture for hydrophilic or more hydrophobic photoinitiators), the amount of crosslinker, and the concentration of monomer (Kuckling *et al.*, 2010).

3.2.2. Click chemistry

As described by Sharples et al., click chemistry refers to specific reaction types facilitated by a catalyst that exhibit rapidity and efficiency, superior biological characteristics, and advantageous reaction circumstances. (Chamkouri & Chamkouri, 2021). The application of "click chemistry" in the design and formation of functional hydrogels has expanded significantly since 2001. Click reactions are characterized by advantages including elevated yields under mild circumstances, reduced by-products, and enhanced specificity and selectivity. A diverse array of functional groups can serve as promising candidates for the synthesis of intricate polymeric materials (Hu et al., 2019). This method is recognized as an efficient approach for the functionalization of molecules, facilitating chemical crosslinking of polysaccharide-based hydrogels, polymer synthesis and activation, as well as the production of hydrogels, microgels and nanogels in drug delivery applications and medical engineering (Pirsa et al., 2023). There are many types of click reactions, such as copper(I)-catalyzed alkyne-azide cycloadditions, catalytic reactions that use free alkyne azides, and the silicosterone reaction with disaccharides (DA). Intergroup interactions are the most important ones. Alkynes and azides are great examples of click chemistry since they work well in biological systems and are very selective. Researchers have made starch-based hydrogels by exploiting a click reaction between thiol and allyl groups of starch. These hydrogels are meant for application in biomedicine and tissue engineering. The hydrogel resulting out of this process swelled well and broke down naturally (Chamkouri & Chamkouri, 2021).

3.2.3. Enzymatic crosslinking

Employing conventional chemical crosslinking techniques, including light crosslinking and covalent crosslinking, the synthesized hydrogels exhibit remarkable rigidity and expedited gelation time. The potential cytotoxicity of leftover chemicals and chemical crosslinking agents continues to pose a significant challenge. Enzymatic crosslinking hydrogels are currently receiving significant attention for enhancing material qualities, such as rapid gelation time and superior biocompatibility. (Xue et al., 2022). Currently, numerous enzymatically catalyzed crosslinking methods exist for in situ hydrogel synthesis. Transglutaminase (TG), in conjunction with calcium ions as cofactors, facilitates the synthesis of amide connections between carboxamide and amine groups (Hu et al., 2019). Calcium-dependent enzymes are often present in bodily fluids and the extracellular matrix. They help tissues including the skin, liver, and blood clots stick together. By selecting enzymes from human sources, this cross-linking mechanism can be modified for therapeutic application in humans. Transglutaminase is found in many parts of the body, hence its natural substrates are also found in many parts of the body. This extensive presence may make it easier for the host tissue and the gel that forms in situ to work together, just like how cells and extracellular matrix components naturally stick together (Sperinde & Griffith, 1997). Another crosslinking technique is the horseradish peroxidase (HRP)-catalyzed crosslinking reaction. When hydrogen peroxide is present, HRP makes it easier for phenol, aniline, and their byproduct tyramine to couple (H_2O_2) (Hu et al., 2019).

PEG-(glutaminamide)



poly(Lys:Phe)



TG

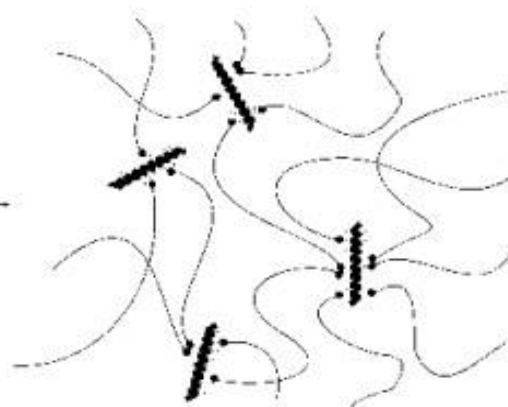


Figure10. TG cross-linking with glutaminamide-functionalized PEG and poly(lysine:phenylalanine) to produce a network (Sperinde & Griffith, 1997).

