Review Article

Hydrogels Design Strategies and their Biomedical Application: A Review

Gauri S. Borkar[1]*, Satyam Z. Chemate[2], Gunwant B. Patil[3], Komal S. Baride[4]

[1,3,4] Department of Pharmaceutics, Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar 414 111, Maharashtra, India.

[2] Professor and Head of Department (Pharmaceutics), Dr. Vithalrao Vikhe Patil Foundation's College of Pharmacy, Vilad Ghat, Ahmednagar 414 111, Maharashtra, India.

***Corresponding author's E-mail:** gauriborkar5888@gmail.com

Received: 14-03-2023; **Revised:** 26-05-2023; **Accepted:** 05-06-2023; **Published on:** 15-06-2023.

ABSTRACT

Hydrogels are three-dimensional networks formed of polymers, proteins, small molecules, or colloids that swell when exposed to water. Because of their ability to encapsulate and protect drugs as well as provide sustained and/or remotely programmable spatial and temporal release, they represent a flexible platform for drug delivery. As a result, they have stimulated a significant amount of research for the delivery of either small active compounds or biopharmaceuticals. Hydrogel could be one potential solution to the problems that drug delivery faces today. The primary objective of this review article is to concern the classification of hydrogel, its advantages, and disadvantages, significance of hydrogel, preparation techniques, structural diversity of hydrogel, cellulose-based hydrogels, chitosan-based hydrogel beads, and applications. Many applications, like drug delivery systems, diagnostics, tissue engineering, optics, and imaging, have benefited greatly from the use of hydrogels. Large molecular weight proteins are necessary for the treatment of various disorders. With the availability of hydrogels, they are accessible.

Keywords: Hydrogel; 3D network; Polymers; Classification; Significance; Crosslinking; Structural diversity; Cellulose-based hydrogel; Chitosan-based hydrogel beads.

QUICK RESPONSE CODE →

DOI: 10.47583/ijpsrr.2023.v80i02.015

DOI link: http://dx.doi.org/10.47583/ijpsrr.2023.v80i02.015

1. INTRODUCTION

A three-dimensional cross-linked polymeric network made of synthetic or natural polymers is referred to as a hydrogel because it can hold water inside of its porous structure. The hydrophilic groups, such as amino, carboxyl, and hydroxyl groups, found in the polymer chains of hydrogels are primarily responsible for their ability to hold water. At physiological temperature and pH, these polymeric materials do not dissolve in water but instead significantly swell in an aqueous media.[1,2]

The word "hydrogels" indicates that the substance has previously swelled in water; dried hydrogels are referred to as "xerogels." If water is removed from the gel without disrupting the polymeric network, either by lyophilization or by extraction with organic solvents, the resulting material is extremely light with porosity as high as 98%; this dehydrated hydrogel is known as aerogel. Surface tension causes the collapse of the gel body during the drying process.[3]

When it comes to the nature of the constituent molecules, their functionality (such as simultaneous imaging and therapy, programmable and controlled release, the hierarchy of microenvironments and nano environments accessible (hydrophobic or hydrophilic), and a plethora of other options, such as attaching ligands, combining them with nanoparticles (NPs), attaching them to other materials, etc.—hydrogels present a wide range of design options.

Mostly made of water, hydrogels can encapsulate drugs, slowing or stopping their degradation, and aggregation, and shortening their lifetime while providing sustained release, controlled by diffusion out of or degradation of the matrix, or remotely controlled by external/endogenous triggers. They also offer an environment similar to natural tissues.[4]

Because most hydrogels provide a hydrophilic locus of solubilization, they are especially appealing for biopharmaceuticals, a rapidly expanding class of newly approved medications that include recombinant proteins and peptides[5,6], monoclonal antibodies, and polynucleotides[7-9], including Small interfering RNAs (siRNAs), a topic of particular interest in recent years.[10-12] However, depending on their structural makeup, hydrogels may also be able to solubilize hydrophobic drugs, for example when mixed with polymer NPs in nanocomposite gels.[13,14]

In terms of their architecture, hydrogels can be made from a wide variety of building blocks (e.g., polymers typically classified as natural or synthetic, peptides[5,8,9], proteins[5], surfactants[15], colloids[16,17], and small molecules[18,19,20], with various chemistries, arrangements of the building blocks, and connections (cross-links), effectively producing a

variety of macroscopic and nanoscopic structures, size range, physical properties, and function. These features decide whether drugs are encapsulated (for example, small molecules[18] or cells[21,22], and how they are released.

On the macroscale, hydrogels can be either "bulk" or macroscopic gels (suitable for the transepithelial route, insertion, or injection in the body), microgels[23] (micrometers in size, also suitable for pulmonary and intrabony delivery[24]), or nano gels[25-27] (10- 100 nm, suitable for systemic administration and studied for intracell delivery.[24,26]

In hydrogels, pore size (if microscopic) affects deformability and cell diffusion, whereas mesh size (in the range of 100 nm) determines the release of medicines through diffusion; this can be changed through degradation and swelling of the matrix, either time-dependent or triggered. Whether drugs are physically bonded to the gel matrix or covalently conjugated to the polymer, particular interactions between the gel matrix and the drug also affect release on a lower length scale (hydrophobic, van der Waals, electrostatic, and soon).[4]

The possibility of injectability[28] of hydrogels, as opposed to implantation in the body through invasive procedures, is a particularly alluring feature. This is either provided by shear thinning properties or by in situ gel formation, which can be triggered by physiological temperature or other external stimuli ("smart" or "stimuli-responsive" gels). (See Fig 1)

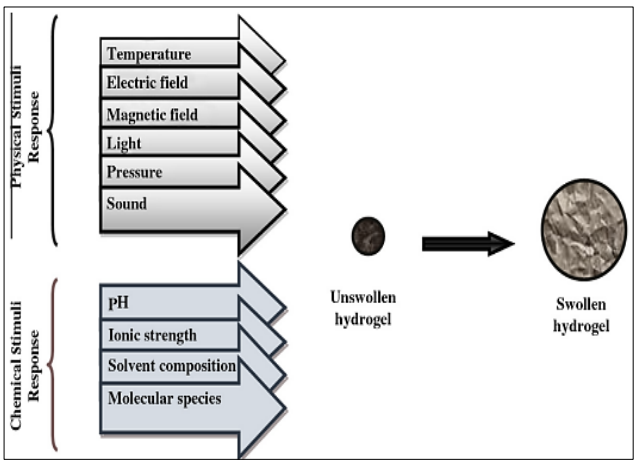

Figure 1: Stimuli response of hydrogel: classification of stimuli response of swelling hydrogel i.e., physical and chemical stimuli responsive swelling hydrogel.

Physical gels, also known as supramolecular gels or "self-healing" gels, are supported by physical interactions rather than covalent bonds. Examples of these interactions include van der Waals, hydrogen bonds, electrostatic forces, and host-guest interactions, which are frequently with cyclodextrins or curcurbit[n]urils. Because of their adaptability and inherently dynamic nature, physical gels are particularly well suited for drug delivery applications. This is why a lot of recent research has concentrated on supramolecular gels. They also lack the toxic crosslinkers and free radicals used in many chemical cross-linking protocols.[4] (See Fig 2)

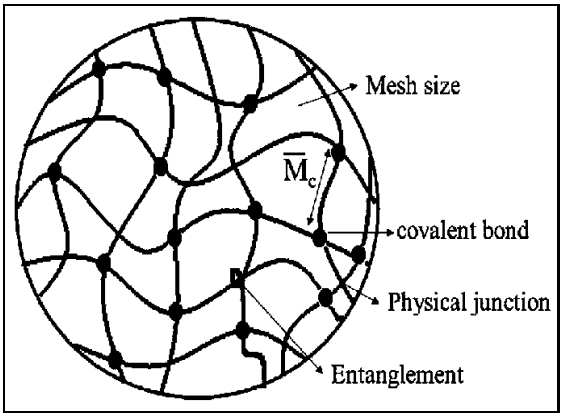

Figure 2: Hydrogel: the molecular structure of hydrogel.

