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HYDROGEL INTRINSIC THEMES: CLASSIFICATION, FORMULATION, AND IMPLEMENTATIONS - A BRIEF REVIEW

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Abstract

We focused on the fundamental concepts of hydrogels in this review, including classification, the polymers involved, synthesis methods, hydrogel types, properties, and applications. Natural polymers, synthetic polymers, polymerizable synthetic monomers, and a combination of natural and synthetic polymers can all be used to make hydrogels. Physical, chemical, and hybrid bonding are used in the synthesis of hydrogels. Bonding can be formed through a variety of methods, including solution casting, solution mixing, bulk polymerization, free radical mechanism, radiation method, and interpenetrating network formation. Mechanical strength, biocompatibility, biodegradability, swellability, and stimuli sensitivity are all important properties of the hydrogels that were created. Furthermore, smart hydrogels have been classified based on their external response, pH, temperature, electric, light, and enzyme. This review goes into great detail about the type of hydrogel, whether it's the internal structure or the external response. Furthermore, we discuss some of the most important applications of these hydrogels in the field of biomedicine, such as drug delivery systems, scaffolds for tissue engineering, actuators, biosensors, and many others.

Keywords: Hydrogel, Gum-ghatti, nanoparticle, smart hydrogel, Cross-linking, Polymerization, Grafting, nanocomposites hydrogels.

1. Introduction

Natural hydrogels can be found in tissues, tendons, and membranes for the kidneys and blood vessels. They are also found on the surface of the stomach, the intestines, and the lungs. In the past decades, many synthetic hydrogels have been formulated for potpourri applications. Synthetic hydrogels are mixtures that belong to a substantial amount of water and extremely swollen, hydrophilic polymer networks. Polymeric networks known as hydrogels can hold large volumes of water. The hydrophilic groups in the polymeric network are what cause a hydrogel structure to form when they hydrate in aqueous media. A three-dimensional network of polymers made of synthetic or natural materials that are extremely flexible because of their high-water content is what is known as a hydrogel[1]. The first known hydrogel was created in 1960 by Wichterle and Lim[2], who created *poly*(2-hydroxyethyl methacrylate) (PHEMA) and employed it in the production of contact lenses to absorb and retain water while retaining the network structure. They can handle a significant amount of water or biological fluids under physiological conditions and have a soft, flexible quality similar to genuine tissues, making them an appropriate material for a variety of applications[1]. The dissent of such peculiarities in hydrogels is because of the consideration of freezing hydrophilic components, like $-SO_3H$, -OH, $-NH_2$, -COOH, $-CONH_2$, and others, as fanned networks along the polymer organization. Water absorption is exacerbated by the swelling protagonist of hydrogels, which is survived because of its solubility appended family, edema surface, and cross-linked interfacial belongings. Crosslinking modulates water absorption while also assisting in the restoration of the mesh topology in the swollen state[3–5]. Crosslinkers are important for two purposes biological materials and the inclusion of hydroxyl group in water absorption[6].

Hydrogels can be made from a single polymeric component (homopolymer hydrogels) or from two or more polymeric components (co-polymeric hydrogels). The arrangement of hydrogels involves the expansion of physical or synthetic cross-connecting specialists to polymerize their subunits. Hydrogels assume a crucial part in biomedical applications because of their extraordinary properties like biodegradability, cytocompatibility, lipophilicity, super absorbency, viscoelasticity, malleability, and frailty. Moreover, hydrogels answer a grouping of enhancements, including temperature, electric field, appealing field, natural particles, and ionic strength[7]. Because of their mucoadhesive and bio adhesive properties, many hydrogels have the potentially increase drug latency, attempting to make them appropriate candidate for drug carriers[8]. Mucoadhesion is a peculiarity that happens when a polymer interacts with the mucosal surface or mucin. Due to electrostatic, mechanical/real cross-associating, substance holding, wetting, or adsorption conversations, mucoadhesive co-activities achieve the improvement of a strong mucoadhesive bond[9].

Hydrogels have been discovered in nature from the beginning of time. Microbes, which are moistened extrinsic structure sections, and botanical frameworks are both moisture subjects identified across nature. Gelatine and agar were both recognised and employed for diverse purposes early in human history, but the modern history of hydrogels as a class of materials tailored for biomedical uses can be reliably documented[1]. The physical and chemical binding sites of hydrogels preserve their three-dimensional structure when swelled. Chemical crosslinking involves covalently bonding polymer chains with a cross-linker whereas external adhesion results in hydrogels with physical entity branch points, H - bonding, non-polar association, and anion exchange complex formation, allowing for dissolvable projecting, article mass alteration, ease of manufacture, restructuring, biodegradability, and non-poisonousness, which artificially cross-connected hydrogels require.

According to Gibas and Janik[10], hydrogel swelling is a multi-step, complicated process. Water, in the form of primary absorbed water, hydrates the polar hydrophilic groups of the hydrogel matrix in the first stage. The water then converses with the susceptible hydrophobic groups in the second stage, resulting in additional absorbed water[10]. The total bound water is made up of both the primary and secondary bound water. In the third stage, physical or chemical crosslinks resist the network's osmosis driving factor towards infinite dilution, enabling extra water to be absorbed. Bulk liquid, also known as clean water, is the water that is absorbed by the best expansion and fills the spaces between the network of chains and the larger pore centres. The solid portion of the hydrogel is a platform of cross-linked polymer chains that together create a three-dimensional network known as a lattice, with a liquid, frequently water, filling the spaces. The cross sections retain the liquid and provide a flexible power that can be completed by the hydrogel's extension and compression, and so are responsible for the hydrogel's strength. The ion stage of hydrogels usually comprises ionizable functional groups attached to the polymer matrix and a number of mobile ions, comprising mitigate and co-ions, due to the presence of the electrolytic solvent that surrounds the hydrogel[1].

Das revealed that interpenetrating polymers or networks (IPN) are typically generated by expanding a first channel in a specific solvent monomer, which then forms the structure of the subsequent planetary gears structure. The IPN's dual systems might be polar and hydrophilic, with the latter being more significant in terms of maintaining the combination network's characteristics[11]. Microgels are polymeric gels with gel particle sizes ranging from 1 to 100 μm. Hydrogels are gels that have bulging or contra properties in water. Cross-variety microgels are outlined by getting insightful polymeric social gatherings together with nanomaterials using a grouping of techniques[12,13]. These hybrid microgels are deemed exemplary systems because they integrate the distinctive properties of nanomaterials (surface, optical, refractive, and plasmonic properties) with the properties of hydrogels (responsiveness to various stimuli such as pH and ionic strength) in a single system[14]. Pelton et al.[15] utilized a precipitation polymerization strategy to convey the first microgels. Despite the fact that, Antonietti et al.[16] were quick to uncover on the utilization of microgels as a toolmaker for the preliminary work on nanomaterials. Except for the reward of *in-situ* nanomaterial preparation, these polymeric particles also act as a useful fixation conduit for newly engineered nanomaterials[17]. Furthermore, the dimension and form of the enveloped nanostructures may be altered by modifying the degree of water retention of microgels by varying parameters such as medium temperature and pH[18].

Microgel particles are traditionally chemically modified by tailoring different ionic functionalities within the gel sieves. This is achieved by integrating co-monomers into the response medium during the polymerization cycle. These functional groups help by facilitating charge transfer between the grafted ionic functional groups and the nanoparticles. As a result, the nanoparticles are more stable because their enormously high surface charge density is curtailed. Thus, the added co-monomers play a vital role in the effective incapacitation of the nanomaterials in the hydrogels[19]. An even more advantage that hydrogels have over other commonly used stabilisation systems such as block polymers[20], micelles[21], dendrimers[22], and graphene sheets[23] is their ability. Because of their responsiveness (swelling/shrinking) to slight changes in incentives such as pH[24,25], magnetic field[14], molecular binding[26], ionic strength[27], and enzymatic activities[28] they are an excellent candidate to be investigated for potential applications in biological/organic molecules sensing[29], photonics[30], environmental sciences[31], catalysis[32], and drug delivery applications[33].

Recognizing hydrogel rheological properties is critical for understanding mechanical properties, viscoelastic behaviour, and interactions between hydrogel components. Rheological properties of hydrogels are the combined effect of factors such as polymer nature, polymer structure, temperature, pH, ionic strength, concentration, and cross-linking of polymeric components within the hydrogel. Furthermore, the rheological properties of polymer solutions should be understood to envision the resulting hydrogels and to aid in revealing some significant properties that can be beneficial in understanding the interaction between the component and the overall system. Knowledge of the system's properties also aids in determining the potential industrial applications of the synthesized hydrogel[34]. Gum ghatti is a high-molecular-weight anionic polysaccharide derived from the Anogeissus latifolia plant in the Combretaceae family. D-glucuronic acid, D-xylose, D-mannose, D-galactose, and L-arabinose make up the primary structure of gum ghatti. Because of its thickening and emulsifying properties, gum ghatti is widely used in the paper, pharmaceutical, and food industries. It is used in the development of pharmaceutical formulations as a sustained release, matrix-forming, film-forming, and mucoadhesive polymer[35,36].

Hydrogels are frequently used to deliver hydrophilic drugs. Hydrophobic drugs, on the other hand, are generally incompatible with hydrogels because the polymer matrix is hydrophilic[37]. This is owing to the hydrophobic medicines' restricted loading amount and uniformity in hydrogel materials[38]. Hydrogels should thus be changed to transport hydrophobic substances. This is a big concern since hydrophobic medicines are widely used in pharmacological therapy today. Low water solubility is predicted to affect around 40% of commercial medications and 60% of compounds in the research and development stage[39]. Two major techniques to enhance hydrogel compatibility with repellent substances are the incorporation of compounds able to form binding interactions (i.e., cyclodextrins) and/or the incorporation of hydrophobic moieties in the hydrogel structure. However, this is not the most frequent form of hydrogel employed for poorly water-soluble drug delivery. More advanced systems have been characterized as hydrogels incorporating micelles/nanoparticles inside their structure[40].

The aim of writing this review is to provide the preparation methods of hydrogels from hydrophilic polymers of synthetic and natural origin with an emphasis on water-soluble natural biopolymers (hydrocolloids). Recent advances in radiation cross-linking methods for the preparation of hydrogel are particularly addressed. Additionally, methods to characterize these hydrogels and their proposed applications are also reviewed. Fundamental concepts of materials used in hydrogels, such as natural and synthetic polymers, methods of synthesis, and types of hydrogels based on crosslinking methods, have been thoroughly reviewed in this review. The current review's goal is to report on current research in the field of hydrogel drug delivery systems. In this review, we discussed various methods for the synthesis of hydrogels. This review focuses on the synthesis and significance of various stimuli-responsive hydrogels. Hydrogel applications in pharmacy and medicine, particularly tissue engineering, have been discussed.

2. Classification of Hydrogels[41]

There are various subcategories of hydrogels. The most common kinds of hydrogels are shown schematically in Fig.1.

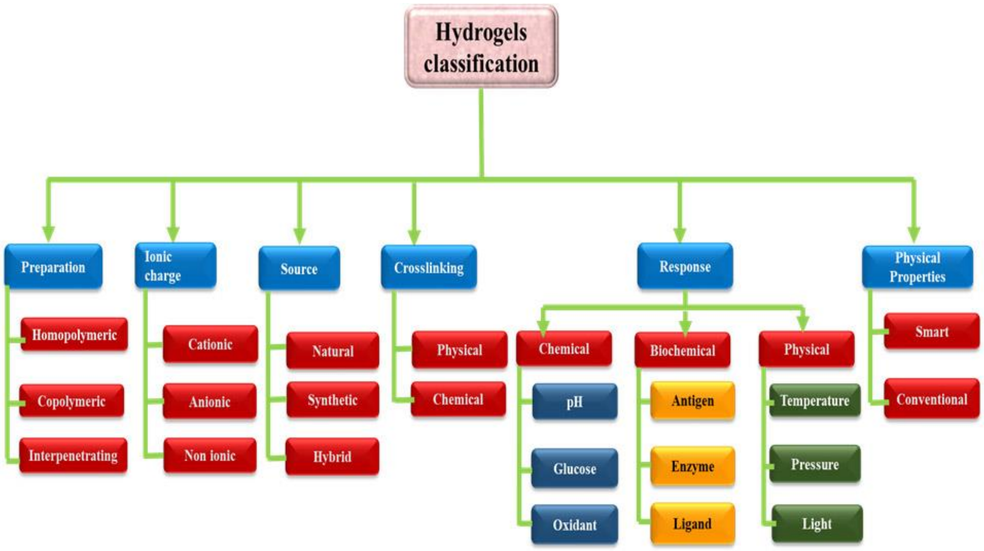

Figure 1. Classification of hydrogels[41]

2.1 Based on Polymeric Composition

Hydrogels are categorized depending on their polymer composition: mono-polymeric, co-polymeric, and multi-interpenetrating polymeric network (IPN) hydrogels. (i) The monomer in homo-polymeric hydrogels is a single species. Depending on the method of polymerization and the characteristics of the monomer, the homo-polymers may have a cross-linked structure.