3.2.4. Grafting

Grafting is a process that includes covalently attaching a monomer to a polymer host molecule. This happens on an existing polymer backbone. High-intensity radiation or chemicals can start the polymer chain. Functional monomers are produced via activation on the resultant macro radicals, which causes the monomer to branch and ultimately crosslink with the macromolecules. Chemical grafting uses chemicals to make the macromolecular structure more active. For example, N-vinyl-2-pyrrolidone can be used to chemically graft starch with acrylic acid. This makes hydrogels that swell in a way that is good for medication and nutrient delivery in the small intestine. High-energy electron beams or gamma radiation can also start grafting. Said et al. (2004) say that grafting carboxymethyl cellulose (CMC) with acrylic acid using electron beam radiation makes CMC hydrogels (Ahmad *et al.*, 2022). The free-radical polymerisation of acrylic acid onto the carboxymethyl cellulose backbone was initiated with an electron beam. Furthermore, the byproducts of water radiolysis facilitate the extraction of protons from the macromolecular backbone. The irradiation of both the CMC and the monomer produces free radicals that subsequently amalgamate to form the hydrogel (Said *et al.*, 2004).

4. Applications of hydrogels

In 1960, Wichterle and Lim devised a network for contact lenses by crosslinking hydrophilic poly(2-hydroxyethyl methacrylate) (PHEMA) polymers, demonstrating the use of hydrogels in biomedicine (Wichterle & Lim, 1960). The main use of hydrogels is in contact lenses, especially the recently created long-wearing lenses that use silicone and PHEMA interpenetrating polymer networks, which provide far better oxygen delivery than lenses made solely of PHEMA. Hydrogels have been used in many biological applications since this first presentation; they will be discussed in the next section (Majcher & Hoare, 2019). Hydrogels are an ideal class of materials for biomedical applications, such as tissue engineering and drug administration, because of their capacity to expand in biological settings (Maitra & Shukla, 2014).

4.1. Contact lenses

Contact lenses work directly with the eye to correct vision, make it easier to provide medication for ocular conditions, and enhance appearance (Farandos *et al.*, 2015). There are two primary categories of contact lenses: rigid and soft lenses. Rigid contact lenses are composed of the polymer polymethyl methacrylate (PMMA). It has qualities including remarkable durability, a high modulus of elasticity, and surface wettability. Its lack of oxygen permeability, however, also has an

impact on the eyes (Geiges, 2001). Czech scientists Otto Wichterle and Drahoslav Lim were the first to form hydrogels in 1960. They made a polymer that could absorb water, which was later employed in soft contact lenses and other medical uses (Wichterle & Lim, 1960). At first, contact lenses were made utilizing a hydrogel system made from Poly(2-hydroxyethyl methacrylate) (pHEMA). Poly(vinyl alcohol), polyacrylonitrile, and other hydrophilic polymers have also been looked into for making hydrogel-based contact lenses (Lai *et al.*, 2000). Researchers are also looking on hydrogel contact lenses that are made from silicone and fluorine. Silicone-based hydrogels are now some of the most common materials used to make contact lenses (Musgrave & Fang, 2019). A soft or hydrogel contact lens must have characteristics such as oxygen permeability, water transfer capability, and a high water content (Munćan *et al.*, 2016). To keep the cornea healthy, it needs oxygen from the air to keep its structure, function, and transparency (Nicolson & Vogt, 2001). The thickness and water content of hydrogel contact lenses have a big effect on how easily they let oxygen through (McMahon & Zadnik, 2000). Hydrogel materials used in contact lenses should also not irritate the eyes, be biocompatible, be pleasant to wear for long periods of time, allow for a continuous tear film to keep vision clean, support ion permeability for optimal eye function, and keep deposits from the tear film. Hydrogel lenses need to have certain optical properties, such as a high light transmittance and the right refractive index (Caló & Khutoryanskiy, 2015). The physiology, integrity, and function of the cornea may be hypoxied by prolonged usage of traditional hydrogel contact lenses. Silicone-based soft contact lenses permit a lot of oxygen through, which lowers the risk of negative effects on the cornea. But using silicone hydrogel lenses for a long time may still mess up the cornea's homeostasis (Stapleton *et al.*, 2006).

There are many ways to make soft contact lenses, such as spin casting, mold casting, and lathe cutting. A little amount of liquid monomer is put into a concave optical mold that has been made just for this purpose during the spin- and mold-casting process. The mold spins, and the

monomer distributes out uniformly over the surface, making the shape of the lens. Then, at high temperatures, polymerization happens, and at the end of the process, any extra monomer is carefully taken out. In the mold-casting method, the back of the lens is made by putting a convex mold into a liquid monomer that is supported by a matching concave mold. The process of polymerization is similar to that of spin casting. This method makes a stiff lens material that is shaped between the two optical surfaces and keeps its concave shape after it dries. (Caló & Khutoryanskiy, 2015).