2. CLASSIFICATION OF HYDROGEL

2.1. On the basis of the nature of the cross-linked junction

2.1.1. Permanent/chemical gel

When networks are chemically cross-linked (replacing hydrogen connections with more powerful and stable covalent bonds), they are referred to as "permanent" or "chemical" gels. When they reach an equilibrium swelling state, depending on the Parameters affecting the polymer-water interaction and crosslink density.[29]

2.1.2. Reversible/physical gel

When the networks are held together by molecular entanglements, and secondary forces such as ionic, hydrogen bonding, or hydrophobic interactions, they are referred to as "reversible" or "physical" gels. Physical interactions between various polymer chains in physically cross-linked gels inhibit dissolution. All of these interactions are reversible and susceptible to disruption by stress or changes in the surroundings.[1,30,31]

2.2. On the basis of origin

2.2.1. Natural polymer

Natural hydrogels possess strong cell adhesion characteristics, they are biodegradable and biocompatible. Natural hydrogels are mostly composed of two types of polymers: polysaccharides such as hyaluronic acid, alginate, and chitosan, and proteins such as collagen, gelatin, and lysozyme.[32,33] They support cellular activities.[29]

They lack essential mechanical characteristics. They may be a pathogen and stimulate inflammatory and immunological reactions.[1]

2.2.2. Synthetic polymer

They can be manufactured to have a significantly wider variety of mechanical and chemical properties than their natural counterparts, making them more useful than natural hydrogels. Hydrogels made of polyethylene glycol are a type of substance that is frequently utilized in

biomedical applications because they are non-toxic, immunogenic, and compatible.[34]

They have an absence of inherent bioactive qualities.[29]

Ex. Acrylic acid -Hydroxyethyl methacrylate (HEMA), Vinyl acetate, Methacrylic acid (MAA).[1]

2.2.3. Hybrid polymer

They are a blend of synthetic and natural polymer hydrogels. Many naturally occurring biopolymers, including dextran, collagen, and chitosan, have been mixed with synthetic polymers, including poly (N-isopropyl acrylamide) and polyvinyl alcohol, to combine the properties of both synthetic and natural hydrogels.[35]

2.3. On the basis of the polymeric composition

2.3.1. Homopolymeric hydrogel

They are a fundamental structural component made up of any polymer network generated from a single monomer species. Homopolymers may have a cross-linked skeletal structure depending on the type of monomer used and the method of polymerization. Polyethylene glycol dimethacrylate, poly (2-hydroxyethyl methacrylate), or poly HEMA, can be used as a cross-linking agent, as a monomer, and as a UV-sensitive initiator to produce homopolymers.[36]

Cross-linked homopolymers are used in drug delivery systems and in contact lenses.[37]

Additionally, it is employed to repair cells in the spinal cord and bone marrow, create scaffolds that encourage cell adhesion, and create artificial cartilage.[38]

2.3.2. Copolymeric hydrogel

Two or more distinct monomer species having at least one hydrophilic component are combined to form copolymeric hydrogels, which are then distributed along the chain of the polymer network in a random, block, or alternating pattern.[39]

These hydrogels were designed for drug delivery applications and were pH and temperature-sensitive. [32]

2.3.3. Multipolymer interpenetrating polymeric hydrogel (IPN)

An important type of hydrogel that has a network system consisting of two separate cross-linked synthetic or natural polymer components. One component of the semi-IPN hydrogel is a cross-linked polymer, and the other is a non-cross-linked polymer. (See Fig 3)

Due to the persistent overlapping of network segments, IPN can overcome thermodynamic incompatibility and only obtain limited phase separation.[29]

The fundamental benefit of IPNs is the ability to create relatively dense hydrogel matrices that have stronger, stiffer mechanical properties, controlled physical properties, and more effective drug loading than other hydrogels.[40]

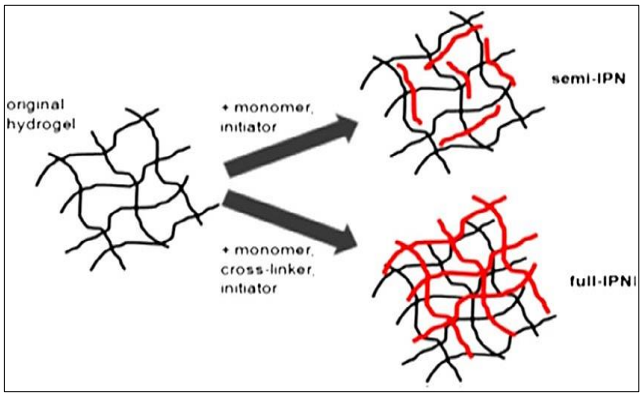

Figure 3: Shows the formation and structure of semi and full IPNs: where hydrogel with monomer initiator forms semi-IPN while hydrogel with monomer & cross-linker initiator forms full IPN.

2.4. On the basis of configuration

According to their physical nature and chemical content, hydrogels can be categorized as follows:

- Amorphous (non-crystalline).
- Semicrystalline: A complicated blend of crystalline and amorphous phases.
- Crystalline.
- Hydrogen bonded.
- Hydro colloidal aggregation.[41]

2.5. On the basis of biodegradability

2.5.1. Biodegradable hydrogel

Hydrogels degrade naturally. Biodegradable polymers include those formed by nature such as Chitosan, fibrin, and agar. Synthetic biodegradable polymers include poly (aldehyde guluronate), polyanhydrides, and poly (N-isopropyl acrylamide).[32]

2.5.2. Non-biodegradable hydrogel

The formation of non-biodegradable hydrogels involves the use of a variety of vinylated monomers or macromers, including 2-hydroxyethyl methacrylate (HEMA), 2-hydroxypropyl methacrylate (HPMA), and acrylamide (AAm).[42]

2.6. On the basis of network electric charge

Based on the presence or absence of an electrical charge on the cross-linked chains, hydrogels can be divided into four groups:

- Non-ionic (neutral).
- Ionic (including anionic or cationic).
- Amphoteric electrolyte contains both acidic and basic groups.
- zwitter ionic contains both cationic and anionic groups.[43]

2.7. On the basis of physical appearance

Depending on the kind of polymerization used during the preparation process, hydrogels can appear as a matrix, film, or microsphere.[36]

3. ADVANTAGES

- Due to their extraordinary water content, they are very flexible and resemble genuine tissue.
- Hydrogels that are sensitive to their surroundings can detect changes in temperature, pH, or metabolite concentration, and when they do, they release the load.
- They are also injectable, biodegradable, and biocompatible.[44-46]
- Additionally, hydrogels are simple to modify and have high transport qualities.[47]
- Timely release of nutrients or medications.[48]

4. DISADVANTAGES

- Costly and weak mechanically, they are expensive.
- They may need to be secured by secondary dressing since they are non-adherent.
- There may be a problem loading with medication or nutrition.
- Hypoxia, dehydration, and red eye reactions are all brought on by the usage of hydrogels as contact lenses.[44,45]

5. SIGNIFICANCE OF HYDROGEL

Physical and chemical properties: Hydrogel's physical and chemical characteristics are influenced by two main factors, namely the size of the particles and the attraction or repulsion of the molecules. It is a realistic design that considers how the solute molecules interact with the gel, especially how they divide between the gel phase and the liquid phase.

Swelling: Hydrogel, a hydrophilic, cross-linked (physically or chemically) polymer chain with a high water-holding capacity, can cause swelling. In general, between 10% and 20% of water is absorbed by the dry hydrogel. Hydrogel's appearance can vary depending on temperature, pH, ionic species, and electric signal, and these variations can be seen under a microscope.

Mechanical properties: Mechanical characteristics might vary based on the composition of the material. It called for a gel that was stiffened by lengthening the cross-linking chain. Ligament, wound dressing, tendon repairs, matrix for drug delivery, tissue engineering, and cartilage replacement materials are the biomedical applications evaluation criteria.

Cross-linking: Cross-linking is one of the hydrogel's key characteristics. The two types of cross-linking hydrogels are chemically and physically bonded gels. The cross-linking process involves several cooperative reactions, including the Michael reaction, the Michaelis-Arbuzov reaction, and nucleophilic addition reactions.

Biocompatible properties: Hydrogels are non-toxic and have biocompatible behavior, according to their biocompatible qualities. Most polymers are employed in vitro and cytotoxic tests. Biosafety and Bifunctionality are the two polymers that make up biocompatibility.