(ii) Two or more different monomers, at least one of which must be watery, combine to form co-polymeric hydrogels. This hydrophilic group may be constructed in a periodic, repetitive, or block pattern along the network chain.

(iii) Two separate, cross-linked chains of synthetic or natural polymers organized in a network make up a multi-polymer IPN hydrogel. One cross-linked and one non-cross-linked chain makes up semi-IPN polymers.

2.2 Based on Configuration or Structure

Hydrogels are divided into amorphous, semi-crystalline, and crystalline categories based on their physical makeup and chemical composition.

2.3 Based on Source

Hydrogels can be classified as natural, synthetic, or semi-synthetic depending on where they come from. Natural hydrogels are derived from natural sources like plants and animals, as opposed to synthetic polymers, which are produced through the conventional polymerization of vinyl monomers. Natural hydrogels have increasingly been displaced by synthetic hydrogels, which have a greater capacity for water absorption, a longer life, and a higher gel strength. They may also be designed to have certain desirable features while being stable in the face of significant temperature swings.

2.4 Based on Durability

Hydrogels are classified into two types based on their durability, which varies depending on the application. Durable hydrogels are non-biodegradable. In general, synthetic hydrogels are more durable than natural hydrogels, which are biodegradable. Degradable polymers can also be divided into groups according to how their bonds are broken. They can be broken down by hydrolytic or enzymatic activity, causing sensitive bonds to dissolve.

2.5 Based on Cross-linking

Depending on the type of cross-links, hydrogels are categorised as having chemical cross-links or physical cross-links. Since they are produced by a chemical reaction with the polymeric matrix, chemically cross-linked chains have long-lasting linkages. Through entangled polymer chains, hydrophobic interactions, or physical interactions like ionic and hydrogen bonds, crosslinking can be carried out physically. As a result, unlike chemical cross-links, which have permanent connections, physical cross-links have transitory junctions.

2.5.1 Physically Cross-linked Hydrogels[42]

In nature, hydrogels exist temporarily and are reversible due to physical entanglements between networks. The assembly of polyvinyl alcohol (PVA)/chitosan, PVA/starch, and PVA/gelatin is accomplished by the freeze-thaw method. There are free chain ends and chain loops in them, which might cause non-homogeneity. PVA is utilised in biomedical engineering for a variety of purposes, including medication administration, synthetic cell entrapment, contact lenses, and nerve contraction. It can be used for intravenous inserts, soft tissue diluents, periosteal revitalisation, artistic surgery, prosthetic organs, drug delivery systems, and bandages for wounds[43–45]. Physical crosslinking leads to the formation of dextran, *poly*(lactic acid), and polyethylene glycol, which can be further deemed for pharmaceutical applications[46–48].Most hydrogels made from alginate, chitosan, hyaluronic acid, and cyclodextrin are physically connected together through H-bonding. Alginate makes up the capsule's outer layer, which is cross-linked by ripening or heat-induced aggregation. These are utilised in regenerative areas, cartilage repair, cell scaffolding, and soft tissue engineering[49–51]. The numerous ways for producing physically cross-linked hydrogels documented in the literature are as follows[52]:

(i) Freeze-thawing

Repeated freeze-thaw cycles can create physical cross-links in materials. Microcrystals are formed in the structure because of freezing and thawing in this mechanism. One typical example is poly (vinyl alcohol) (PVA) hydrogels produced via freeze-thawing. In comparison to PVA hydrogels made using more traditional methods, these hydrogen-bonded hydrogels are more porous, spongy, rubbery, and elastic[53–56]. These gel matrices are increasingly frequently employed in the field of biotechnology, particularly for the immobilisation of molecules (proteins, peptides), entire cells, and molecules[56,57].

(ii) Stereo Complex Formation

For drug delivery systems, hydrogels based on stereo complex formation have recently been created. The key benefit of this approach is how easily a hydrogel can be created by dissolving each substance in water and combining the resulting solution. Poly lactic acid is a good example of a material with good stereo-complex properties (PLA). Tsuji et al.[58,59] were the first to describe PLA's ability to form stereo complexes. The very limited variety of polymer compositions that may be employed, however, is a key constraint of stereo complexation[52].

(iii) Ionic interaction

This section discusses ionic cross-linked polymers made up of counter ions that are di and trivalent. The basis for combining a polyelectrolyte solution with multivalent ions of opposite charge is this method[54]. This category includes hydrogels such as chitosan-glycerol phosphate salt[60] and *poly*[di (carboxylatophenoxy) phosphazene] calcium salt[61].

(iv) Hydrogen Bonding

The H-bonding that takes place between the polymeric networks results in the formation of physically cross-linked hydrogels[54]. The greatest illustration of this kind of hydrogel is the CMC (Carboxymethyl cellulose) based hydrogel, which is created by dispersing CMC in 0.1 M HCl. During this process, hydrogen from the acid took the place of the sodium ions.

2.5.2 Chemically Crosslinked Hydrogels

Covalent crosslinking and polymerization of end-functionalized macromeres are used to create these hydrogels. Chemical crosslinking of hydrogels is accomplished using compounds such as glutaraldehyde, formaldehyde, and dialdehydes. Chemical crosslinking enhances hydrogel's capability to absorb moisture through its hydrated pores even more. Chemical crosslinking of polysaccharide-based hydrogels is possible. Because they are less harmful to the environment, physically crosslinked hydrogels are preferred to chemically crosslinked hydrogels[62–64]. The swelling behaviour of hydrogels largely depends on their crosslinking ratio. In hydrogels, the greater the crosslinking ratio, the more compressed the structure and the smaller the swelling. A low crosslinking ratio, on the other hand, results in soft composites with greater swelling capacity. As a result, by modifying the crosslinking patterns of hydrogels, many specific properties can be altered[42,65,66]. In recent years, numerous methods for controlling the density of crosslinking within the structures of hydrogels have been found to produce controlled toughness and fluffiness. This distinction in features occasionally affects their use in certain biological and pharmacological domains. Table 1 analyses a few hydrogels with special characteristics generated from various crosslinking configurations. The following is a list of some of the techniques for creating chemically cross-linked hydrogels that have been described in the literature[52].

Hydrogels	**Types of cross-linkings**	**Properties**	**References**
Polyvinylglycolic acid (PVGA)	γ-Radiation crosslinking	Enhanced Swelling Properties	[228]
Polyacrylamide (PAM)	Hybrid crosslinking	Enhanced Adhesive Properties	[229]
Tyrosinase	Recombinant crosslinking	Enhanced Injectable Properties	[230]
Carboxymethyl chitosan	Photochemical crosslinking	Enhanced Resorbable Properties	[231]
Dextran hydrogels	Diamines crosslinking	Enhanced Viscoelastic Properties	[232]
Thiolated Hyaluronic acid (HA-SH)	Self-crosslinking	Enhanced Mechanical Properties	[233,234]
Double network hydrogels (ITA, MA)	Physical crosslinking	Enhanced Self-healing Properties	[235]
Hybrid hydrogels	Chemical crosslinking	Enhanced Dynamic Properties	[236]

Silk fibroin	Grafted crosslinking	Enhanced Biocompatible Properties	[237]
β[tris(hydroxylmethyl)phosphino] propionic acid (THPP)	Lysine mediated crosslinking	Enhanced Biocompatible Properties	[238]
PVC with ferulic acid in the presence of lacase	Enzymatic crosslinking	Enhanced Cellular Properties	[239]
PVA/PVP/HA	Crystallized crosslinking	Enhanced Mechanical Strength	[240]
Polyelectrolyte (Chitosan/Alginate hydrogel)	Ionic interactions-based crosslinking	Enhanced elasticity of polymer chain	[241]
PCL	Chemical grafting	Enhanced adhesiveness in substance for tissue engineering	[230]
CMC	Radiation grafting	Enhanced water purifying properties hence used for water purification purpose	[242]
NVCL	Radiation grafting	Promote controlled release of drugs on specific site	[78]
POPGMA	High-energy radiation	Better biocompatible properties	[243]
Gg-*cl*-*poly*(NIPA-*co*-AA)/$CoFe_2O_4$	Free Radical polymerization	Rheology, Electrical conductivity, Drug Removal and Drug Release study	[177,216,244,245]
Gg-*cl*-*poly*(AA)/-*o*-MWCNT	Free Radical polymerization	Rheology, Drug Removal study	[217,246]

Table 1. The features of various hydrogels with varying crosslinking patterns.

i) Chemical Cross-linking

Chemically cross-linked hydrogels frequently use cross-linkers to create cross-linked hydrogel networks based on synthetic and natural polymers, including glutaraldehyde, epichlorohydrin, adipic acid dihydrazide, and polyaldehydes. Furthermore, functional group interactions, such as an amine-carboxylic acid or isocyanate-OH/NH_2 reaction, or the development of Schiff bases with equivalent reactivity might establish covalent bonds between polymer chains[54,67]. Hydrogel composites made of xanthan and PVA and cross-linked using epichlorohydrin are an illustration of a hydrogel that has been chemically cross-linked[68].

ii) Grafting

The polymerization of a monomer on the backbone of a premade polymer is utilised in the creation of grafted hydrogels. Grafting is split into two forms based on the activation initiator used: chemical grafting and radiation grafting[54].

(a) Chemical grafting

Chemical grafting is a reaction between two chemical reagents that activate macromolecular backbones. The grafting of acrylic acid (AA) onto granular maize starch in an aqueous media, which was started by the ceric ion, serves as a demonstration of chemical grafting[54,69].

(b) Radiation grafting

Grafting that is powered byγ rays and *e*-beam radiation is known as radiation grafting. The grafting of acrylic acid onto carboxymethyl cellulose (CMC) in an aqueous solution while being exposed to *e*-beam radiation is an illustration of radiation grafting. The polymerization of acrylic acid by free radicals on the CMC backbone is continued with the help of the electron beam[54,70].

(c) Radical Polymerization

Radical polymerization from low molecular weight monomers can also produce molecularly cross-linked gels that mimic the effects of a cross-linking agent. One of the most popular processes for creating hydrogels is this one. The gel forms rapidly under these conditions thanks to the system's high efficiency. Ammonium persulfate (APS) or potassium persulfate, two free radical initiators, can be used to create this form of hydrogel (KPS)[44,45,48,54].

(d) Condensation Reaction

This component comprises hydrogels constituted through a condensation reaction. This type of hydrogel is often made using hydroxyl group/amine with carboxylic acid hydrogels or their derivatives. The condensation processes described by De Nooy et al.[71,72] are best exemplified by the Passerine and Ugi condensation reactions[73,74]. The crosslinks of the hydrogels produced by this Passerine condensation contain ester linkages. This common method involves condensing isocyanides with a carboxylic acid and a carbonyl molecule (aldehyde or ketone) to create -(acryloxy) amide[54]. This chemical mixture is mixed with an amine in the Ugi condensation method to produce (acryl amino) amide. In this type of hydrogel, the crosslinks are often formed by amide bonds[52].

(e) Enzymatic Reaction

Promising hydrogels can be produced using a revolutionary hydrogel idea to enhance enzymatic response. Sperinde et al.[75] outlined a captivating method for formulating PEG-based hydrogels using an enzyme. In their method, a glutamine group was added to a tetra-hydroxyl-PEG (PEG-Qa). Following that, PEG networks were strengthened by adding transglutaminase to aqueous solutions of PEG-Qa and polyethylene glycol (lysine-co-phenylalanine). The -carboxamide group of PEG-Qa and the -amine group of lysine react when this enzyme is present, resulting in a bond between the polymers known as an amide[54].

2.6 Based on network Electrical Charge

Electrical charge is attached to cross-linked chains. They can be classified as follows based on this:

(i) Temperature fluctuations cause neutral (non-ionic) hydrogels to swell or de-swell. In their polymer networks, they have irreversible permanent connections.