Another prevalent approach in the contact lens industry is lathe-cutting, which shapes lenses from solid "buttons" composed of dehydrated polymer. Usually, these buttons are made by mixing liquid monomers in water tanks and letting them sit for a while. Free-radical initiators commonly start the polymerization process. These initiators are turned on by raising the temperature. As a result, lengthier polymer chains with larger molecular weights and maybe more chain entanglement occur. The surfaces of the polymer material may break down when they come into contact with oxygen, but this isn't a big deal because the lathe-cutting process takes off the exterior layers. Because buttons have a lot of volume compared to their surface area, the material in the middle stays mostly the same. The last lenses are cut out of the centre of the button with great care, making sure that they are all the same quality (Maldonado-Codina & Efron, 2003).

A polymeric hydrogel must have some important physical properties in order to be safe to use in contact lenses (Maldonado-Codina & Efron, 2003). Table 1 presents a summary of the necessary attributes.

4.2. Drug delivery

Modern, advanced, and "smart" drug delivery systems, hydrogels are made to precisely target drugs to certain locations while managing their release. To guarantee delivery at the desired site, enzymatic, hydrolytic, or environmental triggers can frequently initiate the release of medications from hydrogels (Hoare & Kohane, 2008).

Smart hydrogels can be prepared from either

synthetic or natural polymers. But it is hard to keep things consistent with natural hydrogels because of how they mechanically work. Natural polymers can be improved by making a lot of

chemical changes, however working with natural hydrogels is still extremely challenging (Sgambato *et al.*, 2016).

Table 1. Requirements to the hydrogels used for contact lens applications

Characteristics	Requirements	References
Luminous transmittance	The minimum luminous transmittance value for contact lenses is 95%. This value significantly affects the transparency of the lens. A slit lamp microscope is typically used to observe any deposit (proteins, lipids, bacteria, minerals) that may cause a lack of the usual transparency of the lens	(Caló & Khutoryanskiy, 2015; Osuagwu & Ogbuehi, 2014)
Refractive index	The refractive index of the human cornea surface may vary. Ideal hydrogels should have a refractive index value matching the range 1.372–1.381	(Caló & Khutoryanskiy, 2015; Patel <i>et al.</i> , 1995)
Sufficient oxygen-permeability	The oxygen permeability of the lens is directly proportional to water content and inversely to thickness. In the contact lens industry the oxygen permeability is expressed as Dk. In order to prevent anoxia through out the cornea the oxygen transmissibility of the lens (Dk/t , where 't' is the thickness of the lens) required to be 35 for the open eye and 125 for the closed eye	(Efron <i>et al.</i> , 2007; Hadassah & Sehgal, 2006; Harvitt & Bonanno, 1999)
Wettability and permeability to water	The water-permeability of the lens is strictly related to thickness. A constant water diffusion rate is normally reached within the first hour of the experimental analysis. It directly depends on the wettability of the lens. The initial value for hydrogel contact lens is usually around 25	(Caló & Khutoryanskiy, 2015; Ketelson <i>et al.</i> , 2005)
Stability	The stability of the material used affects the shelf-life and the manufacturing process of the lens	(Caló & Khutoryanskiy, 2015)
Excellent mechanical properties	The mechanical properties of the lens, such as the elastic modulus(E), have a great impact on their adhesion to the corneal epithelium and on the comfort for the wearer	(Caló & Khutoryanskiy, 2015)
Biocompatibility	The biocompatibility of the material is essential for the ocular health of wearers who tend to use the lenses for an extended period of time	(Caló & Khutoryanskiy, 2015)

On the other hand, it is easier to change the chemical and physical properties of synthetic polymers. Synthetic polymers that are hydrophilic and break down naturally are the most suitable choices for making smart hydrogels that can be used for drugs administration. These compounds help smart hydrogels have low blood-material interaction, low toxicity, and few adverse effects. Low blood-material adherence is important because it helps diminish phagocytic clearance and

the opsonization effect (Zhao *et al.*, 2021).