Porosity and permeation: The concentration of the chemical cross-links between the polymer strands, the net charge of the polyelectrolytes, and the concentration of the physical entanglement of the polymer strands are the three factors that determine the size of the pores that can be created in a hydrogel by the phase separation process.[49,50]

6. PREPARATION TECHNIQUE

Physical cross-linking, chemical cross-linking, grafting polymerization, and radiation cross-linking are some of the preparation procedures used. These alterations can enhance the mechanical characteristics and viscoelasticity for applications in the biomedical and pharmaceutical areas.[51]

Both synthetic and natural polymers can be used to make hydrogels, in general. In comparison to natural polymers, synthetic polymers are chemically stronger and hydrophobic by nature. Although their mechanical strength results in a slow rate of degradation, it also contributes to their durability.[52]

Alginate, Chitosan, Carrageenan, Hyaluronan, and Carboxy methyl cellulose (CMC) are examples of natural biopolymers. Cross-linked networks of synthetic polymers such as Polyethylene oxide (PEO), Polyvinyl pyrrolidone (PVP), Polylactic acid (PLA), Polyacrylic acid (PAA), Polymethacrylate (PMA), Polyethylene glycol (PEG) have also been reported.[1]

To create hydrogels from cellulose and its derivatives, there are three different crosslinking methods: physical, chemical, and polymerization.[53]

6.1. Physical cross-linking

Due to their relatively simple manufacture and the benefit of not requiring cross-linking agents, physical or reversible gels have attracted more attention. The integrity of the substances to be entrapped (such as cells, proteins, etc.) and the requirement for their removal before application are both impacted by these agents.[54]

Once employed for medication delivery, physical crosslinking preserves biological organisms and enhances hydrogel structures. Physical crosslinking employs a variety of techniques.[53]

6.1.1. Heating/cooling a polymer solution

The helix formation, helices connection, and junction zone formation are what cause the gel to develop. The random coil structure of carrageenan is evident in hot solutions over the melting transition temperature. It changes into hard helical rods when it cools.[55] (See Fig 4)

Examples include polyethylene oxide-polypropylene oxide and polyethylene glycol-polylactic acid hydrogel.[48]

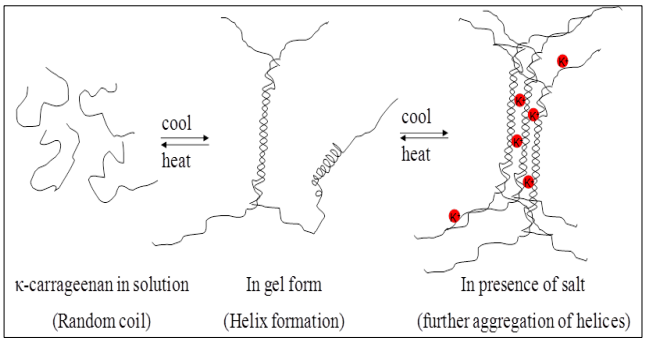

Figure 4: Heating/cooling a polymer solution: Gel formation due to aggregation of helix upon cooling a hot solution of carrageenan.

6.1.2. Complex coacervation

By combining polyanions and polycations, complex coacervate gels are created. This method's fundamental tenet is that polymers with opposing charges bind together and create soluble or insoluble complexes depending on the concentration and pH of the relevant fluids.[47]

Coacervation of polycationic chitosan and polyanionic xanthan is one such instance. Positively charged proteins below their isoelectric point have a high propensity to bind to anionic hydrocolloids and create polyion complex hydrogels.[56] (See Fig 5)

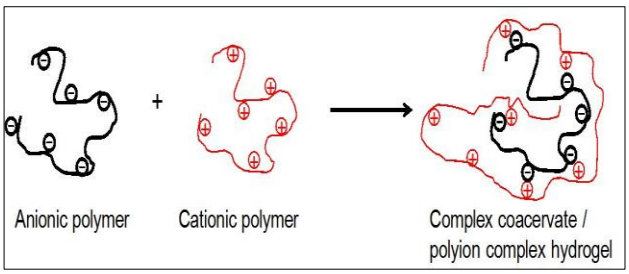

Figure 5: Complex coacervation: Anionic and cationic polymer forms complex coacervates.

6.1.3. Ionic interaction

By including di- or tri-valent counterions, ionic polymers can be cross-linked. A multivalent ion having opposing charges, such as Ca2+ + 2Cl-, can be used to gel a polyelectrolyte solution (for example, Na+ alginate-). Chitosan-glycerol phosphate salt, chitosan-dextran hydrogels, and chitosan-polylysine are some further examples.[56]

6.2. Chemical cross-linking

This procedure involves grafting monomers onto the backbone of the polymers and using a crosslinking agent to join two polymer chains.[57]

Natural and artificial polymers can be cross-linked by reacting with cross-linkers such as aldehydes (such as glutaraldehyde and adipic acid dihydrazide) that have functional groups like OH, COOH, and NH2.

By utilizing epichlorohydrin as a cross-linker, heating, and freezing techniques, hydrogels can also be made from cellulose in NaOH/urea aqueous solutions.[58]

6.2.1. Citric acid

Citric acid (CA) is a natural organic compound with three OH groups that can form a network in most hydrogel preparations. It is also affordable, nontoxic, hydrophilic, and hydrophilic.[53]

It has an extra binding site, and a hydrogen bond, and aids in balancing hydrophilicity.[59-61]

CA, often commonly referred to as a food additive, is utilized in cleaning goods, water softening, anticoagulants, and tissue that comes into contact with food.[62,63]

To allow the hydrogel network to robustly crosslink, CA also enhances the tensile strength, thermal stability, and barrier characteristics.[64-66]

6.2.2. Epichlorohydrin

As well as improving pore size distribution, chemical stability, mechanical resistance, and adsorption/desorption capacity, Epichlorohydrin (ECH) also aids in these other areas.[67]

The use of ECH in the production of chitosan hydrogels boosts the metal sorption capacity of the material and prevents chitosan dissolution during metal sorption in an acidic environment.[68,69]

6.2.3. Glutaraldehyde

A functional polymeric material can be created from protein, amino polysaccharides, and synthetic polymers by crosslinking glutaraldehyde with the hydroxyl group, according to research.[70-72] To change the effectiveness of the ligand and boost the film's ability to absorb water, glutaraldehyde is combined with chitosan as a crosslinking agent.[73,74]

6.3. Bulk polymerization

Vinyl monomers are primarily used in the manufacturing of bulk hydrogels although other types of monomers can also be used. Any hydrogel formulation typically includes a tiny amount of a cross-linking agent.

A wide range of shapes, such as rods, particles, films and membranes, and emulsions, can be generated from the polymerized hydrogel.[75]

6.4. Free radical polymerization

The propagation, chain transfer, initiation, and termination phases are all part of the conventional free-radical polymerization chemistry. Numerous thermal, ultraviolet, visible, and redox initiators can be used for the radical formation in the initiation step; the radicals then react with the monomers to change them into active forms.[76]

6.5. Solution polymerization

The presence of a solvent acting as a heat sink is the main benefit of solution polymerization versus bulk polymerization. Water-ethanol combinations, water, ethanol, and benzyl alcohol were utilized as solvents.[77] (See Fig 6)

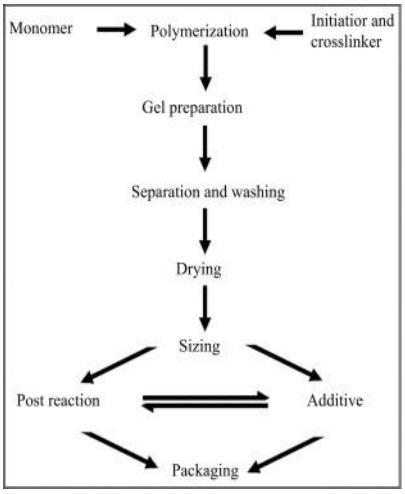

Figure 6: Block diagram: Solution polymerization procedure.

6.6. Suspension Polymerization

Spherical hydrogel microparticles between 1 mm and 1 mm in size are created using the suspension polymerization process. This approach involves dispersing the monomer solution into tiny, stabilizer-coated droplets made of non-solvent rather than water.[78] (See Fig 7)

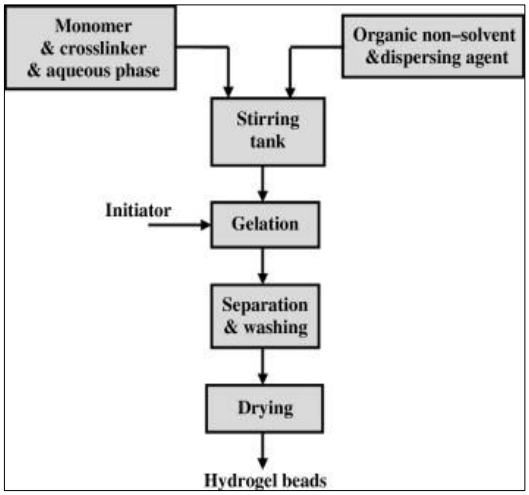

Figure 7: Block diagram hydrogel preparation: Suspension polymerization procedure.