(ii) (ii) Ionic (anionic or cationic): Ionization causes the gel to acquire fixed charges. The amount of solvent absorbed in the network increases as a result of electrostatic repulsions.

Since anionic hydrogels contain acidic pendant groups, ionisation takes place when the environment's pH is higher than the ionizable groups' pK_a. Electrostatic repulsions between the polymeric network chains come from an increase in pH because it increases the degree of ionization, which increases the number of fixed charges. This in turn increases the hydrogel's propensity to love water, leading to higher swelling ratios.

Basic pendant groups, such as amines, that ionise at pH values lower than the pK_b of the ionizable groups make up cationic hydrogels. In this instance, as the pH falls, electrostatic repulsions increase and swelling increases.

- Amphoteric electrolytes: They are composed of monomers containing both acidic and basic groups. The ionic groups that are connected to the chains determine their characteristics. They can be attracted to oppositely charged solutions, resulting in either inter-ionic or intra-ionic interactions.
- Zwitterionic electrolyte: These are also known as polybetaines since each of their monomers contains anionic and cationic groups.

2.7 Based on the Basis of Response to Stimuli

Stimuli-responsive or smart polymers have garnered a lot of interest in recent years for their usage in medication delivery techniques. These polymers react to a variety of physical or chemical stimuli, such as variations in pH, temperature, ionic strength, light, the presence of enzymes or a specific ligand, and electric or magnetic fields[76].Some polymer systems respond to sensory tasks, such as a polymer's response to both pH and temperature[77,78]. Because they undergo conformational changes in reaction to changes in the external environment, temperature and pH sensitive polymers are better options for drug delivery systems. These changes can optimise medication loading, drug delivery site, and drug release rate. Hydrogels that are environmentally sensitive can detect changes in pH, temperature, ions, light, or metabolite concentration. Tissue engineering is being investigated using natural hydrogel materials such as agarose, methylcellulose, and hyaluronan. Fig.2 represents the different methods of crosslinking. Some of the environmental responsive hydrogels system include[79];

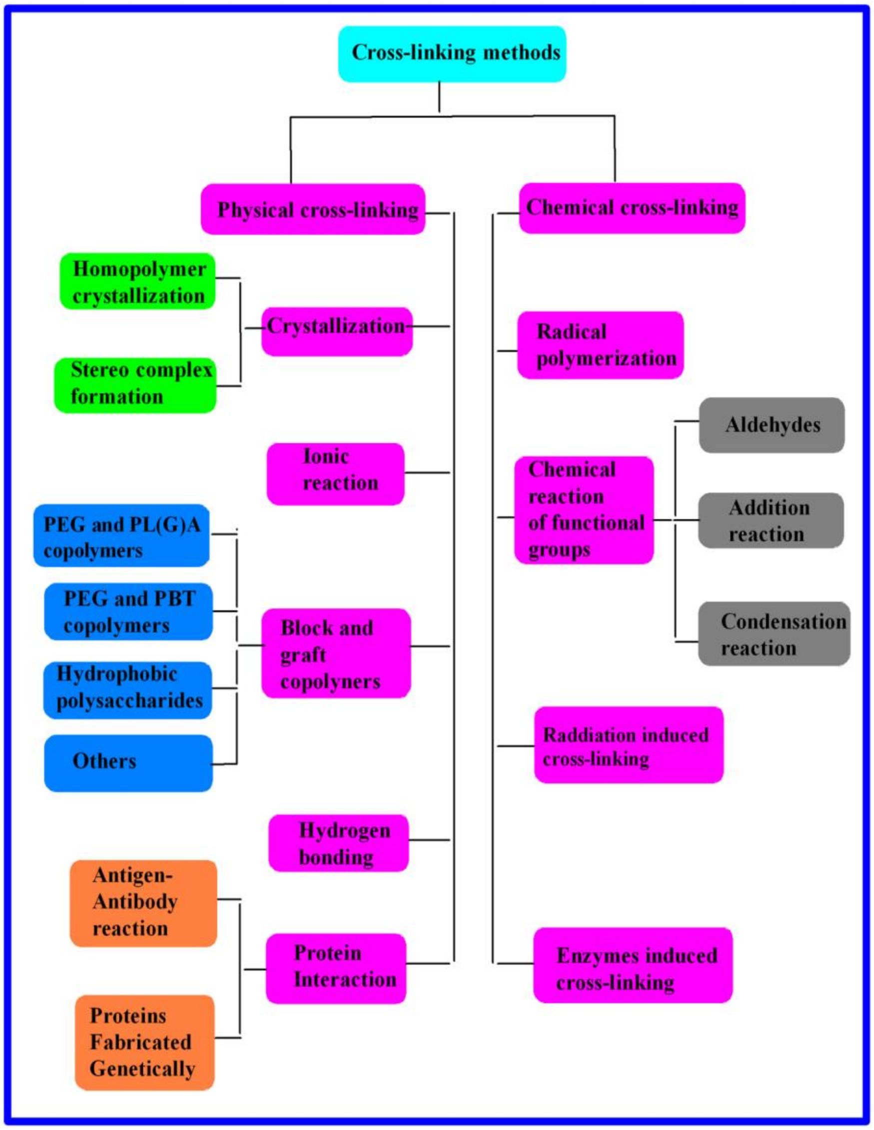

Figure 2. Methods of crosslinking of hydrogels

3. Synthesis of Hydrogels

Natural or synthetic polymers can be used to make hydrogels. Natural hydrogels are hydrogels derived from nature. The ingredients of natural hydrogels include alginate, chitosan, hyaluronic acid, fibrin, gelatin, cellulose, and dextran. Hydrogels derived from synthetic polymers, on the other hand, are referred to as synthetic hydrogels. Synthetic polymers include substances like ethylene glycol, acrylic acid, vinyl acetate, N-(2-hydroxypropyl) methacrylamide, methacrylic acid, ethylene glycol dimethacrylate, N-isopropyl acrylamide, polylactic acid, and polyethylene oxide. Hydrogels can be manufactured using a variety of techniques, and this review provides an overview of the various methods of preparation. The most common techniques used to generate hydrogels include physical cross-linking, chemical cross-linking, polymerization grafting, and radiation cross-linking. The following are some of the most modern ways of producing hydrogels:

3.1 By Photo-Fenton Method

For wastewater management, advanced oxidation processes (AOPs) have virtually superseded the biological treatment of plants. The study focuses on ways synthesize such materials that employ sunlight, making them more efficient and cost-effective. In comparison to the other system of H_2O_2 and UV irradiation, research has shown that the TiO_2/UV, Fe^{2+}/H_2O_2/UV (Photo-Fenton reaction) system is more effective at treating industrial wastewater[80]. As a result, efforts have been made to create various types of iron nanomaterials, such as Fe_3O_4. However, due to their large surface area, most nanoparticles tend to agglomerate in water. Therefore, using nanocomposite hydrogels with different monomers such polyvinyl alcohol, polyethylene glycol, polystyrene, and polyvinylpyrrolidone as well as natural goods like starch, cellulose, gelatin, and chitosan will provide great protection for these nanoparticles. A Photo-Fenton reaction was used to create biodegradable polyethyleneimine nanogels. It was revealed that the nanogels had a remarkably stable homogeneous structure. The most important aspect of the reaction was that it was conducted in an aqueous solution without the use of a crosslinker or an initiator. The nanogels that were created were then used in gene delivery[81].

3.2 Ultra-Filtration

Pressure or concentration gradients produce separation across a semipermeable membrane in this form of membrane filtration. As opposed to water and low molecular weight solutes that penetrate, suspended particles and high molecular weight solutes are maintained in the retentate (filtrate)[42]. In the production of responsive cyclodextrins in aqueous nanogels based on polyethylene, unreacted monomers and smaller polymeric impurities are removed using ultrafiltration (N-vinylcaprolactum)[82].

3.3 Solvent Method

This method of extraction employs a solvent to separate a material from a combination of one or more compounds. Dialdehyde carboxymethylcellulose and collagen were combined in a biphasic solvent to produce stable hydrogel composites, as reported in the literature. The biocompatibility of the hydrogels produced was outstanding[83]. A self-assembled nanogel from mannan-C16 was produced as a result of the interaction of the hydrophobic alkyl chains in an aqueous environment. These nanogels were then employed in therapeutic treatments since they had no negative side effects[42,84]. The solvent approach is termed more cost-effective than any other method of preparation.

3.4 Self-assembly Method

Self-assembly is the process by which a disorganised system of pre-existing components generates an ordered structure or pattern as a result of specific and local interactions between the components. The procedure is referred to as hydrogel self-assembly when hydrogels are [42]the primary constituents. Using this technique, the hydrophobic dextrin polymer dexC16 was created. This method was found to offer good control over the level of dextran-hexadecathiol interaction, providing a number of choices for the creation of amphiphilic materials with specific properties[85]. DNA nanohydrogels with adjustable size and stimuli-responsive characteristics were generated using the self-assembly technique. Aptamer-based nanohydrogels (Y-gel-Apt) have been found to be effective for targeted and stimuli-responsive gene therapy[86].

3.5 Carbodiimide Crosslinking Method

Carbodiimides (RN=C=NR′) are unsaturated chemicals with organic synthesis and biotechnology uses. These carbodiimides have the potential to be employed in the synthesis of peptides. These are expected to be more effective in forming crosslinking networks via carboxylic acid hydroxyl groups and separating biological membranes[87].To better understand the effects of pH, carboxyl and amino group breakdown, and the role of carbodiimides in amide formation. This method was used to create hyaluronic acid-based hydrogels with high biocompatibility and tensile strength[88].

3.6 Semi-batch Method

The semi-batch approach is one of the most distinctive ways to produce nanogels. The product is given in little quantities. This technology is unusual in that it uses homogenous solutions to adjust the size of nanoparticles during the production process. In the absence of a surfactant, a unique pH and temperature sensitive nanogel can be created using a semi-batch method[42]. Because of the semi-batch process, carboxylic groups are spread within and outside of colloidal particles in the case of polymers (NIPAM-*co*-AAc). Targeted drug delivery applications can use the developed semi-batch nanogels.

Due to their low stability, the generated nanohydrogel particles assumed a spherical shape with some aggregation[89].

3.7 Co-Precipitation Method

The precipitates of chemicals that are ordinarily soluble at the circumstances utilised are frequently utilised in the co-precipitation process to synthesise a compound. Consequently, this approach may be used to analyse chemical and trace elements. Novel iron oxide nanoparticles (Fe_3O_4 NPs) were produced using co-precipitation and employed in theranostic procedures. Initially, an itaconat-functionalized starch macromonomer known as starch-IA was produced using the esterification procedure. Starch-IA/Fe_3O_4 nano hydrogels were subsequently produced by combining the black Fe_3O_4 NPs with starch-IA[90]. In a different work, magnetic chitosan-*g-poly*(N-vinylcaprolactam) nanogels were shaken in an aqueous system of doxorubicin (DOX) at room temperature to create doxorubicin (DOX) loaded nanogels[91].

4. Preparation methods of hydrogels

In hydrogels, polymer chains are present. Thus, the characteristics of the polymer dictate those of the hydrogel[92]. Not all polymers can be utilised to create hydrogels because water absorption is the main property of a hydrogel. In hydrogels, crosslinks bind the polymer chains together to create a three-dimensional matrix. The physical properties of polymer chains, including their elasticity, viscosity, solubility, glass transition temperature (T_g), strength, toughness, and melting point, to name a few, are affected by cross-linking[93]. Cross-links stop rotational movement between polymer chains, increasing the T_g of cross-linked polymers. The solubility of the polymer decreases as a result of cross-linking, which increases the molecular weight of polymer chains while impeding translational mobility. Although being insoluble, these cross-linked polymers absorb a substantial quantity of solvent, producing in gels. The amount of solvent absorbed by a network polymer depends on the frequency of cross-linking, or the number of cross-links per unit of volume. The flexibility of polymer chains to follow solvent molecules decreases as cross-linking density increases. A hydrogel may contain both physical and chemical cross-links. After the synthesis of polymer chains or concurrently with it, cross-linking can take place. As a result, monomers, prepolymers, and polymers can be used to create hydrogels[94] (Table 2).