Compared to other biomaterials used to deliver drugs, hydrogels have a lot of water content, which means that they are not bound to proteins strongly. This usually lessens inflammatory responses (Hoare & Kohane, 2008). Selecting the right crosslinker or base material might make hydrogels biodegradable or enable dissolution of hydrogels. While considering drug release from hydrogels, the terms "controlled release,"

"sustained release," "extended release," and "long-term delivery" are typically used interchangeably. Irrespective of the terminology (Majcher & Hoare, 2019).

The goal of developing long-term drug delivery systems is to reduce the steepness of the release curve, resulting in a plateau phase and prolonging the release duration within the therapeutic window. The drug release kinetics are affected by a number of things, such as the drug concentration in the matrix, how easily the drug can move and dissolve in both the hydrogel and the release medium, the balance between the drug and hydrogel components' adsorption and desorption, the rate and extent of water absorption (swelling) and how it affects gel porosity, the hydrogel's degradation rate, changes in the gel's pH caused by polymer breakdown, and the drug's distribution equilibrium between the gel and the surrounding medium (Mohanani *et al.*, 2011). Drug release behaviour is complicated due to the complex structure of these dynamic interactions, which has led to the creation of many mathematical models intended to forecast release rates. These models consider the several contributing components and how they affect the overall kinetics of drug release.

The following are some of the most used models for simulating drug release from hydrogels: (1) zero-order kinetics, which is important for reservoir-type systems (such as those surrounded by hydrogels that regulate the release by acting as a membrane (Möckel & Lippold, 1993; Stithit *et al.*, 1998); (2) first-order kinetics, which are used to describe how drugs are released from hydrogels when diffusion is the only thing that controls it (Costa & Lobo, 2001); (3) the Baker-Lonsdale model works well for modelling how drugs diffuse out of spherical matrices, including gel microparticles or micro/nanogels (Costa & Lobo, 2001); (4) the Hixson-Crowell model can be used when the drug needs to dissolve in the gel matrix before it can be released by diffusion (Costa & Lobo, 2001); (5) The Korsmeyer-Peppas model is useful when drug diffusion through a hydrogel is slowed down because the drug and the polymer matrix interact with each other or have an affinity for each other (Costa & Lobo, 2001; Ritger & Peppas, 1987); and (6) The Hopfenberg model is important for describing hydrogels that lose material inconsistently from their surfaces during the release process (Costa & Lobo, 2001).