6.7. Grafting cross-linking

Hydrogels made by bulk polymerization typically have a weak structural foundation. A hydrogel can be surface-coated onto a more durable support to enhance its mechanical characteristics.[54] An example of this type of procedure uses N-vinyl-2-pyrrolidone to graft starch with acrylic acid.[79]

7. STRUCTURAL DIVERSITY OF HYDROGEL

7.1. Microgel

Colloidal dispersions (or suspensions) of gel-like particles and swelling macromolecular networks make up microgels (100 nm–10 m). However, microgels are promising for a variety of applications in various fields, including controlled drug release, separation technology, bio-, and chemical sensors, and have been found to possess unique properties of both hydrogels and colloidal particles, such as structural integrity, compartmentalization, orthogonal functionalization, softness, deformability, permeability, stimuli-responsiveness, reversible swelling, and adaptivity.[80-83]

7.2. Nanogels

Nanogels are hydrogel particles with a size between 0 and 100 nm made of crosslinked polymer networks using physical or chemical means. Nanogels combine the qualities and characteristics of nanoparticles and hydrogels. Fundamentally, there are not many differences between nano gels and microgels other than the application scenarios brought on by size effects (e.g., nano gels are easily able to penetrate due to their extremely small size and, more specifically, can cross the blood-brain barrier) and some specific functions (e.g., nano gels have non-immunological responses and invasion by the reticuloendothelial system is prevented).[84-88]

7.3. Multi-layered hydrogels

Homogeneous hydrogels, which have uniform bulk properties, are increasingly constrained by the need for complex functions, whereas hierarchical hydrogels, which contain multiple layers or membranes, exhibit growing advantages in terms of structural complexity and functional diversity, and are essential in a wide range of applications.[89]

7.4. Porous hydrogels

Even though, hydrogels made of a 3D-crosslinked porous network exhibit a considerable capacity for water absorption. For various applications, such as biocompatible scaffolds, superabsorbent materials, high penetration materials, drug release vehicles, etc., swelling qualities are still one of the important performance indicators of hydrogels. According to the range of pore sizes, porous hydrogels can be classified into three groups: super macroporous hydrogels (tens to hundreds of m), macroporous hydrogels (100 nm–10 m), and microporous hydrogels (10–100 nm).[90]

7.5. Hybrid hydrogels

Chemically, functionally, and morphologically different building blocks, such as biologically active proteins, peptides, synthetic macromolecules, or nano/microstructures that are joined by physical or chemical means, are used to produce hybrid hydrogels. Hydrogels should all be hybrid hydrogels in theory, except for a specific structure or component. As a result, there are numerous varieties of hybrid hydrogels, including hydrogels made of nanocomposite (NC) materials, macromolecular microsphere composite (MMC) materials, interpenetrating networks (IPN), double networks (DN), and double network-nanocomposite (DN-NC) materials. The five hybrid hydrogel types discussed above are considered high-strength hydrogels because their primary purpose is to increase mechanical strength.[90]

7.6. Topological hydrogels

Interest in supramolecules with topological properties is high. Another powerful hydrogel that can be quite stretchy is a topological hydrogel. Through host-guest interactions (see previous Section) and a few physical or chemical crosslinks, topological hydrogels can be created. Topological hydrogels are also known as slide-ring or slip-link gels due to their structural characteristics.[91,92]

In addition to host-guest interactions, Yu et al.[92] announced the discovery of a novel topological hydrogel with Turing microstructure. Specifically, a switchable hydrogen-bond topological network was built to produce a dynamic hydrogel made of cellulose, ionic liquids, and water with reversible Turing-pattern microstructures.

7.7 Emulsion hydrogels

Emulsion hydrogels, also known as emulsion gels, are a type of semi-solid colloidal solution that combines the functional and physicochemical characteristics of both emulsions and gels. Emulsion hydrogels are sometimes referred to as emulsions that resemble solids or gels.[90]

Controlling the emulsion types, matrix materials and interactions, oil content, filler and particle size distribution, gelling processes, etc. can alter the rheological, structural, and microstructural features of emulsion gels.[93,94]

8. CELLULOSE-BASED HYDROGELS

Cellulose is one of the safest materials on earth and has the benefits of being biocompatible, biodegradable, renewable, mechanically strong, and environmentally safe.[95]

It has the qualities of being tasteless, odorless, and insoluble in most organic solvents as well as water. Since it is a hydrophilic substance with strong van der Waals forces and inter- and intramolecular hydrogen bonding, dissolution is difficult.[96]

Limitations for cellulose are related to dissolution. Most organic solvents and water are known to barely breakdown cellulose. However, due to their accessibility and simplicity, other solvent systems, such as ionic liquids (ILs), NaOH/urea, and NaOH/thiourea, are frequently used by researchers to dissolve cellulose.[53]

8.1. Cellulose dissolution

For cellulose to have further applications, it must be dissolved. Ionic liquids, LiOH/urea, NaOH/urea, and NaOH/thiourea are a few of the solvent systems that have been researched for the dissolving of cellulose. Liquidation of cellulose to guarantee that the cellulose is homogeneous throughout the creation of the solution, it is crucial to use various solvent systems.[53]

8.1.1. NaOH/Urea

One solvent system that receives attention is sodium hydroxide/urea (NaOH/urea), which is low in toxicity, easy to use, and inexpensive.[97]

Chen et al. suggest that the interaction takes place when cellulose forms a shell-like hydrogen-bond-induced inclusion complex with alkali and urea. Previous studies have shown that the temperature of the solvent, the molecular weight, the crystallinity, the stirring rate, and the stirring time all affect how easily cellulose dissolves.

8.1.2. NaOH/thiourea

The NaOH-cellulose hydrogen-bonded surface may allow urea/thiourea hydrates to self-assemble, according to researchers.[53]

Using NaOH and thiourea, Ruan et al.[97] investigate the manufacturing of cellulose multifilament fibers. The findings indicate that NaOH/thiourea can be the new cellulose drug, offering a different and workable route to the production of regenerated cellulose fibers and their purpose.[98]

According to Mohsenzadeh et al.[98], cellulose is better dissolved in NaOH/thiourea, which also boosts the yield of biodegradation products.

According to Morgado et al.[99], research inclusion complexes of NaOH, thiourea, water, and cellulose that form at low temperatures are more likely to disrupt intramolecular hydrogen bonds in the cellulose, and NaOH hydrates are readily drawn to the chain of cellulose to establish new hydrogen bonds.

8.1.3. Ionic liquids

Salts known as ionic liquids (ILs), which can be divided into weakly coordinated anions and cations, melt below the boiling point of water. Because they are non-volatile, recyclable, stable, polar, non-flammable, have greater thermal stability, and are soluble in both water and organic solvents, ILs are regarded as environmentally acceptable solvents.[53]

The characteristics of the silk-cellulose bio-composite were investigated by Stanton et al. and colleagues using 1-allyl-3-methylimidazolium chloride. Results demonstrate that the silk-cellulose bio-composite can be successfully

dissolved by 1-allyl-methylimidazolium chloride (AMIMCl) to form a thin film.[100,101]

Lethesh et al.[101] demonstrate the great efficacy of cellulose dissolution utilizing imidazolium IL [C2mim] [OPh] based on phenolates.

8.2. Cellulose derivatives

Although cellulose is a good starting material, its applicability is constrained by the difficulty of its dissolution. A chemical process that produces different derivatives is another method for expanding its uses.[53]

8.2.1. HPMC

Due to its thickening, gelling, and swelling qualities, hydroxypropyl methylcellulose (HPMC) is a popular cellulose derivative in controlled-release applications.[53]

By crosslinking chitosan, Zeeshan et al.[102] exploited HPMC in scaffold engineering applications. They demonstrate that chitosan-induced crosslinking of HPMC can offer structural support and morphological aspects for the healing phase that comes after the stimulation of cellular qualities.