Starting material	Example	Cross-linking type	Crosslinker	Synthesis method	Reference
Monomer HEMA	PHEMA	Chemical	EGDMA	Free radical polymerization using initiators such as for example, peroxides and azo compounds	[247]
Polymers PEG and PMAA	PEG-PMAA	Physical H-bonding	None	Complexation reaction	[248]
Prepolymers MDI, Partially	Polyurethanes: MDI/PCLPEG/	Chemical	Polyols	Free radical polymerization	[94]

polymerized PCL, PEG, Chain extenders: DEG, MDEA, DMPA	DEG, MDI/PCL-PEG/DMPA, and MDI/PCL-PEG/MDEA				
Gum ghatti, acrylic acid, N-isopropyl acrylamide, $CoFe_2O_4$	Gg-*cl*-*poly*(NIPA-*co*-AA)/$CoFe_2O_4$	Chemical	MBA	Free radical polymerization	[177,216,244,245]
Gum ghatti, Acrylic and oxidized multiwalled carbon nanotube	Gg-*cl*-*poly*(AA)/-*o*-MWCNT	Chemical	MBA	Free radical polymerization	[217,246]

Table. 2 Materials used as building blocks in the synthesis of hydrogels

5. Natural Polymer Hydrogels

Hydrogels can be characterized as natural, synthetic, or a combination of the two hydrogels generated from natural polymers are known as natural polymer hydrogels. Natural polymers include polysaccharides, polynucleotides, and polypeptides. Natural polymers can be formed from a number of natural resources and are classified as neutral, cationic, or anionic in nature[95]. These polymers are easily accessible, plentiful, affordable, non-toxic, biodegradable, and have other appealing biological features. The link between form and function has long piqued people's curiosity, particularly in natural physiologically active substances. Breakthroughs in structural and functional substances have resulted in an increasing number of innovations in materials for use in biomedical technology throughout the last few decades. Natural polymers have unique, larger structures formed by covalently attached monomeric components[96,97]. Biopolymers hydrogels have several biological applications, such as controlled and targeted medication release, tissue engineering, and wound healing[34].

6. Polysaccharide Hydrogels

A separate class of naturally occurring polymers with a variety of structural traits is the polysaccharide family. Due to their excellent biological characteristics, polysaccharides can be employed to create renewable biomaterials. They are made up of long-chain carbohydrates with repeated monomeric units joined together by glycosidic bonds. These could be biomaterials with unique physiological characteristics and biological activity that could be used for a range of purposes. Natural carbohydrates have been thoroughly investigated for use in industrial, medicinal, pharmaceutical, and tissue engineering applications. Examples include cellulose, starch, chitin, chitosan, gum ghatti, xanthan gum, carrageenan, alginates, dextran, pullulan, and pectin[34,98].

6.1 Chitosan

A mucopolysaccharide called chitin can be found in the carapaces of insects, fungus, and crustaceans. In terms of volume, it is the second most prevalent polysaccharide in the world after cellulose. Chitin is heavily acetylated and has a sugar backbone with 1, 4-linked glucosamine units[54,99]. That's a cellulose derivative containing amine groups in lieu of the hydroxyl groups, making it polycationic. Chitosan is a significant chitin derivative that is generally produced via alkaline deacetylation of chitin[100,101]. Chitosan's low toxicity and biodegradability have led to a wide range of applications in the pharmaceutical industry. Furthermore, chitosan has been shown to offer a variety of positive pharmacological effects, including antiulcer, anti-acid, hypocholesterolemic, wound-healing, spermicidal, anti-tumor, and hemostatic qualities. It is currently being used as a matrix material in the pharmaceutical industry for tissue engineering and drug delivery applications. Numerous studies have been conducted to determine chitosan's significance to the pharmaceutical sector. It is largely employed as an excipient in tablets, controlled-release dosage forms, gels, absorption enhancers, drug dissolving, wound healing products, and micro/nanoparticle creation[54].

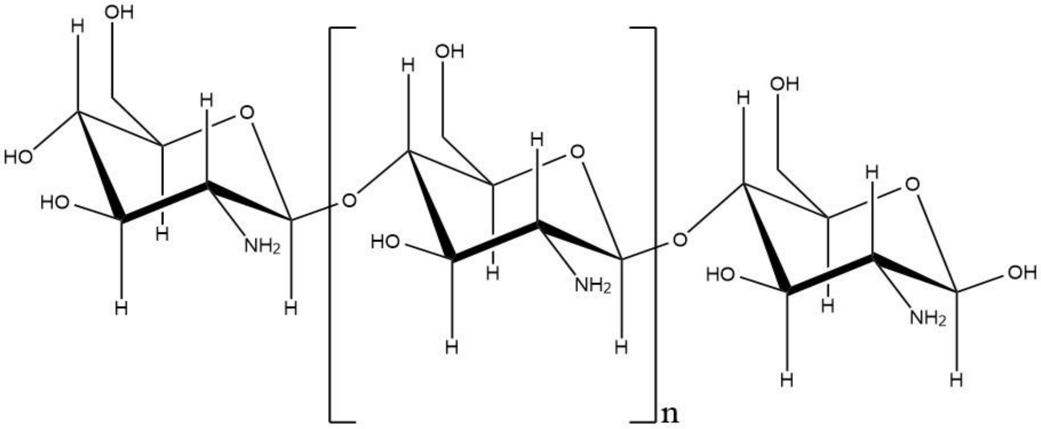

Figure 3. Structure of Chitosan

6.2 Guar Gum

Guar gum is extracted from the endosperm of Cyamopsis tetragonoloba bean seeds. It is a polysaccharide combination known as galactomannan. The latter is made up of a skeleton of D-mannose (β-D-mannopyranose) with branches1→ 6 linkages connect D-galactose (α-D-galactopyranose) units. Guar gum is utilised in the culinary, pharmaceutical, cosmetics, and textile sectors, as well as as a lubricant in oil well drilling[102]. This polymer has a lot of hydroxyl groups. When guar gum is mixed with water, it generates hydrogen bonds that give the solution extraordinary viscosity and thickening. Because of its great water swellability, non-toxicity, and low cost, it is also employed in the production of hydrophilic matrix tablets[103,104].

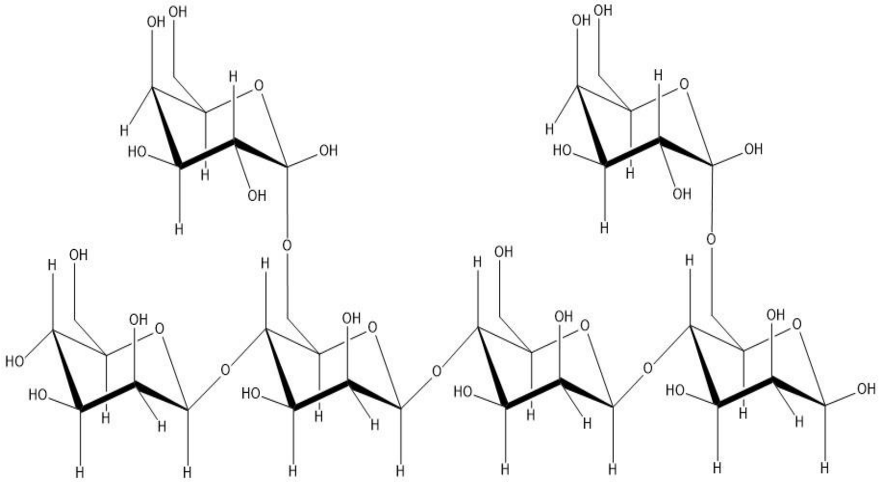

Figure 4. Structure of Guar gum

6.3 Arabic gum

Arabic (acacia) gum is a delicious, sticky tree exudate generated from the stems and branches of acacia senegal and acacia seyal that is high in non-viscous soluble fibres. It is a branched-chain complex polysaccharide that can be neutral or slightly acidic. Acacia gum hydrolysis yields four sugars: D-galactose, L-rhamnose, L-arabinose, and D-glucuronic acid[105–107]. Acacia gum's backbone is made up of 1,3-linked β-D-galactopyranosyl units. The side chains are made up of two to five 1,3-linked β-D-galactopyranosyl units connected to the main chain by 1,6-bonds[108]. Acacia gum is commonly blended with tragacanth gum and utilised as a suspension and emulsifying ingredient in oral and topical medicinal formulations. It is also used as a tablet binder in the pharmaceutical business[109,110].

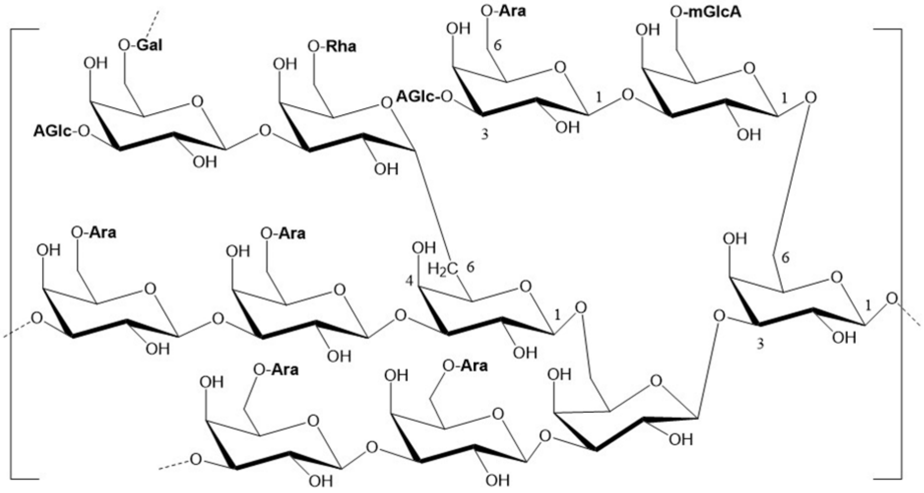

Figure 5. Structure of Gum Arabic

6.4 Xanthan Gum

Xanthan gum (XG) is a biopolymer that has received a lot of interest in the academic and industrial worlds. Because of the presence of tunable hydroxyl (-OH) groups, XG is an effective polyelectrolyte. It has been widely utilised as a suspending agent in the pharmaceutical and cosmetic industries, as well as an addition in food as a thickening agent[111]. In the 1950s, a team of scientists from the Northern Regional Research Laboratory (NRRL) of the United States discovered XG. The first xanthan products were manufactured in 1960, and they became commercially available in early 1964. The FDA authorised the use of XG as a non-toxic and safe polymer in several food products in 1969. China became a big xanthan producer in 2005. XG's primary chain is made up of *β*-(1→4)-linked molecules. D-glucopyranosidase enzyme A glucuronic acid wedged between two mannose units makes up a short branch of glucan and alternating glucoses. The backbone of the XG is like the chemical structure of cellulose. As a result, the side chains are made up of *β*-(1→3)-*α*-linked D-mannopyranose- (1→2)*β*-D-glucuronic acid (1→4)-*β*-D-mannopyranose on alternate residues. The terminal D-mannose contains a pyruvic acid residue linked to the 4 and 6 sites via a keto group[112].

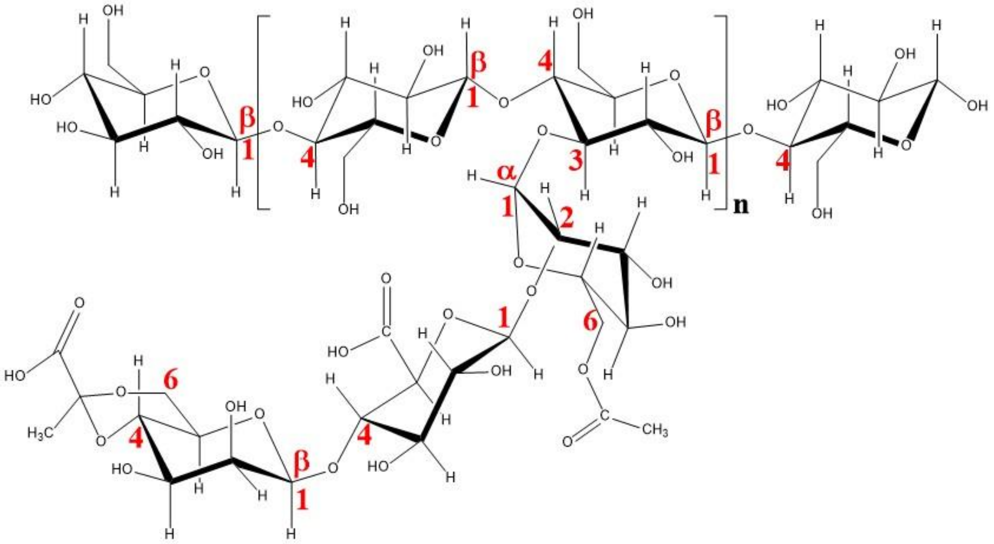

Figure 6. Structure of Xanthan gum

6.5 Gum ghatti

Gum ghatti (Gg) is a complicated anionic polysaccharide obtained from the exudation of the Anogeissus latifolia tree (Combretaceae family). Gg has a main chain of 1→6 linked *β*-D-galactopyranose units and alternating 4-*O*-substituted and 2-*O*-substituted *α*-D-mannopyranose units with a side chain of single L-arabinofuranose units[113]. It is mostly utilised in the food sector as an additive, thickening agent, and preservation. Many studies on gum ghatti-based hydrogels have recently been conducted, including gum ghatti/*poly* (acrylamide-*co*-acrylic acid), gum ghatti/*poly* (acrylamide-*co*-acrylonitrile), gum ghatti-*cl*-*poly* (acrylamide), gum ghatti-*cl*-*poly* (acrylamide-*co*-methacrylic acid, and gum ghatti crosslinked with *poly* (acrylic acid-*co*-acrylamide), and the resultant hydrogel polymers might be used in medicine delivery devices and waste water treatment[114,115].