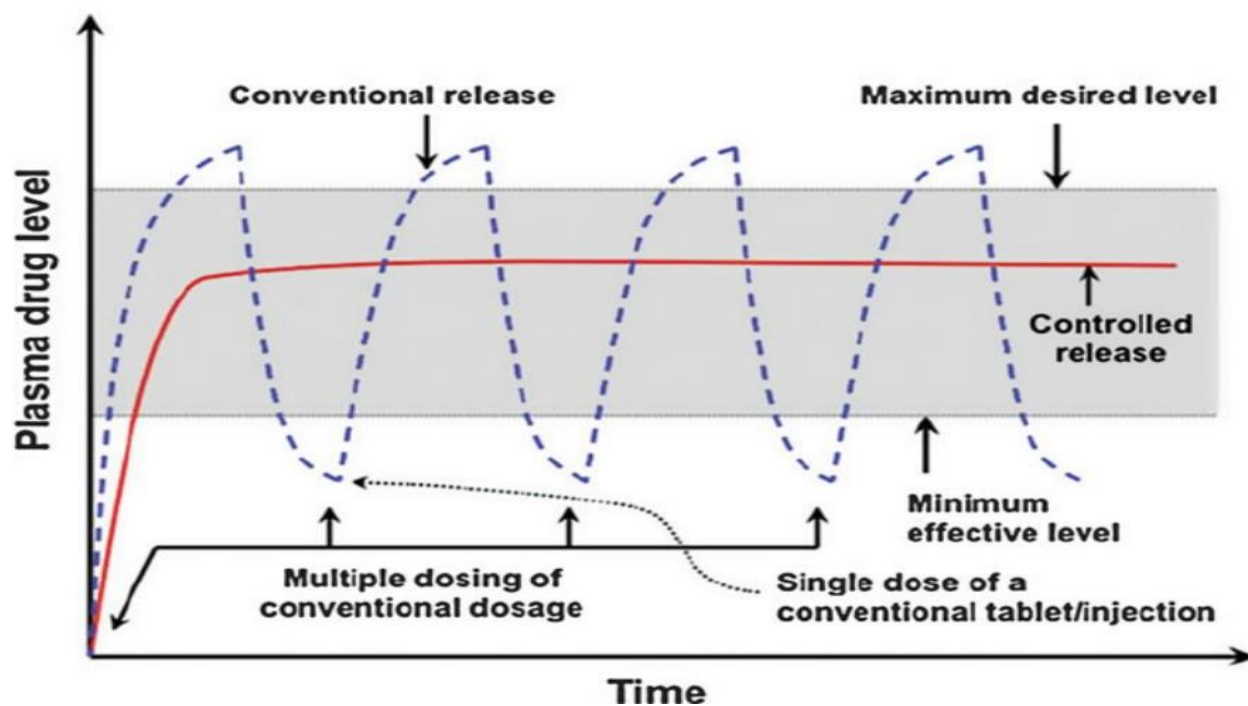


Figure 10. Therapeutic window (Majcher & Hoare, 2019)

The most common models and empirical equations used in hydrogels are zero-order kinetics, which work best for reservoir-based delivery systems like transdermal hydrogel devices; first-order kinetics, which work for hydrogels that don't have a specific drug affinity and where diffusion alone controls release; and the Korsmeyer-Peppas model, which works for systems where non-specific drug-polymer interactions affect release and involve both partitioning and diffusion mechanisms. It is very important to find out or guess the drug's diffusion coefficient in the hydrogel in order to use these models correctly. A diffusion cell is a standard way to do this. It has a hydrogel sample of defined thickness that divides a source compartment (which has the drug in buffer) from a receiver compartment (which has only buffer). You can then figure out the drug's diffusion coefficient in the gel by looking at how much of it shows up in the receiver over time (Majcher & Hoare, 2019).

Similar to the dual aspects of a coin, there are inherent disadvantages linked to their use. The principal drawback in medication distribution is the hydrophobic nature of the majority of medicines. The hydrophilic polymeric core is likely unsuitable for accommodating incompatible hydrophobic medicines, posing a dilemma as many currently utilized and successful therapeutics for diseases are hydrophobic. The tensile strength of these hydrogels is inadequate, occasionally resulting in premature drug release prior to reaching the target site (Narayanaswamy & Torchilin, 2020).

4.3. Wound dressing

The skin is the largest organ in the body. It has three primary layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the outermost layer, while the dermis is the innermost layer. It is often hurt by physical, chemical, or thermal insults. These kinds of wounds damage the structure and functional capabilities of the skin (Lazarus *et al.*, 1994). When a wound occurs, it starts a sequence of physiological processes that work together to heal the tissue that was wounded (Gonzalez *et al.*, 2016). An ideal wound dressing

should: (1) keep the wound moist, (2) let gases pass through easily, (3) soak up blood and exudates, (4) minimize adhesion to the skin, (5) stop tissue necrosis, (6) stop infection, (7) keep the wound warm, (8) help skin cells move around, (9) encourage the growth of new blood vessels (angiogenesis), and (10) be biocompatible and biodegradable while having low toxicity (Dhivya *et al.*, 2015).

Hydrogels are three-dimensional structures made up of hydrophilic polymers that are bonded together in a way that is either chemical or mechanical. These networks don't dissolve in water, but they can soak up wound exudates and help oxygen diffusion, which speeds up the healing process (Boateng *et al.*, 2008; Kumar & Jaiswal, 2016). Hydrogels are made up of a three-dimensional polymer network that is very hydrated and can hold water that is several times its dry weight. This keeps the wound site very moist. Hydrogel structures can be moulded into many sizes and shapes because of their unique physical properties (Bilici *et al.*, 2016; Van Vlierberghe *et al.*, 2011). Therefore, hydrogel-based materials are the ideal dressings for covering skin wounds (Koehler *et al.*, 2018). In addition, hydrogels are a flexible platform for incorporating cells, antibacterial agents, growth hormones, and other biomacromolecules (Gupta *et al.*, 2002). Hydrogels used to repair wounds should create a three-dimensional environment that is favourable to cells and helps tissue to regrow, even if the cells are not immersed in the scaffold. All hydrogels that are meant for use in medicine must also meet certain biocompatibility standards and have certain physical and mechanical qualities that make them good for treating skin wounds (Jones & Vaughan, 2005). Furthermore, they must furnish the suitable environment for angiogenesis and cell proliferation. Table 1 illustrates several critical attributes of wound dressings that are essential for facilitating skin wound healing (White, 2011). Many wound care methods believe hydrogel dressings to be important because they create the perfect environment for cleaning wounds and help the body get rid of dead tissue (Flanagan, 1995). Hydrogel treatment helps new