As a composite hydrogel, HPMC was also used by Seyedl. ar et al.[103] in scaffold engineering applications. They demonstrate how the use of the HPMC composite hydrogel can make osteoplasty procedures less invasive, take less time, and result in a more uniform distribution of cells.

Hydrogels are primarily created with HPMC for use in medical applications as membranes, films, and scaffolds.[53]

8.2.2. Hydroxyethylcellulose

A cellulose ether with good hydrophilicity, biocompatibility, and biodegradability, Hydroxyethylcellulose (HEC) may be produced simply and is water-soluble. The production of hydrogels using HEC revealed considerable pore development and high-water molecule diffusion into the network. Furthermore, a study demonstrates the HEC hydrogel's high and controllable encapsulation for in vitro release.[53]

8.2.3. Carboxymethyl cellulose

Hydrogel made of Carboxymethyl cellulose (CMC) may be used for adsorbents, medication administration, wound healing, and enzyme immobilization. Hydrogels containing CMC and nanoparticles can be used for tissue engineering, medication transport, and antibacterial activity.[104-107] The CMC hydrogel's performance has improved with the addition of nanoparticles.[53]

8.3. Preparation

Based on the intended uses, procedures such as chemical crosslinking, physical crosslinking, polymerization, or a mix of these can be used to create hydrogel from cellulose and its derivatives.[53]

9. CHITOSAN-BASED HYDROGEL BEADS

Chitosan, a common polysaccharide biomaterial made from -(1-4)-2-acetamido-2-deoxy-D-glucopyranose and 2-amino-2-deoxy-D-glucopyranose with pKa values ranging from 6.3 to 6.5, is produced by deacetylating chitin.[108]

9.1. Preparation

9.1.1. Physical modification

9.1.1.1. Blending with polymers

Chitosan has reportedly demonstrated good mechanical and chemical qualities when combined with synthetic polymers like polyvinyl alcohol (PVA) and polyvinyl chloride (PVC).[109]

Due to their biodegradability, biocompatibility, bio adhesiveness, and bio functionality, polysaccharide-based hydrogels containing chitosan and other natural biopolymers, like sodium alginate and cellulose, have drawn more and more interest.[110]

Ionic contact between the carboxyl residues of alginate and the amino groups of chitosan, alginate, and chitosan can create a polyelectrolyte complex (PEC).[111]

Alginate solutions are often added dropwise into chitosan solutions containing metal cations, while stirring slowly with a magnetic field, to create the core-shell structure of chitosan-alginate hydrogel beads.[109]

9.1.1.2. Nanocomposite chitosan beads with inorganic nanomaterials

a) Blending with nano clay

By mixing chitosan with nano clays such as graphene oxide (GO), montmorillonite (MMT), zeolite, alumina, bentonite, and laponite, among others, chitosan-based nanocomposites can be created.[109] The mechanical strength, antibacterial activity, and drug-loading capabilities of chitosan beads can all be significantly enhanced by the addition of nano clay.[112]

b) Blending with metal nanoparticles

To increase their antimicrobial capability, polymeric hydrogels are increasingly being combined with metal or metal oxide. Chitosan is one of the natural biopolymers that strongly complexes with metals or metal oxide nanoparticles because it has free amino groups.[113]

For instance, chitosan and silver nanoparticles (AgNPs) have a stronger antibacterial activity than the individual components included in the nanocomposites.[109]

9.1.2. Chemical modification

Chitosan has been subjected to chemical modification to produce improved hydrogel beads with superior physicochemical properties and a variety of purposes. [110]

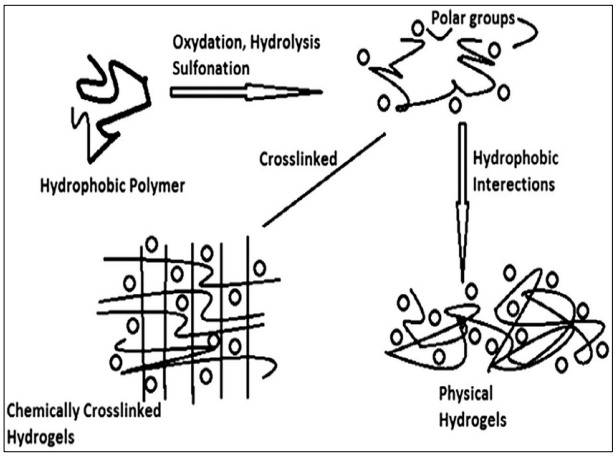

Figure 8: Chemical modification: Chitosan can be chemically altered through a wide range of processes, including oxidation, hydrolysis, sulfonation, and alkylation because it has a lot of polar groups, amino and hydroxyl groups.

9.1.2.1. Crosslinking

The three most often utilized crosslinkers for modifying chitosan beads are glutaraldehyde, ethylene glycol diglycidyl ether, and epichlorohydrin.[109] In general, crosslinkers act as a link between two polymer chains—whether they are the same chain or not—creating a 3D network that increases mechanical resistance and chemical stability in acidic conditions.[114] (See Fig 8)

9.1.2.2. Grafting

For the manufacture of grafted chitosan, four different grafting methods are widely employed: enzyme-catalyzed grafting, free radical-mediated grafting, electrochemical approaches, and radiation. Each grafting technique's effectiveness may differ depending on the procedure's variables.[115-117]

10. APPLICATIONS

10.1. Application of hydrogels in medicine

10.1.1. Tissue engineering

Like extracellular matrix (ECMs), which have received a lot of attention for use in tissue engineering and regenerative medicine, hydrogels of highly hydrated polymer networks are similar.[118]

10.1.2. Wound dressing

Due to their cross-linked nature, hydrogels can contain both water and drugs. They may hold and hold onto wound exudates because of their capacity to hold water.[47]

10.2. Application of hydrogel in drug delivery

10.2.1. Oral cavity

For the local treatment of mouth disorders like stomatitis, fungal infections, periodontal disease, viral infections, and oral cavity malignancies, drugs are integrated into hydrogels and delivered to the oral cavity.[47]

10.2.2. GI tract

Drugs are delivered through hydrogels to specified gastro intestinal tract (GIT) locations. Drugs loaded with colon-specific hydrogels exhibit tissue specificity and a change in pH or enzymatic action that leads to drug breakdown in the presence of microflora.[119]

10.2.3. Ocular

The ocular drug delivery system is where hydrogels are most frequently used. Most hard and soft contact lenses and hydrogel films are made of polymers.[47]

10.2.4. Colon specific

Due to the high concentration of polysaccharide enzymes in the colon region of the GI, colon-specific polysaccharide hydrogels have been specifically developed. Dextran hydrogel is designed to deliver drugs specifically to the colon.[51]

10.2.5. Subcutaneous

Since hydrogels are naturally biodegradable, we can create implantable hydrogels that are biodegradable by utilizing this characteristic.

10.2.6. Gene

To effectively target and distribute nucleic acids to particular cells for gene therapy, hydrogels' composition must change. The use of hydrogels in the treatment of numerous hereditary or acquired disorders has more potential.[119]

10.3. Other applications of hydrogels

10.3.1. Cosmetics

Pecogels are appropriate for cosmetic uses like mascara or sunscreen cream. Additionally, the moisturizing properties of these organic polymeric gels are combined with more sophisticated drug-delivery systems designed to release biomolecules like vitamin C or B3 in certain commercially available substances, such as Hydro Gel Face Masks.[51]

10.3.2. Environmental application

The two most popular ones are spirulina and chlorella. These microbes are already employed to purge toxins and contaminants from water supplies. Hydrogels of both natural and synthetic origin were utilized.[52]

10.3.3. Bacterial culture

A sizable number of microorganisms for water filtration, the synthesis of macromolecules, or the straightforward culture of bacteria alone can be held inside the matrix of hydrogels.[52]

CONCLUSION

Recently, several networks made of hydrogel have been created and customized to fit the requirements of various applications. Due to their high-water contents and soft consistency, hydrogel-based delivery devices can be used topically, subcutaneously, or orally. More than any other

category of artificial biomaterials, hydrogels resemble live tissue in nature. These networks have the benefit of not using organic solvents. Swelling of the structure is the primary method by which pharmacological ingredients are released from hydrogels. To ensure the efficient and prolonged release of the encapsulated drug, various chitosan-based encapsulating methods have been developed to suit specific needs such as controlled swelling behavior and delayed digestion.