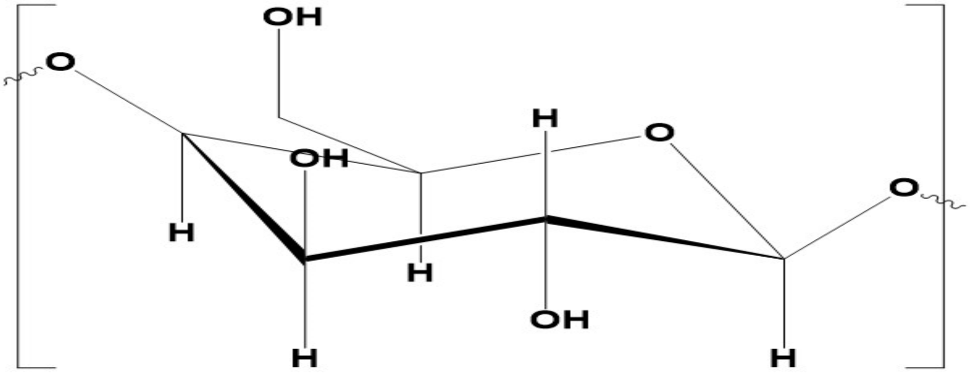

Figure 7. Structure of Gum ghatti

6.6 Synthetic Polymer Hydrogels

Because they have more specialised physical and chemical properties than natural polymers, synthetic polymers are intriguing for application in the production of synthetic polymer hydrogels. It is possible to make synthetic polymers with long chain topologies and high molecular weight. Consequently, the biological activity of synthetic polymer hydrogels is lower than that of natural hydrogels. Synthetic polymer hydrogels can be created using chemically crosslinked polymers or functionalized vinyl monomers. Synthetic polymers used in the production of hydrogels include *poly*(vinyl alcohol)(PVA), *poly*(ethylene glycol) (PEG), *poly*(ethylene oxide) (PEO), *poly*(2-hydroxyethyl methacrylate) (PHEMA), *poly*(acrylic acid) (*P*AA), *poly*(N-isopropylacrylamide)(NIPA), and *poly*(acrylamide)(*P*AAm), among others. The following sections discuss certain synthetic polymer hydrogels.

6.6.1 Hydrogels Based on *Poly*(Acrylic Acid) Derivatives

Because of the availability of anionic carboxyl groups, acrylic acid-based hydrogels are pH-sensitive, revealing more swelling at basic pH but less swelling at acidic pH when compared to hydrogels containing non-ionic or neutral attached groups. At basic pH, the electrostatic resistance of carboxylate ions produced by carboxylic group decarboxylation results in significant swelling. Due to their exceptional adhesive properties, acrylic acid-based hydrogels have been produced and used extensively in a variety of fields, particularly in the biomedical industry. UV irradiation was used to create glycidyl methacrylate and dextran copolymer hydrogels from *poly*(acrylic acid). The hydrogels showed pH-sensitive swelling at pH 7.4 when dextranase was present[116]. Lee et al[117] produced a glycerol crosslinked *poly*(acrylic acid) hydrogel by polymerizing acrylic acid with benzoyl peroxide and novozym 435. This hydrogel inflated 100% greater when the pH was neutral, acidic, or basic. Additionally, using free radical co-polymerization to make a poly (acrylic acid) hydrogel while using N,N′-methylenebisacrylamide as a crosslinking agent[118]. By bombarding an acrylic acid solution with an electron beam of up to 75 kGy, Nho et al[119] created *poly*(acrylic acid) hydrogels and researched physical characteristics such swelling ratio, mucoadhesion, and gel compositions.

6.6.2 Hydrogels Based on *Poly*(N-isopropyl acrylamide) Derivatives

The use of smart hydrogels in the layout of long-term drug delivery systems has recently gained traction, and the current situation necessitates the development of innovative hydrogel systems with higher efficacy. Temperature-sensitive hydrogels are one of the most extensively researched types of smart hydrogels in drug delivery research[120]. Because its lower critical solution temperature (LCST) of about 33 °C, which is close to human body temperature, makes *poly*(N-isopropyl acrylamide) (*P*NIPAAm) a well-researched thermo-responsive polymer. Pure *P*NIPAAm hydrogels, on the other hand, are not suitable candidates for biomedical applications because to their poor mechanical stability[121] and limited biocompatibility[122]. The use of *P*NIPAAm hydrogel as a possible drug carrier is further hampered by its ineffectiveness in terms of sustained drug-releasing capacity; that is, the impregnated drug is typically released in a relatively short period of time. As a result, it is critical to combine *P*NIPAAm with appropriate polymers to fully realise its potential in drug administration[123–125].

7. A few prevalent kinds of hydrogels

Environmentally sensitive hydrogels, also referred to as "*intelligen*t" or "*smart*" hydrogels, are currently the subject of extensive scientific research in a variety of fields, including biomedical, biotechnology, pharmaceutical, and separation science. In this section, four common hydrogel forms are discussed below:

7.1 pH-sensitive hydrogels

A pH-sensitive polymer is made up of basic (such as ammonium salts) or acidic (such as carboxylic and sulfonic acids) groups that gain or lose protons in response to pH changes in their environment. Polyelectrolytes are polymers containing an abundance of ionizable groups. When *poly*(acrylic acid)(PAA), an anionic polyelectrolyte, is deprotonated in a basic environment, the electrostatic repulsions between the chains increase significantly, allowing water molecules to pass through and causing the hydrogel to expand significantly. Furthermore, in an acidic environment, the acidic polymer protonates, leading to a reduction in charge density and polymer volume implosion (Fig.8). Cationic polyelectrolytes, like *poly*(N, N 9-diethylaminoethyl methacrylate), become ionised in an acidic pH and expand (Fig.8). Due to the presence of both acidic and basic moieties, amphiphilic hydrogels suffer two-phase shifts in environments with acidic and basic conditions as opposed to neutral media.

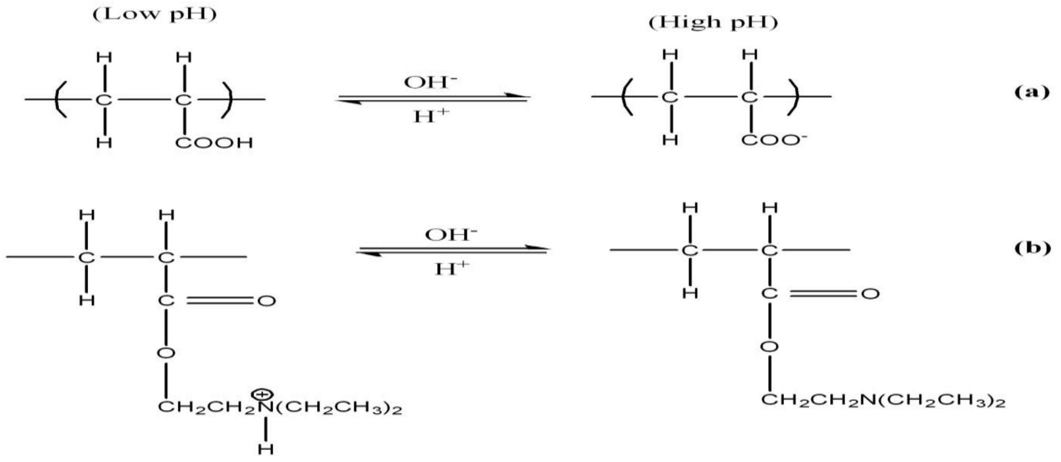

Figure 8. Polyelectrolyte ionisation in a pH-dependent manner. (*a*) *poly*(acrylic acid) and (*b*) *poly*(N,N′-diethylaminoethyl methacrylate).

7.2 Temperature-sensitive hydrogels

Because they contain groups like methyl, ethyl, and propyl, which ideally react with water molecules via hydrogen bonds to cause the hydrogel to expand, temperature-sensitive hydrogels (thermogels) are aqueous monomer/polymer solutions with a somewhat hydrophobic feature. These hydrogen bonds and temperature are connected. A few of the temperature-sensitive hydrogels' architectures are shown in Fig.9.

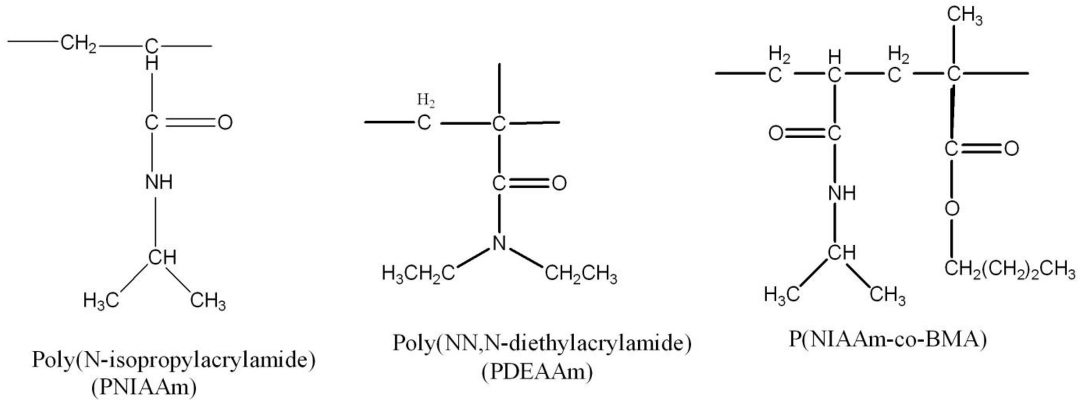
Poly(N-isopropylacrylamide) (PNIAAm)
Poly(NN,N-diethylacrylamide) (PDEAAm)
P(NIAAm-co-BMA)

Figure 9. Some temperature-sensitive polymers structures

This is evident because thermosensitive polymers frequently contain hydrophobic groups. As the temperature rises, the majority of polymers become more water soluble. However, in some circumstances, water solubility declines as temperature rises (inverse or negative temperature dependence)[126]. This peculiar behaviour produces a polymer phase transition, which is an entropy-driven process, when the temperature increases to a crucial threshold known as the "lower critical solution temperature" or LCST. Water works well as a solvent for the polymer in hydrogels with negative thermosensitivity, which are found directly below the LCST. Hydrogen bonding interactions between the polymer and water molecules cause the polymer to dissolve more quickly in water.

7.3 Electro-sensitive hydrogels

As the name suggests, electro-sensitive hydrogels contract or expand in the presence of an applied electric field. They frequently contain polyelectrolytes, just like pH-sensitive hydrogels. Mobile ions are drawn to the electrodes by the network's force on counter ions and stationary charged groups when an electric field is present. As a result, the hydrogel at the cathode and anode can swell and compress regionally. According to Flory's theory of osmotic stress, the hydrogel bends as a result of ion concentration changes within the hydrogel network and culture media[127,128]. The degree of bending is determined by the hydrogel structure and electrical field parameters such as stimulus strength, direction, and duration. When electrically stimulated, electro-sensitive hydrogels can change water permeability by selectively becoming permeable for a particular molecular size and expanding and contracting their micropore size[129]. Electro-responsive hydrogels are a significant family of smart materials with prospective uses in biomechanics, sensing, energy transduction, sound dampening, chemical separations, controlled drug delivery[130], and tissue engineering[131,132]. They can transform electrical energy into mechanical energy. Electro-sensitive and biocompatible smart muscle-based devices have been developed using hydrogels made of acrylamide and derivatives of carboxylic acids, such as *P*AA[133,134].