blood vessels to form and complicated skin structures like hair follicles and sebaceous glands heal. This lowers the chance of scarring. It keeps the wound from drying out by keeping important moisture in, which helps with pain and gives a cold, relaxing feeling. The high water content of hydrogels also keeps germs and oxygen from getting to the wound, which keeps it from getting infected. Hydrogels also help fibroblasts grow by keeping fluid from leaking out of the wound surface and protecting it from toxic outside factors. This is important for quicker healing. Hydrogels keep the milieu on the surface of the wound steady, which is the best way to support biosynthetic processes and cellular activity (Witthayaprapakorn, 2011). Because hydrogels are transparent, wound healing can be tracked without taking off the dressing. Semi-occlusive hydrogel dressings have the ability to promote angiogenesis, which helps granulation tissue form by supplying the wound site with enough oxygen and nutrients (Subramanian &

Vijayakumar, 2015).

4.4. Tissue engineering

By combining biological and technical concepts, tissue engineering aims to create effective biological substitutes that preserve, restore, or enhance tissue function (Chaignaud *et al.*, 1997). In order to promote the formation of new tissue, this field mostly depends on scaffolds, cells, and other stimuli. Tissue engineering and regenerative medicine have been greatly impacted by the use of naturally occurring materials as scaffolds or matrices to promote and enhance cell growth and proliferation (Mano *et al.*, 2007). There are different ways to crosslink hydrogels, and they can have physicochemical properties that can be changed to closely match the native extracellular matrix of tissues.

Table 2. Characteristics of an ideal wound dressing (Tavakoli & Klar, 2020).

Feature	Description
No toxic component	Free from toxic materials that can damage and lead to dire consequences
Prevention of bacterial infection	Preventing bacterial infections, which could impair wound healing and prolong its duration
Adhesiveness	Providing an optimum amount of adhesive material to the wound site (excessive adhesive sustains an injury)
Moisture	Maintaining the optimum moisture level to promote cell migration and proliferation
Thermal insulation	Maintaining the optimal temperature of wound site to reduce pain
Absorption of excess exudate	Regulating the amount of exudates present in the wound
Oxygen	permeability Allowing the diffusion of oxygen to the wound bed to accelerate cell activity
Mechanical and physical properties	Resembling the structure of native skin
Minimal tissue trauma (pain)	Minimizing patient pain during application and removal
Cost effectiveness	Providing an affordable wound dressing
Free availability	Accessible for all patients or healthcare center

Incorporating chemically and physiologically active recognition components, like growth factors (GFs) and stimuli-responsive compounds, can also enhance their biofunctionality (Annabi *et al.*, 2014; Malda *et al.*, 2013). Consequently, the environment afforded by hydrogels enables cells to proliferate, differentiate, and generate tissue-like structures (Zhang & Khademhosseini, 2017).

The goal of tissue engineering is to produce scaffolds that look like the body's natural extracellular matrix so that tissues can regenerate. Hydrogels have gotten a lot of attention in this field since they are strong, safe for living things, break down easily, and look a lot like the extracellular matrix in nature (Cascone & Lamberti, 2020). When there has been a loss of function, hydrogels have been used as scaffolds to fabricate or restore missing tissue. Hydrogels are mostly used in bone, cartilage, vascular, meniscus, tendon, skin, cornea, and soft tissues. purchased. Collagen-chitosan 3D printing improves nerve fibre regeneration and functional recovery in animal models while also successfully reducing the formation of scars and cavities (Sun *et al.*, 2019). HA in combination with fibrin and alginate is another example. This was used to help regenerate peripheral nerve tissue as an ink ingredient for 3D printing (Ning *et al.*, 2019). Furthermore, HA-cellulose hydrogels have the ability to restore central nerve function (Loh *et al.*, 2018).