The use of cellulose in the production of hydrogels is expanding as a result of its many benefits, including its high mechanical strength, biocompatibility, biodegradability, and eco-friendliness. For cellulose-based hydrogels, pre-treatment, cellulose dissolution, and hydrogel production methods are among the many elements that must be taken into account. According to the study, hydrogels offer excellent qualities that will make them very useful as the next generation of biomaterials.

REFERENCES

1. Nasitha A., Krishnakumar K., and Kumar BD, Hydrogel in Pharmaceuticals: A Review, 2016;3(3):265–270.

2. Das N., Preparation methods and properties of hydrogel: A review. Int. J. Pharm. Pharm. Sci., 2013;5(3):112–117.

3. Sowjanya P., Komali BV, CH. Ajay Babu, A Review Article on Hydrogels, Int. J. Res. Pharm. Nano Sci., 2013;2(5):548- 553.

4. Dreiss CA, Hydrogel design strategies for drug delivery, Curr Opin Colloid Interface science, 2020;48:1-7.

5. Asai D, Kanamoto T, Takenaga M, Nakashima H, In situ depot formation of anti-HIV fusion-inhibitor peptide in recombinant protein polymer hydrogel. Acta Biomater. 2017; 64:116–125.

6. Nehls EM, Rosales AM, Anseth KS, Enhanced user-control of small molecule drug release from a poly (ethylene glycol) hydrogel via azobenzene/cyclodextrin complex tethers, J Mater Chem B, 2016;4:1035–1039, https://doi.org/10.1039/ C5TB02004B.

7. Wang LL, Burdick JA, Engineered hydrogels for local and sustained delivery of RNA-interference therapies, Adv Healthc Mater, 2017;6:1–16.

8. Leach DG, Dharmaraj N, Piotrowski SL, Lopez-Silva TL, Lei YL, Sikora AG, STINGel: controlled release of a cyclic dinucleotide for enhanced cancer immunotherapy, Biomaterials, 2018;163:67–75.

9. Pianowski ZL, Karcher J, Schneider K, Photoresponsive self-healing supramolecular hydrogels for light-induced release of DNA and doxorubicin, Chem Commun, 2016;52:3143–3146, https://doi.org/10.1039/C5CC09633B.

10. Ding F, Mou Q, Ma Y, Pan G, Guo Y, Tong G, A crosslinked nucleic acid nano gel for effective siRNA delivery and antitumor therapy, Angew Chem Int Ed, 2018;57:3064–3068.

11. Wang LL, Sloand JN, Gaffey AC, Venkataraman CM, Wang Z, Trubelja A, Injectable, guest-host assembled polyethyleneimine hydrogel for siRNA delivery, Biomacromolecules, 2017;18:77–86.

12. Wang Y, Malcolm DW, Benoit DSW, Controlled and sustained delivery of siRNA/NPs from hydrogels expedite bone fracture healing, Biomaterials, 2017;139:127–138, https://doi.org/ 10.1016/j.biomaterials.2017.06.001.

13. Da Silva MA, Dreiss CA, Soft nanocomposites: nanoparticles to tune gel properties, Polym Int, 2016;65:268–279.

14. Bini RA, Silva MF, Varanda LC, da Silva MA, Dreiss CA, Soft nanocomposites of gelatin and poly(3-hydroxybutyrate) nanoparticles for dual drug release, Colloids Surf B Biointerfaces, 2017;157:191–198, https://doi.org/10.1016/ j.colsurfb.2017.05.051

15. Chu Z, Dreiss CA, Feng Y, Smart wormlike micelles, Chem Soc Rev, 2013;42:7174–7203.

16. Bastiancich C, Bianco J, Vanvarenberg K, Ucakar B, Joudiou N, Gallez B, Injectable nanomedicine hydrogel for local chemotherapy of glioblastoma after surgical resection, J Contr Release, 2017;264:45–54.

17. Zhang ZQ, Song SC, Multiple hyperthermia-mediated releases of TRAIL/SPION nano complex from thermosensitive polymeric hydrogels for combination cancer therapy, Biomaterials, 2017;132:16–27, https://doi.org/10.1016/j.biomaterials.2017.03.049.

18. Mayr J, Saldías C, Díaz Salida's D, Release of small bioactive molecules from physical gels, Chem Soc Rev, 2018;47:1484–1515.

19. Cheetham AG, Chakroun RW, Ma W, Cui H, Self-assembling prodrugs, Chem Soc Rev, 2017;46:6638–6663.

20. Ren C, Gao Y, Guan Y, Wang Z, Yang L, Gao J, Carrierfree supramolecular hydrogel composed of dual drugs for conquering drug resistance, ACS Appl Mater Interfaces, 2019;11:33706–33715.

21. Wang L, Neumann M, Fu T, Li W, Cheng X, Su BL, Porous and responsive hydrogels for cell therapy, Curr Opin Colloid Interface Sci, 2018;38:135–157, https://doi.org/10.1016/ j.cocis.2018.10.010.

22. Mao AS, Shin JW, Utech S, Wang H, Uzun O, Li W, Deterministic encapsulation of single cells in thin tunable microgels for niche modeling and therapeutic delivery, Nat Mater, 2017;16:236–243.

23. Agrawal G, Agrawal R: Functional microgels, Recent advances in their biomedical applications, Small, 2018;14:1–18.

24. Li J, Mooney DJ, Designing hydrogels for controlled drug delivery, Nat Rev Mater, 2016.

25. Hajebi S, Rabiee N, Bagherzadeh M, Ahmadi S, Rabiee M, Roghani-Mamaqani H, Stimulus-responsive polymeric nanogels as smart drug delivery systems, Acta Biomater, 2019;92:1–18, https://doi.org/10.1016/ j. actbio.2019.05.018.

26. Mauri E, Perale G, Rossi F, Nanogel functionalization: a versatile approach to meet the challenges of drug and gene delivery, ACS Appl Nano Mater, 2018;1:6525–6541.

27. Cuggino JC, Blanco ERO, Gugliotta LM, Alvarez Igarzabal CI, Calderón M, Crossing biological barriers with nanogels to improve drug delivery performance, J Contr Release, 2019;307:221–246, https://doi.org/10.1016/j.jconrel.2019.06.005.

28. Thambi T, Li Y, Lee DS, Injectable hydrogels for sustained release of therapeutic agents, J Contr Release, 2017;267: 57–66.

29. Bharskar GR, A Review on Hydrogel, World J Pharm Pharm Sci, 2020;9(7):1288-1298.

30. Hennink WE and C. F. van Nostrum, Novel crosslinking methods to design hydrogels, Adv. Drug Deliv. Rev., 2002;54(1):13—36.

31. Gulrez S., Al-Assaf S., and Phillips G., Hydrogels: Methods of Preparation, Characterisation and Applications in Molecular and Environmental Bioengineering, 2011.

32. Singh SK, Dhyani A and Juyal D, Hydrogel: Preparation, Characterization and Applications, Pharma Innovation, 2017;6(6):25-32.

33. Malpure PS, Patil SS, More YM, Nikam PP, A Review On- Hydrogel, Am. J. Pharm Tech Res. 2018;8(3): 41-61.

34. Devi A, Nautiyal U, Kaur S, Komal. Hydrogel: a smart drug delivery device, Asia Pac. J. Health Sci., 2014;1(4S):92-105.

35. Zaman M, Siddique W, Waheed S, Muhammad SS, Mahmood A, Qureshi J, Int. J. Biol., Pharm. Allied Sci., 2015;4(12):6581-6603.

36. Ahmed EM, Review Hydrogel: Preparation, characterization and applications, J. Adv. Res., 2013;7:1-17.

37. E. M. Ahmed, —Hydrogel: Preparation, characterization, and applications: A review, J adv. Res., 2015;6(2):105–121.

38. Rana P, Ganarajan G, Kothiyal P, Review on Preparation and Properties Hydrogel Formulation, World J Pharm Pharm Sci, 2015;4(12):1069-1080.

39. Yang L, Chu JS, Fix JA, Colon specific drug delivery: new approaches and in vitro/in vivo evaluation, Int J Pharm., 2002;235:1-15.

40. Sankula R, A Review on Hydrogel Pharmaceutical Preparations, 2019;8(02):6–9.

41. Yadav S and Madan J, Hydrogels: A review, Int. J Pharm. Life Sci., 2011;6:6711-6717.

42. Tan H, Marra KG, Injectable, biodegradable hydrogels for tissue engineering applications, Materials, 2010;3:1746-1767.