7.4 Light-responsive hydrogels

Photo-responsive hydrogels undergo a change in characteristics when exposed to the suitable wavelength of light. These variations are frequently caused by light-induced structural changes of certain functional groups located throughout the polymer backbone or side chains. Hydrogels that are light-sensitive can enlarge or contract when exposed to ultraviolet (UV) or visible light. Compared to UV light, visible light has a number of benefits, including greater accessibility, lower cost, ease of use, and clean functioning. Adding a photo-responsive functional group (chromophore) causes temperature changes in the polymer network, which is the basis for the visible light-induced volume change in hydrogels (e.g. trisodium salt of copper chlorophyll). The chromophore absorbs light at a specific wavelength, which is then locally converted to heat and increases the hydrogel's "*local*" temperature.

8. Properties of Hydrogels

Hydrogel utilization necessitates the disposition of the pertinent attribute of the hydrogel in question and the exploration of its interplay with biomaterials. To judge this physical phenomenon to its properties, exhaustive research regarding its optical, mechanical, and chemical nature has to be performed. For these examinations, it is essential to alter extant or create new know-how to report the synthesized hydrogels[135]. A downright description moreover lets for future scrutiny with other materials engaged in the field of application.

A wide range of features of hydrogels, such as their swelling/deswelling behavior, permeability, absorption capacity, mechanical properties, biodegradability, biocompatibility, cytotoxicity, electrical properties, optical properties, etc[136], make them intriguing materials for a few different applications. The properties of the hydrogels are significantly influenced by the characteristics of the polymer chains and the cross-linking structures in these aqueous solutions. Following is a discussion below of how certain qualities vary depending on various conditions.

8.1 Mechanical properties

Mechanical properties of gel formulations can render a window seat view of gel properties like hardness, cohesiveness, and adhesiveness. These properties can be used to modify attributes that are appropriate for peculiar applications, such as injectable thermosensitive hydrogels. Formulations were susceptible to texture profile analysis (TPA), where a probe acts with the sample to create a force-time plot. It is best known that the mechanical properties of semi-solid preparations are dependent on both the concentration of polymer and additives within the gel. TPA allows a relationship to be seen between changing variables within a formulation and its mechanical properties[137].

Depending on the type of material, the mechanical qualities might change and vary. By raising the crosslinking amount or reducing it by heating the material, it is possible to obtain a gel with improved rigidity. A wide range of factors is related to changes in mechanical characteristics. For example, white gelatin has a noticeably increased Young Modulus by crosslinking[136], but silk fibro in has an extremely higher Young Modulus that will decrease following regeneration[138]. A Dynamic Mechanical Analysis (DMA) device or a rheometer may measure these characteristics (Young modulus, Poisson modulus, Storage and Loss moduli, tanδ), according to the hundreds of methodologies that are now readily available on the market but won't be further discussed here[139].

It is important to remember that in a hydrogel, the combination of the gel network and water results in the Young Modulus. The same reasoning holds true for the development of a heterogeneous scaffold material, such as a replacement for the vertebral bodies, if we need to seed osteoblast cells, we are going to require more stiff material than if we cultivate adipocyte[140]. The mechanical characteristics of dual network (DN) hydrogels are also improved as compared to single-network hydrogels thanks to the energy dissipation of dual-network structures and the function of "sacrificial linkages". Since its creation approximately 20 years ago, DN hydrogels have found use in a variety of industries. Exemplary polyvinyl alcohol DN hydrogels and alginate DN hydrogels have been applied in biomedicine, intelligent sensors, ion adsorption, and other domains[141].

8.2 Rheological properties

In 1929 Professor Eugene Bingham[142] coined the term rheology. The rheology word was derived from the Greek word *rew* (rheo) indicates *flow*. Rheology is the examination of the deformation and flow of materials. Rheology conceives that almost all materials have attributes of both a solid (elastic) and a liquid (viscous) known as as *viscoelastic material*, meaning thereby is, not an ideal solid or ideal liquid[143]. A pure solid is represented by Robert Hooke's law of elasticity (1687) as a material with pure elasticity that reverts to its original shape after stress is removed. On the other level, Isaac Newton's law of flow (1687) represented a pure liquid as a material with pure ideal viscosity which flows under the smallest stress and does not revert to its original shape[144,145]. Simply, a rheometer works by relating a materials property to how far it moves when being sheared. The measurements that a rheometer gets include torque, deformation angle, and angular velocity. From those three measurements all other information is calculated, including modulus, shear stress, shear strain, and shear rate. In practice, a sample is loaded into the rheometer in between two plates which either rotate or oscillate based on the material being studied. Factors such as plate geometry, plate size, temperature, and force are controlled in regard to what is being studied.

A Newtonian fluid, such as water, has a linear relationship between shear stress and shear rate. As shear rate increases, shear stress to increases. The linear line that is created when plotted has a constant viscosity which is the slope of the line Fig.10.

$$\tau = \eta \times \gamma^{\bullet} \qquad \text{(Eq. 1)}$$

Where τ is shear stress, η is shear viscosity, and $\gamma^{\bullet}$ shear rate.

Eq.1. Describes Newton's law of viscosity. The relationship between shear rate and shear stress presents Newton's law of viscosity. Non-Newtonian fluids considers ones that do not have a invariant viscosity with ever-changing rate of shear. Shear-thickening fluids enhance viscosity when shear rate is augmented, and shear-thinning has reduced viscosity when shear rate is attenuated. Other non-Newtonian fluids include Bingham plastics which necessitate a token amount to begin flow, but once flow starts, they act as Newtonian fluids with a linear relationship of shear stress and shear rate (see Fig.10).

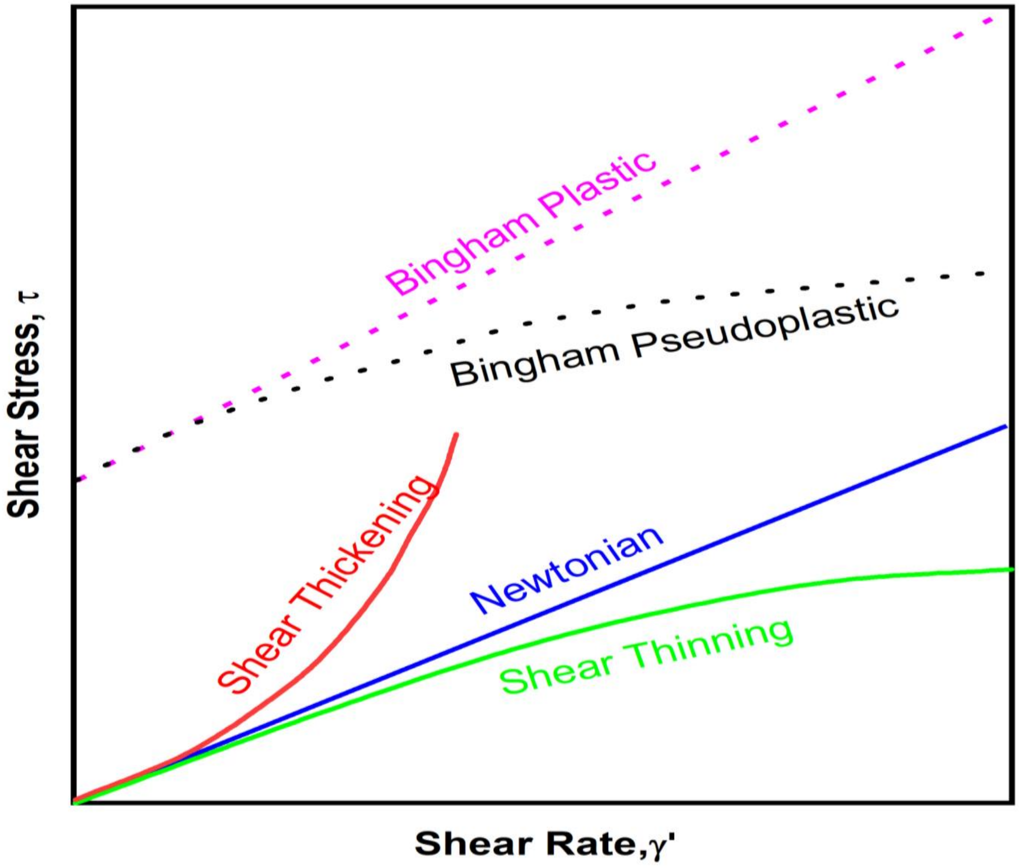

Figure 10. Shear stress vs shear rate of different types of fluids

Rheological investigations were performed on biopolymers and synthetic polymer preparations using oscillatory mode in a variety of tests, to not break up the polymer network that rotational studies may cause. These investigations permit flow sweeps before gelling and after gelation, this lets for the solution and gel to be classified as Newtonian or non-Newtonian. Additionally, by looking at the storage modulus (G′) and loss modulus (G″) we are able to find the gelling point of the samples and also discuss the strength of the gels by looking at G′ values. Oscillation time examination will render information as to what temperature gelation happens and oscillating temperature ramp examination supplies information at the length of time that gelation happens. The gelation temperature and time at which the biopolymers and synthetic polymer solution goes from solution to a gel dictate whether it will be a befitting injectable drug. The formulation at low temperatures (below body temp) must be liquid-like to let for effortless injection and then rapidly gel at body temperature and deliver therapeutics at a controlled rate.

Numerous rheological testing systems may be used to evaluate rheological performance. A basic polymer rheology textbook by Ostwald et al[2] is suggested for[146] comprehensive previous knowledge of the mathematical theories of rheological measurement. Cone-plate and parallel-plate testing fixtures, the two most popular ones, will be briefly examined, along with each of their unique applications, advantages, and disadvantages. Numerous rheological experiments, including yield stress, creep, recovery time, oscillation, and ramp tests, may be performed using the cone-plate setup[147]. The design of the cone-plate fixture, which sandwiches the material being evaluated among a flat bottom plate and a top cone with a modest angle, typically between 1-4°, is responsible for the vast range of rheological testing. Excellent material evaluations are possible because the cone's modest angle causes the shear-rate and shear stress across the sample to be almost constant. The cone-plate method has the drawback that it can only suspend tiny particles ($\leq 10\ \mu$m) and cannot be utilized for suspensions of bigger particles. In contrast, there is no restriction on particle size for the parallel-plate setup, which sandwiched the substance under test between two flat plates. Materials with greater particle sizes ($\geq 10\ \mu$m) can be examined due to the design of the parallel plate setup. The downside of the parallel-plate fixture is that the shear rate across the sample rises with radius, therefore the parameters obtained are average values throughout the range, which should be considered when comparing results from different investigations. When conducting a rheological test, the cone-plate fixture is advised; however, the parallel-plate fixture is advised in situations when the cone-plate fixture may not be utilised because of particle size. The shape of the probing fixture and the testing instrument you choose can both have an impact on the information a rheological test produces. The results of sample measurements carried out by two consecutive studies utilising the same material and testing settings, but different testing fixtures might vary, therefore testing discrepancies must be taken into consideration. To compare the results of different studies, it is important to note the testing equipment used (e.g., cone-plate or parallel-plate), fixture geometry used (e.g. 20 *mm*), and testing circumstances. When conducting a rheological evaluation, the cone-plate fixture is advised; however, the parallel-plate fixture is advised in situations when the cone-plate fixture may not be utilised because of particle size[148].