Alginate, a naturally occurring polysaccharide polymer obtained from brown seaweed and other microorganisms, has potential use in tissue engineering and medicine when utilised as a polymer in the production of hydrogels (Chen *et al.*, 2019). Alginate is ideal for a number of biotechnological processes, including as moulding, spraying, and 3D printing, due to its special capacity to be physically crosslinked by divalent cations like Ca^{2+} at room temperature. The physical hydrogels that are produced have good biocompatibility, minimal toxicity, and are reasonably priced. Alginate hydrogels are perfect for preserving the phenotypic of cartilage and promoting the development and multiplication of encapsulated cartilage cells. Collagen type II and advanced cartilage genes are produced after 21 to

28 days of cartilage cell culture. Alginate also aids in bone regeneration by supporting mesenchymal stem cells (MSCs) and other primary bone cells. The extracellular collagen matrix generated by encapsulated MSCs can integrate with the host tissue (Zhang *et al.*, 2020). Chitin-derived chitosan, another well-known natural biopolymer, is created from renewable resources such as insects, fungi, oyster skin, and marine industrial waste. It can be applied to tissue engineering because of its excellent biodegradability (Zhang *et al.*, 2016). This polymer, which is created by enzymatic crosslinking, encourages mesenchymal stem cells and chondrocytes to proliferate. It has been utilised in tissue engineering to replace prosthetic hip joints and stents (Batista *et al.*, 2019). Because they resemble the extracellular matrix of the body and offer biochemical cues that promote cell division and growth, natural hydrogels are employed as scaffolds in tissue engineering. Optical crosslinking is frequently used to create polymer scaffolds for tissue engineering. This method enables the production of scaffolds with intricate forms and exact control over the timing of gel formation by facilitating fast polymerisation at physiological temperatures in biological contexts. Furthermore, hydrogels employed in biomedical and tissue engineering applications must have mechanical qualities that closely resemble those of real tissues (Ismail *et al.*, 2019).

5. Challenges and Future Perspectives

The domain of hydrogel research has been steadily evolving and receiving increased acknowledgement over time. Figure 11 depicts the increase in the volume of articles concerning hydrogels since 2002. This growth has an exponential tendency, particularly from 2018 onwards.

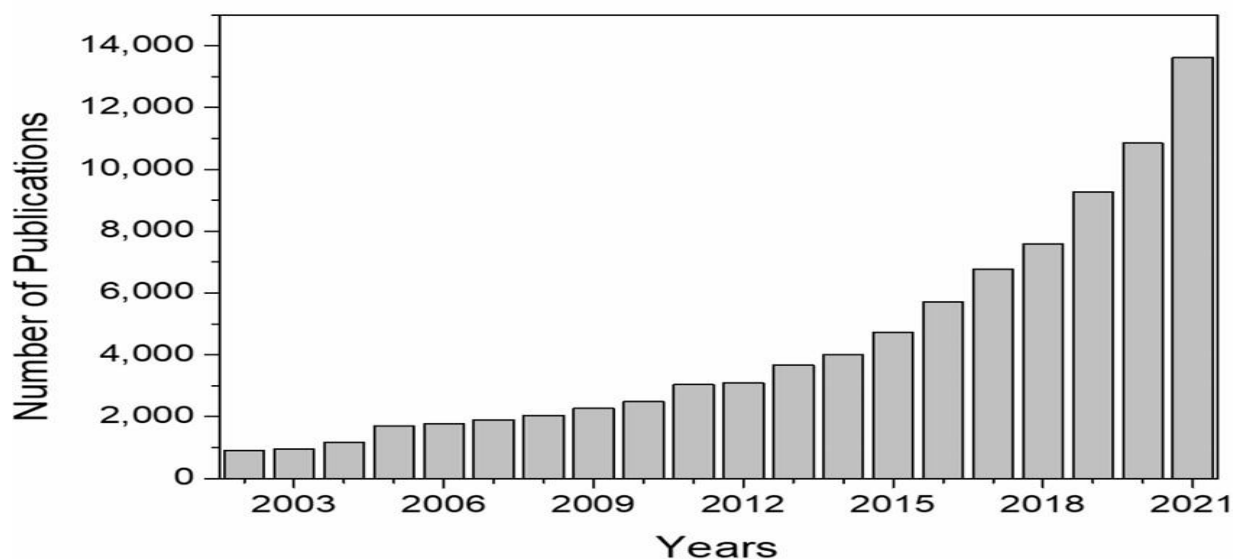


Figure 11. Trends in the number of publications regarding hydrogels (Cui *et al.*, 2022)

The growth is ascribed to the exceptional versatility of hydrogels, which can be customised based on various parameters, including the type of cross-linking (chemical or physical), the polymer's nature, the cross-linking agent, the integration of additional materials, and the system's scale (hydrogels, microgels, nanogels, etc.).