43. Meshram PS, Kale SD, Labale PS, Mate KS, Hydrogel Polymer: A Unique Material for Bio-Separation, Bio-Sensing and Drug Delivery, Int. Adv. Res. J. Sci., Eng. Tech. 2017; 4(3).

44. Sankula R, A Review on Hydrogel Pharmaceutical Preparations, 2019; 8(02): 6–9.

45. Article R and Jawad S, —A Review on novel approach of drug delivery, 2020;9(6):791–800.

46. Thakur G and Rousseau D, Hydrogels: Characterization, Drug Delivery, and Tissue Engineering Applications, Encyclopedia of Biomedical Polymers and Polymeric Biomaterials 2014;3853–3878.

47. Singh SK, Dhyani A, Juyal D, Hydrogel: Preparation, Characterization, and Applications. The Pharma Innovation. 2017;6(6, Part A):25.

48. Reddy VRK, Nagabhushanam MV, Naik ER, Swallable hydrogels and cross-linking Agents- Their role in drug delivery system, Res. J. Pharm Tech. 2017;10(3):0974-3618.

49. Garg S, Garg A, Hydrogel: Classification, properties, preparation and technical features, Asia J biomaterial res. 2016;2(6):163-170.

50. Shetye SP, Godbole A, Bhilegaokar S, Gajare P, Hydrogels: Introduction, characterization and application, Int. J res. Methodol, 2015;1(1):47-71.

51. Singh A, Sharma PK, Garg VK, and Garg G, Hydrogels: a review.

52. Malpure PS, Patil SS, More YM, Nikam P, A review on-hydrogel, Am J PharmTech Res. 2018;8(3):42-60.

53. Zainal SH, Mohd NH, Suhaili N, Anuar FH, Lazim AM, Othaman R, Preparation of cellulose-based hydrogel: A review, J Mater Res Technol. 2021;10:935-52.

54. Bharskar GR, A review on hydrogel, World J. Pharm. Pharm. Sci. 2020;9:1288-98.

55. Funami T, Hiroe M, Noda S, Asai I, Ikeda S, and Nishinari K, Influence of molecular structure imaged with atomic force microscopy on the rheological behavior of carrageenan aqueous system in the presence or absence of cations, Food Hydrocolloids, 2007;21:617–629.

56. Magnin D, Lefebvre J, Chornet E, and Dumitriu S, Physicochemical and structural characterization of a polyionic matrix of interest in biotechnology, in the pharmaceutical and biomedical fields, Carbohydrate Polymers, 2004;55:437–453.

57. Chauhan S, Harikumar SL, Kanupriya, Hydrogels, A Smart Drug Delivery System, Int. J Res. Pharm Chem., 2012;2(3):604- 615.

58. Chang C, Zhang L, Zhou J, Zhang L, and Kennedy JF, Structure and properties of hydrogels prepared from cellulose in NaOH/urea aqueous solutions, Carbohydrate Polymers, 2010;82(1):122–127.

59. Gyawali D, Nair P, Zhang Y, Trang R-T, Zhang C, Samchukov M, Citric acid-derived in situ crosslinkable biodegradable polymers for cell delivery, Biomaterials, 2010; 31:9092-105.

60. Reddy N, Yang Y. Citric acid crosslinking starch films, Food Chem, 2010; 118:702-11.

61. Stone SA, Gosavi P, Athauda TJ, Ozer RR, In-situ citric acid crosslinking of alginate/polyvinyl alcohol electrospun nanofibers, Mater Lett, 2013; 112:31-5.

62. Menzel C, Olsson E, Plivelic TS, Andersson R, Johansson C, Kuktaite R, Molecular structure of citric acid crosslinked starch films, Carbohydr Polym, 2013; 96:270-6.

63. Wang S, Ren J, Li W, Sun R, Liu S, Properties of polyvinyl alcohol/xylan composite films with citric acid, Carbohydr Polym, 2014; 103:94-9.

64. Ghorpade VS, Yadav AV, Dias RJ, Citric acid crosslinked cyclodextrin/hydroxypropylmethylcellulose hydrogel films for hydrophobic drug delivery, Int J Biol Macromol, 2016; 93:75-86.

65. Seligra PG, Jaramillo CM, Fama L, Goyanes S, Biodegradable and non-retrodegradable eco-film based on starch-glycerol with citric acid as crosslinking agent, Carbohydr Polym, 2015; 138:66-74.

66. Ghorpade VS, Yadav AV, Dias RJ, Citric acid crosslinked bcyclodextrin/carboxymethyl cellulose hydrogel films for controlled delivery of poorly soluble drugs, Carbohydr Polym, 2017; 164:339-48.

67. Kittipongpatana OS, Kittipongpatana N, Physicochemical in vitro digestibility and functional properties of carboxymethyl rice starch crosslinked with epichlorohydrin, Food Chem, 2013; 141:1438-44.

68. Meybodi ZE, Imani M, Atai M, Kinetic of dextran crosslinking epichlorohydrin: a rheometry and equilibrium swelling study, Carbohydr Polym, 2013; 92:1792-8.

69. Hasanah AN, Elyani I, Sriwidodo Muchtadiri, Muhtadi A, Musfiroh I, Epichlorohydrin as crosslinking agent for synthesis of carboxymethyl cellulose sodium (Na-CMC) as pharmaceutical excipient from water hyacinth (Eichhornia Crassipes L.), Int J Chem Sci, 2015;13(3):1227-37.

70. Dmitriev I, Kuryndin I, Bobrova N, Smirnov M, swelling behavior and network characterization of hydrogels from linear polyacrylamide crosslinked with glutaraldehyde, Mater Today Comm, 2015; 4:93-100.

71. Nagireddi S, Katiyar V, Uppaluri R, Pd (II) adsorption characteristics of glutaraldehyde crosslinked chitosan copolymer resin, Biol Macromol, 2016; 94:72e84.

72. Tian Z, Liu W, Li G, The microstructure and stability of collagen hydrogel crosslinked by glutaraldehyde, Polym Degrad Stabil, 2016; 130:264-70.

73. Igberase E, Osifo P, Ofomaja A, The absorption of Pb, Zn, Cu, Ni, and Cd by modified ligand in a single component aqueous solution: equilibrium, kinetic, thermodynamic and desorption studies, Int J Anal Chem, 2017:6150209.

74. Khairuddin NMA, Afifi AM, Hashim NA, Mohamad SE, Kalantari K, Immobilization of bovine serum albumin on the chitosan/PVA film, Sains Malays, 2018;47(6):1311e8.

75. Sing SK, Dhyani A, Juyal D, Hydrogels: Preparation, characterization and Applications, Pharma Innovation, 2017; 6(6): 25-32.

76. El-Sherbiny IM, Yacoub MH, Hydrogel scaffolds for tissue engineering: Progress and challenges, Global Cardiology Sci Practice, 2013; 38.

77. Thakur VK, Thakur MK, Kessler MR, Handbook of Composites from Renewable Materials, Polymeric Composites, Scrivener Publishing.Vol.6, 2017.

78. Dwivedi S, Khatri P, Mehra GR, Kumar V, Hydrogel- A conceptual overview, Int J Pharm Biol Arch, 2011; 2(6): 1588-1597.

79. Chen J, D. Li, Koshikawa H, Asano M, and Maekawa Y, Crosslinking and grafting of polyetheretherketone film by radiation techniques for application in fuel cells, J Membrane SCI, 2010; 362: 488–494.

80. Pérez-Juste, J, Pastoriza-Santos, I, Liz-Marzán, LM, Multifunctionality in Metal@Microgel Colloidal Nanocomposites, J. Mater. Chem. A., 2013;1:20–26.

81. Lu Y., Ballauff M., Thermosensitive Core–Shell Microgels: From Colloidal Model Systems to Nanoreactors, Prog. Polym. Sci., 2011; 36: 767–792.

82. Brijitta J, Schurtenberger P, Responsive Hydrogel Colloids: Structure, Interactions, Phase Behavior, and Equilibrium and Nonequilibrium Transitions of Microgel Dispersions, Curr. Opin. Colloid Interface Sci., 2019; 40: 87–103.

83. Duffy, C.; O'Sullivan, M.; Jacquier, J, Preparation of Novel Chitosan Iron Microgel Beads for Fortification Applications, Food Hydrocolloid, 2018;84:608–615.