8.3 Swelling Properties

Future uses of hydrogel matrix in the disciplines of ophthalmology, biomedicine, pharmaceuticals, and tissue engineering will be governed by its swelling characteristics. The hydrogel's polymer chains interact with solvent molecules and begin to stretch until they reach a fully relaxed and solvated state, where they stabilize. Contrarily, the crosslinked network uses a different approach. chain-pulling internal force. Equilibrium is reached when these two opposing forces are balanced against one another. This equilibrium ratio (Eq.2) serves as a broad representation of how hydrogels swell.

$$\text{Equilibrium swelling ratio} = \frac{W_{swollen}}{W_{dry}} \quad \text{(Eq.2)}$$

Where, $W_{Swollen}$ weight of the swollen hydrogel, W_{dry} weight of the dry gel

The swelling kinetics may be used to determine the hydrogel’s swelling kinetics. The dry hydrogel's weight (W_{dry}) is calculated first. The dry hydrogel is then submerged in water until the optimum swelling is achieved. The swelled hydrogel ($W_{Swollen}$) is then weighed after the extra water has been drained away. Given is the swelling ratio: (Eq.3).

$$\text{Equilibrium swelling ratio} = \frac{W_{swollen}-W_{dry}}{W_{dry}} \quad \text{(Eq.3)}$$

Many research groups have investigated the swelling/shrinking dynamics of *P*NIPA hydrogel in response to temperature changes. Yoshida and colleagues talked about the shrinking kinetics of *P*NIPA hydrogel. They stated that comb-type *P*NIPA hydrogels folded fist first, followed by hydrogels lacking grafted side chains[149,150]. In the cross-linked *P*NIPA network, they also specified a comb-shaped grafted hydrogel made of PEO graft chains[151]. For hydrogels used in biological and pharmacological applications, swelling properties are crucial. The solute diffusion coefficient, surface wettability, and mechanical characteristics of the hydrogel are all influenced by an essential parameter known as the equilibrium swelling ratio. Many parameters, including the kind of monomer, the amount of crosslinker, and environmental variables including temperature, pH, and ionic strength, influence the swelling characteristics. Kiil [152,153] created a mathematical model to describe how water causes swelling, drugs dissolve, and drugs have both internal and exterior mass transport resistance in an HPMC matrix.

8.4 Electrical properties

Electroconductive is a combination of the words "electroactive" and "conductive." A polymer possessing the characteristics of both hydrogels and conductive systems is referred to as an electroconductive hydrogel, and Gong et al[154] may have invented the term first, who described a 7,7,8,8-tetracyanoquinodimethane (TCNQ)-loaded hydrogel-based conductive charge transfer salt complex. Numerous investigations on composites made from CEP and hydrogels have been conducted since the initial articles by Guiseppi-Elie and Wallace. Water dispersion polymerization of aniline using PVP as a steric stabiliser, followed by γ-irradiation that caused cross-linking of the PVP component, was used to create an electrically conductive composite material that was made of polyaniline nanoparticles dispersed in a polyvinyl pyrrolidone (PVP) hydrogel[155]. A hydrogel made of acrylamide and acrylic acid that was doped with a polypyrrole/carbon black composite served as the foundation for the artificial muscle material created by Moschou et al.[156]. By electropolymerizing the conducting polymer inside a porous insulating hydrogel matrix. Lira et al.[157] created polyaniline-polyacrylamide composites. The polyaniline that was found inside the pores made the novel substance that resulted in electroactive. Devices for electrochemically controlled drug delivery used these composite materials. Kumar and Gangopadhyay reported on the fabrication of a hydrogel composite in which polyaniline (linear) was trapped inside a cross-linked polyelectrolyte hydrogel, poly (2-acrylamido-2-methyl propane sulphonic acid) (PAMPS)[157]. In order to show that the produced material may be used to deliver drugs under regulated conditions, Nikpour et al.[158] created conducting polymer composites of PPy with poly (methylmethacrylate). Polypropylene glycol was employed as the liquid porogen and sodium chloride powder was used as the solid porogen. As a sensor material for aqueous ammonia. Koul et al.[159] reported on the fabrication of a polyaniline (acrylonitrile-butadiene-styrene) composite membrane. The composite film's resistance changed as a result of exposure to various aqueous ammonia concentrations,demonstrating the material's suitability as a sensor. Park and Park 2002[160] investigated the electrical properties of the conducting composite poly (methylmethacrylate-co pyrrolmethylstyrene)-*g*-polypyrrole (PMMAPMS-*g*-PPy). The PMMAPMS-*g*-PPy was synthesized by the electrochemical reaction of PMMAPMS and pyrrole in the electrolyte solution containing lithium perchlorate and a mixture solvent of acetonitrile and dichloromethane. Electrodes have frequently been made using polypyrrole (PPy) sheets with enzymes trapped inside that were electropolymerized from aqueous solutions. A glucose biosensor based on GO*x* entrapment inside a composite p(HEMA)/PPy hydrogel membrane was created by Brahim et al. in 2002[161]. On the platinum electrode surface, a combination of HEMA, tetraethylene glycol (TEGDA) as a crosslinker and enzyme, and HEMA was then polymerized by UV irradiation while in an argon environment. The hydrogel network's trapped pyrrole monomer was then electrochemically polymerized. Cholesterol oxidase (ChlO*x*; E.C 1.1.3.6) was captured onto the p(HEMA)/PPymatrix to create an amperometric biosensor for cholesterol analysis[162]. An amperometric biosensor for therapeutically significant analytes was created using the bioactive composites of p(HEMA) hydrogels that include polypyrrole (galactose[163], glucose and cholesterol). The hydrogel-based biosensor made from the overoxidized polypyrrole shown good screening for physiological impurities such ascorbic acid, uric acid, and acetaminophen[164].

8.5 Optical properties

A probe on the optical properties of the gel, like swelling state with regard to environmental consequences, was undertaken based on surface plasmon and waveguide mode spectroscopy. This results in the formation of a synthetic hydrogel network around a parent polymer chain, with the primary polymer altering the hydrogel's behaviour. The mechanical behaviour is the most immediately apparent advantage of using interpenetration techniques, although water binding, surface, and optical properties are also impacted. Compatibility phenomena, which take place at two levels, have a particularly powerful impact on optical properties. The first crucial stage in the production of SIPN is controlled by the initial solubility of the matrix monomer and "filler" polymer.

Nonreactive solvents can be used to speed up the dissolving process and then removed, although this has no positive impact on the compatibility of matrix and "filler" polymers in the dehydrated form. Because water is a necessary third component in hydrogel-based IPNs, extra and distinct compatibility problems in the hydrated state are involved. In hydrated systems, transparency typically results from preferred water clustering around the more hydrophilic moieties, which to some extent separates the hydrophobic blocks into phases. Although optically clear SIPNs with high water content have significant potential for use in ocular applications, translucent or opaque materials have potential uses in both ocular implants and devices that do not require optical clarity as well as non-ophthalmic biomaterials like wound dressings and synthetic articular cartilage[165–168].

8.5.1 Measurement Methods for Optical Hydrogel Properties

A variety of techniques can be used to measure the optical characteristics of hydrogels. These characteristics are listed in Table 3 along with the most popular measurement techniques. Each technique is briefly described, and each property's importance for employing hydrogels as a PIV channel material is highlighted[169].

Table 3. Overview and explanation of optical measurement techniques for hydrogels and their applicability to this review.

8.5.2 Requirements for Optical Properties

A Particle image velocimetry (PIV) channel material must have index of refraction (IOR) matching to the experimental fluid as a minimum requirement. PMMA and silicone have historically been used as common PIV channel materials in modern cardiovascular research[170,171]. The IOR of silicone ranges from 1.40 to 1.44, and that of PMMA is 1.491[171,172]. Water-based solutions with glycerin, sodium iodide, and xanthan gum have been used as blood replacement fluids to mimic the viscosity of human blood[170,173]. Chemicals are added, and this alters the fluid's IOR. IORs for water and glycerin/water mixtures are, respectively, 1.3325[174] and 1.414[172]. Therefore, the hydrogels chosen for this review had to have an IOR of less than 1.55. Transparency is another necessity for PIV channel materials in order to accurately record particle movements inside the vessel. Only transparent hydrogels with light transmissions of greater than 90% were taken into account in this review[169].

8.6 Biological Properties

Biocompatibility and non-toxicity, appropriate mechanical qualities, good viscosity, stability, biodegradability, and other important characteristics of injectable hydrogels for various medical applications are among their key attributes. The hydrogel must possess the necessary biological and mechanical characteristics, and these characteristics must be comparable to those of the tissue it will replace[175].

9. Applications of hydrogels

Hydrogels have several uses. This is owing to their distinct architectures and compatibility with a wide range of operating environments. The biocompatibility of the materials used to make hydrogels, along with their chemical nature in biological environments, which can be nontoxic, extends their implementations to the medical sciences. Hydrogel's flexibility, which is due to their water content, allows them to be used in a wide range of conditions, from biological to factory. The applications and key uses of hydrogels are shown in the examples below. This is not a comprehensive list; rather, it concentrates on the most useful uses of hydrogels in industrial and medical.

9.1 Drug delivery

To avoid the constraints of standard drug formulations, sustained release systems (DDS) that administer medications at fixed rates for predetermined durations of time have been developed. The extraordinary qualities of hydrogels make them an attractive choice for medication delivery applications. High porosity hydrogel structures can be created by regulating the degree of matrix cross-linking and the hydrogel's affinity for the aqueous environment where swelling takes place. Hydrogels are extremely permeable to many types of medications due to their porous architecture, allowing pharmaceuticals to be loaded and released under regulated conditions[176]. The key benefit is that a high concentration of an active pharmaceutical material can be delivered to a specific site over a longer period of time thanks to hydrogels capacity for sustained release of pharma during drug delivery trials. Electrostatic interactions and covalent bonding are examples of physical methods that can be used to improve the binding of a loaded drug to the hydrogel matrix. Certain drugs can be held in place by hydrogels, shielded from harmful environments, and released with the best kinetics. Changes in pH, temperature, the presence of enzymes, or far-off physical stimuli might cause a drug to release on demand[177].

9.2 Dyes and heavy metal ions removal

Trace metals contamination in wastewater from several industrial operations has been linked to serious issues with ecological and public health systems. Removing heavy metal ions from a variety of water sources is extremely important from a scientific and practical standpoint. Heavy metal toxicity has been removed from aqueous media using synthetic cross-linked polyacrylate hydrogels[176]. However, because these synthetic materials are so expensive, they may not be a viable solution on a large scale. Heavy metal ion pollution may be cleaned using well-known adsorption methods, which have the added benefit of recycling the treated effluent in addition to being flexible in design and operation. Furthermore, because the adsorption process is often reversible, the adsorbent can usually be regenerated to make the system more cost-effective. The hydrogels have been shown to have exceptionally high methylene blue adsorption, making them excellent dye adsorbent components. Among hydrogel-forming materials, polyelectrolytes are particularly crucial for the removal of heavy metal ions. Due to polyelectrolytes' propensity to attract oppositely charged metal ions and form complexes, they are widely used in this industry. In fact, the presence of both cationic and anionic charges on the micro- or nano-gel provides additional advantages for simultaneously eradicating two distinct species. Hydrogels are adaptable and sustainable materials with several environmental uses.

The claim states that the presence of both cationic and anionic charges on the micro- or nano-gel provides additional benefits for simultaneously eradicating two distinct species. Hydrogels are adaptable and sustainable materials with several environmental uses.

To remove metal ions from aqueous media, biopolymer-based hydrogels such chitosan, alginate, starch, and cellulose derivatives were utilised. It was found that the functional groups in the hydrogel might change how heavy metal ions absorb and how quickly they can bind to surfaces. This is because the removal of metal ions involves more complex procedures than straightforward sorption, such as ion exchange and chelating[178,179].

9.3 Contact lenses

Ophthalmology, especially contact lenses, is a critical use for synthetic hydrogels in bio-applications. A tiny optical tool called a contact lens is placed on the cornea and used to change the power of the cornea. Leonardo da Vinci first proposed the idea of using contact lenses in 1508 and suggested putting the eye in a bowl of water. Professor Otto Wichterle[180,181] invented *poly*(2-hydroxyethyl methacrylate) (PHEMA) lenses at the end of 1960; this invention represents the most important step in contact lens development and the beginning of the soft lens era. The majority of the requirements for use in a range of physiological circumstances can be met by the hydrogels used in the production of contact lenses. To be comfortable to wear, a hydrogel substance used as a contact lens must meet certain criteria. High water content, strong mechanical qualities, oxygen permeability, surface wettability, good optical properties, resistance to hydrolysis and sterilisation, nontoxicity, and biological tolerance for live cells are among the prerequisites.

9.4 Scaffolds in tissue engineering

The use of resources, engineering, and cells to enhance or replace organic organs is known as tissue engineering. This demands the identification of acceptable cell types and their cultivation in a suitable scaffold under suitable circumstances. Hydrogels are attractive scaffold materials as their topologies are similar to the extracellular matrix of many tissues and they can often be produced under fairly benign circumstances and delivered with minimal invasiveness[182]. Physical characteristics, mass transport capabilities, biological characteristics, the intended scaffold usage, and the environment in which the scaffold will be used all have an impact on the appropriate scaffold design and material selection for each specific application. For instance, using different material structures is required since the scaffold used to create false skin and fake bone must be different from one another. Hydrogels for tissue engineering scaffolds can be generated using synthetic and organic materials. Table 4 provides many of the most recent instances of possible hydrogel uses.