The growth is ascribed to the exceptional versatility of hydrogels, which can be customised based on various parameters, including the type of cross-linking (chemical or physical), the polymer's nature, the cross-linking agent, the integration of additional materials, and the system's scale (hydrogels, microgels, nanogels, etc.). Their elevated water content, biodegradability, and regulated release properties render them outstanding options for water reservoirs in horticulture and agriculture, especially in areas experiencing water constraint for crop irrigation (Cui *et al.*, 2022). Hydrogels are also thought to be good materials for many biomedical uses, including as wound dressings, controlled drug delivery systems, tissue engineering (TE), contact lenses, and hygiene products. This is because of their important physical and biological properties. These include their capacity to expand, stick to tissues, and help encapsulated medicinal substances release under controlled conditions (Mamidi & Delgadillo, 2021; Sharma *et al.*, 2022).

In addition to those already mentioned, there are numerous methods for designing and manufacturing hydrogel systems for a variety of applications today, all of which aim to elevate the performance of hydrogels by improving their properties. As was previously said, typical hydrogels are difficult to use in biomedicine because of their poor mechanical qualities, low stability, and inability to fully recreate crucial elements of the cellular microenvironment. The use of IPN has emerged as a great way to get around these restrictions, as was indicated in the previous section (Dhand *et al.*, 2021). However, these requirements can be met by different composite techniques. As an example, bioactive glasses can impart bioactivity, biocompatibility, and osteogenic effects, because integrating them into composite hydrogels has been extensively researched (Zeimaran *et al.*, 2021).

Traditional synthetic hydrogels are generally soft and brittle, in contrast to the mechanical strength and durability found in numerous natural tissues (Naficy *et al.*, 2011). They are especially fragile when established via hydrogen bonding, as these connections are continually undermined by adjacent water molecules (Némethy *et al.*, 1963). In the past several years, different methods have been used to add strong sacrificial links to

hydrogels. These methods include making double-network, nanocomposite, and polyampholyte hydrogels. These changes have made hydrogels much stronger and more flexible. Still, hydrogels are still thought of as "soft materials" since their elastic modulus is low (usually less than 10 MPa), and they cannot be extensively elongated and do not withstand wear and deterioration effectively (Hu *et al.*, 2015).

6. Conclusions

Hydrogels are versatile materials in biomedical applications because they are biocompatible, have adjustable characteristics, and can imitate natural tissues due to their unique three-dimensional hydrophilic networks. Physically cross-linked hydrogels, which are made by hydrogen bonding or hydrophobic interactions, can change shape and respond to stimuli. Chemically cross-linked hydrogels, on the other hand, are stronger and last longer. Hydrogels have shown a lot of promise in tissue engineering, drug delivery, wound dressings, and contact lenses. For example, their high water content and oxygen permeability make them perfect for contact lenses, and their controlled release mechanisms make drug delivery systems work better. Hydrogels help wounds heal by keeping them moist and helping nutrients spread. Their structural closeness to the extracellular matrix helps tissue engineering by facilitating cell growth and differentiation. In spite of these developments, difficulties continue to persist. Mechanical fragility, poor stability in physiological settings, and problems with scaling up production make it harder for more people to successfully employ it. Nanocomposites or double-network hydrogels should be used in future research to make materials stronger, more biodegradable, and more responsive to stimuli for targeted therapies. New developments in 3D printing and smart hydrogels that respond to pH, temperature, or enzymes could change the way we do personalised medicine. Also, working together across disciplines is important to solve problems with biocompatibility and regulations.

In conclusion, hydrogels have a lot of potential to improve biomedical technologies. By overcoming current challenges and using novel methods of

synthesis, they can open up new possibilities in regenerative medicine, diagnostics, and other fields, making way for the next generation of therapeutic solutions.

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