84. Ramos, J.; Forcada, J.; Hidalgo-Alvarez, R, Cationic Polymer Nanoparticles and Nanogels: From Synthesis to Biotechnological Applications, Chem. Rev., 2014;114:367–428.

85. Ye, Y.; Yu, J.; Gu, Z, Versatile Protein Nanogels Prepared by in Situ Polymerization, Macromol. Chem. Phys., 2016;217: 333–343.

86. Hamidi, M.; Azadi, A.; Rafiei, P, Hydrogel Nanoparticles in Drug Delivery, Adv. Drug Deliver. Rev., 2008;60:1638–1649.

87. Kendre, P. N.; Satav, TS, Current Trends and Concepts in the Design and Development of Nanogel Carrier Systems, Polym. Bull., 2019;76:1595–1617.

88. Hu, Z.; Chen, G, Novel Nanocomposite Hydrogels Consisting of Layered Double Hydroxide with Ultrahigh Tensibility and Hierarchical Porous Structure at Low Inorganic Content, Adv. Mater., 2014;26:5950–5956.

89. Jinlong Lia,b, Xin Jiac, and Lijun Yinc, Hydrogel: Diversity of Structures and Applications in Food Science, Food Reviews International, 2021;37(3):313–372.

90. Chen, S.; He, H.; Tang, G.; Wu, B.; Ma, M.; Shi, Y.; Wang, X, Topological Structure Influences on the Gel Formation Process and Mechanical Properties of L-Lysine Based Supramolecular Gels, RSC Adv., 2015;5:101437–101443.

91. Bin Imran, A.; Esaki, K.; Gotoh, H.; Seki, T.; Ito, K.; Sakai, Y.; Takeoka, Y, Extremely Stretchable Thermosensitive Hydrogels by Introducing Slide-Ring Polyrotaxane Cross-Linkers and Ionic Groups into the Polymer Network, Nat. Commun., 2014;5:5124.

92. Zhao, D.; Zhu, Y.; Cheng, W.; Xu, G.; Wang, Q.; Liu, S.; Li, J.; Chen, C.; Yu, H.; Hu, L, A Dynamic Gel with Reversible and Tunable Topological Networks and Performances, Matte, 2020; 2: 390–403.

93. Jiang, Y.; Liu, L.; Wang, B.; Yang, X.; Chen, Z.; Zhong, Y.; Zhang, L.; Mao, Z.; Xu, H.; Sui, X, PolysaccharideBased Edible Emulsion Gel Stabilized by Regenerated Cellulose, Food Hydrocolloid, 2019; 91: 232–237.

94. Chen X, Chen J, You T, Wang K, Xu F, Effects of polymorphs on dissolution of cellulose in NaOH/urea aqueous solution, Carbohydr Polym, 2015a; 125:85-91.

95. Luo X, Zhang L, New solvents and functional materials prepared from cellulose solutions in alkali/urea aqueous system, Food Resour Int, 2010;52(1):387-400.

96. Liu G, Li W, Chen L, Zhang X, Niu D, Chen Y, Molecular dynamics studies on the aggregating behaviors of cellulose molecules in NaOH/urea aqueous solution, Colloids Surf, 2020;594:124663.

97. Ruan D, Zhang L, Lue A, Zhou J, Chen H, Chen X, A rapid process of producing cellulose multi-filament fibers from a NaOH/thiourea solvent system, Macromol Rapid Commun, 2006; 27:1495-500.

98. Mohsenzadeh A, Jehanipour A, Karimi K, Taherzadeh MJ, Alkali pretreatment of softwood spruce and hardwood birch by NaOH/thiourea, NaOH/urea, NaOH/urea/thiourea and NaOH/PEG to improve ethanol and biogas production, J Chem Technol Biotechnol, 2012;87(8):1209-14.

99. Morgado DL, Frollini E, Castellan A, Rosa DS, Coma V, Biobased film prepared from NaOH/thiourea aqueous solution of chitosan and linter cellulose, Cellulose, 2011; 18:699-712.

100. Stanton J, Xue Y, Pandher P, Malek L, Brown T, Hu X, Impact of ionic liquid type on the structure, morphology and properties of silk-cellulose biocomposite materials, Biol Macromol, 2017.

101. Lethesh KC, Evjen S, Venkatraman V, Shah SN, Fiksdahl A, highly efficient cellulose dissolution by alkaline ionic liquids, Carbohydr Polym, 2019; 229:115594.

102. Zeeshan R, Mutahir Z, Iqbal H, Ali M, Iqbal F, Ijaz K, Hydroxypropylmethyl cellulose (HPMC) crosslinked chitosan (CH) based Scaffolds containing bioactive glass (BG) and zinc oxide (ZnO) for alveolar bone repair, Carbohydr Polym, 2018; 193:9-18.

103. Seyedlar RM, Nodehi A, Atai M, Imani M, Gelation behavior of in situ forming gels based on HPMC and biphasic calcium phosphate nanoparticles, Carbohydr Polym, 2014; 99:257-63.

104. Rasoulzadeh M, Namazi H, Carboxymethyl cellulose/ graphene oxide bio-nanocomposite hydrogel beads as anticancer drug carrier agent, Carbohydr Polym, 2017; 168:320-6.

105. Haleem N, Arshad M, Shahid M, Tahir MA, Synthesis of carboxymethyl cellulose from waste of cotton ginning industry, Carbohydr Polym, 2014; 113:249-55.

106. Salama A, Shukry N, El-Sakhawy M, Carboxymethyl cellulose-g-poly(2-(dimethylamino) ethyl methacrylate) hydrogel as adsorbent for dye removal, Int J Biol Macromol, 2014; 73:72-5.

107. C. Choi, J.P. Nam, J.W. Nah, Application of chitosan and chitosan derivatives as biomaterials, Ind. Eng. Chem., 2016; 33.

108. Qu B, Luo Y, Chitosan-based hydrogel beads: Preparations, modifications and applications in food and agriculture sectors–A review, Int J Biol Macromolecules. 2020; 152:437-48.

109. J. Wang, S. Zhuang, Removal of various pollutants from water and wastewater by modified chitosan adsorbents, Crit. Rev. Env. Sci. Tec., 2017; 47: 2331–2386.

110. C. Qin, J. Zhou, Z. Zhang, W. Chen, Q. Hu, Y. Wang, Convenient one-step approach based on stimuli-responsive sol-gel transition properties to directly build chitosan-alginate core-shell beads, Food Hydrocoll, 2019; 87: 253–259.

111. Lewandowska K, Sionkowska A, Kaczmarek B, Furtos G, Characterization of chitosan composite.

112. Liang J, Wang J, Li S, Xu L, Wang R, Chen R, Sun Y, The size-controllable preparation of chitosan/silver nanoparticle composite microsphere and its antimicrobial performance, Carbohydr. Polym., 2019; 220: 22–29.

113. Vakili M, Rafatullah M, Salamatinia B, Abdullah AZ, Ibrahim MH, Tan KB, Gholami Z, Amouzgar PJ, Application of chitosan and its derivatives as adsorbents for dye removal from water and wastewater: a review, Carbohydr. Polym., 2014; 113: 115–130.

114. Jayakumar R, Prabaharan M, Reis R, Mano J, Graft copolymerized chitosanpresent status and applications, Carbohydr. Polym., 2005; 62: 142–158.

115. Yu J, Zheng J, Lu Q, Yang S, Wang X, Zhang X, Yang W, Reusability and selective adsorption of Pb2+ on chitosan/P (2-acrylamido-2-methyl-1-propanesulfonic acid-co-acrylic acid) hydrogel, Iran. Polym. J., 2016; 25: 1009–1019.

116. Hu Q, Luo Y, Polyphenol-chitosan conjugates: synthesis, characterization, and applications, Carbohydr. Polym., 2016; 151: 624-639.

117. Chamkouri H, Chamkouri M, A review of hydrogels, their properties and applications in medicine, Am. J. Biomed. Sci. Res., 2021;11(6):485-93.

118. Remington, the Science and Practice of Pharmacy., Delhi: Wolters Kluwer health Pvt. Ltd; 21st ed.; 2006: 884.

119. Khapare SS, Bhandare MG, Talele SG, Jadhav A, An Emphasis on Hydrogels for Pharmaceutical Applications, Am. J Pharmatech Res. 2016; 6(3):62-68.

Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.