Application	Hydrogel	Description	References
Tissue engineering	PVA/GO-HA nanocomposite	Artificial cartilage regeneration potential, excellent printing accuracy, and good pore regularity	[183]
	PVA	Low wear and friction, as well as adhesion that resists fatigue, long-term stability while transmitting electrical, optical, auditory, chemical, and mechanical impulses between tissues and outside devices	[184]
	PVA/PAA composite	Potential for vascular access and other blood-contacting medical device applications due to high strength, super hydrophilicity, lower platelet adhesion (than polyurethane catheters), lower thrombosis-induced occlusion, and other properties	[185]
	Polyhydroxybutyrate (PHB) - Chitosan (Cs)	Biodegradation had been slowed by including HNT in the PHB-Cs matrix	[186]
	Gum tragacanth/PVA/halloysite	With HNTs loading up to 20% wt, the gel content and swelling of hydrogels decreased. The biocompatibility and osteogenic potential of hydrogel were examined after being seeded with mesenchymal stem cells from rabbit bone marrow.	[187]
Antibacterial materials	NIPAAm/PF127–Ag nanoparticles	Antibacterial materials	[188]
Electronic skin/ Bioelectronics	PVA/PEDOT: PSS composite	Flexible and stretchable skin and sensitive strain sensors, for example, are examples of wearable technologies.	[189]
	PEDOT: PSS	Self-healing hydrogel bioelectronic devices, injectable hydrogel, room-temperature gel formation	[190]
	Fe_3O_4/MoS_2/PANI	Electronic skin, medication delivery, electromagnetic interference shielding, and wave absorption are all examples of applications.	[191]
	MWCNTs@PDA/P4VP	A self-healing hydrogel using environmentally friendly components and flexible biosensors	[192]

	Fe^{3+} ions blended PVAA/PAM hydrogel	Artificial ionic skin that is highly stretchable and deformable, ionic conductivity, and self-healing with a pressure sensor to monitor human mobility	[193]
Drug delivery systems	PMAA/laponite RDS	System of controlled release (pH-sensitive)	[194]
	PVA/montmorillonite loaded with capecitabine	4 T1 cancer cell lines were successfully treated both in vitro and in vivo	[195]
	PEG/PCL block polymer hydrogel	Thermosensitive hydrogel	[196]
	Lysine-modified PVCL	Nano-hydrogel with pH and temperature control	[197]
	PAA cross-linked with PEGDA	Possible use in intestinal drug release: 3D created with digital light processing, pH-responsive hydrogel, oral delivery, and faster drug release at high pH	[198]
	Gelatin/poly(N-isopropylacrylamide) (PNIPAM)	Thermoresponsive nanocomposite hydrogels, Close to body temperature, at about 37 °C, the system displayed a reversible sol-gel transition.	[199]
	Gg-*cl*-*poly*(NIPA-*co*-AA)/$CoFe_2O_4$	Thermoresponsive nanocomposite hydrogels and faster drug release at pH-7.4	[177]
Sensors	PANI-GO	Pb^{2+} ion determination and elimination in water	[200]
	PANI/PAAm	A small variation in body motion can be detected using a portable piezoelectric sensor	[201]
	PDMAM/Zirconia nanocomposite	Arsenic in aqueous solution quartz crystal microbalance (QCM) sensor	[202]
	PAM/halloysite nanotubes	Dye adsorption and a strain sensor	[203]
Energy storage (Materials for electrodes and electrolytes)	PANI/PAM composite	Advanced technologies include things like fuel cells, supercapacitors, dye-sensitive solar cells, and reusable lithium batteries	[204]
	Vinyl hybrid silica nanoparticle cross-linked PAM	Supercapacitor electrolyte that is both stretchy and compressible	[205]
	PANI nanofibers	Supercapacitor electrode suitable for ultrathin fibril structure with an increased specific capacitance of 636 F g^{-1}	[206]
	PVA-Na_2SO_4	Supercapacitor electrolyte and barrier	[207]
	Graphene/PPy	A 363 F cm^{-3} specific capacitance, enhanced mechanical flexibility, and a long cycle life	[208]
	Graphene/PANI composite	Brilliant stability (99 percent initial capacitance retention after 1000 charge/discharge cycles) and 323.9 F g^{-1} specific capacitance	[209]

	PANI, PPy, PEDOT, and PANI/graphene hydrogels	Bioactive scaffolds for stimulating and regenerating tissue as well as electrode materials for supercapacitors are examples of potential applications	[210]
Ions/Pollutant removal	PVA-g-MA/PAA/GO	Removal of methylene blue and crystal violet from aqueous solutions	[211]
	PVA/Bentonite (acid-treated)	Ionic dye removal from water	[212]
	PAM/bentonite	Pb^{2+} and Cd^{2+} uptake from aqueous solution	[213]
	TiO_2 and ZnO nanoparticles encapsulated PMMA microcapsules	Methylene blue should be removed from aqueous solutions.	[214]
	Montmorillonite supported-PAM-co-PAA	Within 20 minutes, remove 97 percent methylene blue at 200 *mg*/L with a little dosage of hydrogel (0.5 *g*/L).	[215]
	Gg-*cl*-*poly*(NIPA-*co*-AA)/$CoFe_2O_4$	Metformin hydrogen chloride should be removed from aqueous solutions	[216]
	Gg-*cl*-*poly*(AA)/-*o*-MWCNT	Sodium diclifenac should be removed from aqueous solutions	[217]
Catalysis	PAM/MoS_2	Aqueous separation and catalysis, self-healing hydrogel	[218]
	Gold nanoparticles embedded sodium polyacrylate hydrogels	Catalysts for nitrophenol and dye hydride reduction	[219]
	PAM/graphene composite embedded with Ag+ ions	Organic analyte catalytic reduction using pseudo zero-order kinetics	[220]
	MPEG-b-PGMA-b-PMMA	Aid in the creation of nanoparticles of the bimetallic alloy gold:silver (Au:Ag), silver, and other metals	[221]

Table 4. Applications for hydrogels

9.5 Fire retardant

Hydrogels can be applied in many fields of science and life because of their special qualities. The possibility of using hydrogels as a type of fire retardant material in and of themselves, as a medium in fire retardant materials used, among other things, as extinguishing agents for fires and suppression agents for the self-ignition of coal in mines (where their low viscosity and high ability to penetrate the protected material is used), protective layers in fabrics and the so-called robot skin (most often applied in the layer-by-layer system), filling in the fire retain (mainly in combination with silicate and phosphate derivatives)[222]. A hydrogel and a cloth were laminated to create a brand-new category of fire-resistant material. The hydrogel includes 90% water, which has a high heat capacity and enthalpy of vaporisation. Water warms up and evaporates when the laminate is exposed to fire, absorbing a significant quantity of energy. Until until it is completely dehydrated, the hydrogel's temperature cannot rise over 1000C. The fabric maintains the temperature difference between the hydrogel and the skin since it has a poor heat conductivity[223]. Being a two-dimensional inorganic nanomaterial with a high specific surface area and strong thermal stability, MXene is effective at suppressing smoke as well as acting as a physical barrier for heat and flammable gas products[224]. One of the greatest thermal insulation materials on the market is rigid polyurethane foam (RPUF), however because of its flammability, it might cause a fire. Owing to its porous structure, the material's enormous specific surface area is what makes flames spread quickly and easily when exposed to heat sources. The majority of the burning that occurs with RPUF happens on the surface. As a result, if a flame-retardant coating can be produced on the surface of RPUF, it may effectively inhibit or stop the flames spread there, increasing fire safety[225].

9.6 Batteries

Flexible batteries have attracted a lot of attention from researchers recently as they work to build wearable intelligent devices, which are expected to become vital in our daily lives due to their broad range of potential applications. Flexible battery solutions should have advantages such as steady electrochemical characteristics, compact size, and mechanical flexibility to frequent deformations that wearables may experience in real-world use. Due to its inherent safety, superior chemical stability, cost effectiveness, and sufficient energy density when compared to typical LIBs, rechargeable aqueous Zn-based batteries are particularly beneficial for building flexible and wearable batteries[226]. Smart batteries are in great demand due to the growing popularity of intelligent products, which range from soft robots and wearables to artificial intelligence. Smart batteries may self-adjust their functionalities based on the operating environment thanks to hydrogels. Despite advancements in hydrogel-based smart batteries, there is still a discrepancy between the performance expectations for batteries and the designable functions of various hydrogels[227].

10. Advantages of hydrogels

(i) Posse's great degree of elasticity is comparable to that of real tissues.

(ii) They are biocompatible and biodegradable, which is why they can be injected.

(iii) They may be pH or temperature sensitive and release medication when these conditions change.

11. Disadvantages of hydrogels

(i) Temperature-sensitive hydrogels are *P*NIPA-based hydrogels. They can trigger an increase or decrease in drug release based on temperature stimulation.

(ii) The movement of maggots causes a feeling.

(iii) Lens deposition, hypoxia, dehydration, and ocular responses are all caused by contact lenses.

12. Conclusions

This estimate that up the fundamental concepts of hydrogels, such as the materials involved, the synthesis approach, the classification of hydrogels, the methods of crosslinking, the types of bonding, and, most importantly, the properties of hydrogels for a wide range of applications. The unique properties and applications of hydrogels are highly dependent on the polymers and crosslinking agents used, as well as the method of synthesis and bonding. Hydrogels are polymeric materials with a spectrum of uses depending on the synthetic process used to create them. Furthermore, the cross-linked structure of the hydrogel can be achieved depending on the type of synthesis or raw materials used. Because of the weakness of their interaction, physical hydrogels have reversible networks. Chemical hydrogels, on the other hand, have permanent networks with only a minor degree of swelling. The synthesis of both types of hydrogels has received a lot of attention because they both have good properties. Furthermore, the ability of hydrogels to combine with other structures such as nanoparticles to create multifunctional systems merits special attention in order to enable successful applications. In the following decade, research on stimuli-sensitive hydrogels will yield new promising results in a variety of fields. This estate of hydrogels enables hydrogels to be complexed with substituents that make them biosensors.

The majority of recent hydrogel research papers describe complex materials with numerous components. Each component serves a specific purpose in the intended application. A hydrogel, for example, containing monomers with different properties (e.g., hydrophilic and hydrophobic) exhibits distinct surface properties. Furthermore, the surface of a hydrogel can be grafted with another polymer to change its properties. Physically modifying the gel surface is another way to change surface properties. Photolithography and soft lithography are two common physical modification techniques for creating small structures on hydrogel surfaces.

The addition of nanoparticles or the fabrication of hydrogels with multiple networks strengthens a hydrogel's mechanical properties. Obtaining a uniform dispersion of nanoparticles in the hydrogel matrix is difficult, but it is critical for the hydrogel's consistency and properties. The addition of other materials improves the desired property while adding new and interesting features to the hydrogel. Silver nanoparticles, for example, add antibacterial properties to wound dressing hydrogels, and graphene improves the performance of supercapacitor hydrogel electrodes.

Hydrogels have been extensively studied as tissue matrices or scaffolds in the field of tissue engineering. Future hydrogel development could include combining modern biotechnological techniques for preparation and designing hybrid hydrogel systems, which could be useful in the field of drug delivery.

Numerous hydrogel-based drug delivery systems and scaffolds have been designed, studied, and in some cases patented, but few have made it to market. More progress in these two areas is expected. The low commoditization of hydrogels in drug delivery and tissue engineering is due, in part, to their high production costs. In a nutshell, hydrogels and hydrogel-based nanomaterials have proven to be a miracle in the biomedical sector.

Scope of the review

In summary, polymeric macromolecular hydrogels have a variety of special qualities that make them eligible and enable them to display remarkable qualities, allowing them to be used as potential candidates for applications in nearly all fields, including biomedical, industrial, environmental, and agricultural areas. In order to improve hydrogels for their useful uses, major changes are occasionally undertaken. In achieving the special requirements of sophisticated applications in the field of drug delivery, more dedication should be put forth in the future. The most desired delivery method would continue to be cross-linked structures of monomers, pre-polymers, and polymers. The creation of hydrogels without the use of organic solvents or non-toxic cross-linkers will be a wonderful strategy. For targeting drug release or tissue engineering development of hydrogel functionalization, injectable hydrogels that are easily created inside the body without requiring surgery would become an appealing strategy for the consumers. Since the created hydrogel has a low mechanical strength, its applications are still limited in a number of fields. Thus, the primary focus of research for the ensuing decades will be on hydrogels with increased mechanical strength.

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Conflict of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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