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(REVIEW ARTICLE)

Hydrogel based drug delivery system: A review

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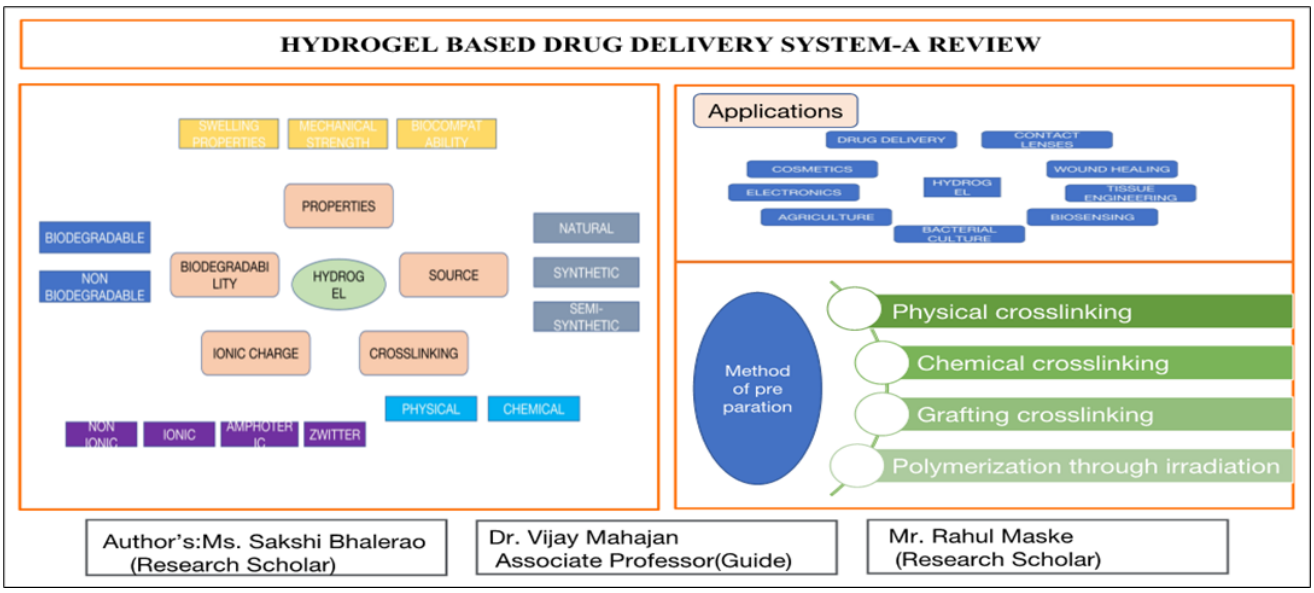
Abstract

Hydrogels are the three-dimensional hydrophilic network which is crosslinked physically or chemically. Hydrogels are also called as hydrophilic gels because they absorb considerate amount of water. The characteristic properties of hydrogels are swelling, mechanical properties, biodegradable, elasticity, biocompatible, easy to modify, flexibility, etc. They are classified based on source, polymeric composition, biodegradability, configuration, cross linking, physical appearance, chemical charges, and drug release. Hydrogels can be synthesized from natural, synthetic, semisynthetic polymers via physical, chemical crosslinking, through grafting, coacervation and polymerization. The hydrogels are useful in daily life and their major applications are drug delivery to oral cavity, GI tract, rectal, ocular, protein, subcutaneous, transdermal, controlled drug delivery, preparation of contact lenses, wound healing, tissue engineering, biosensing, bacterial culture preparation, and various other fields like agriculture, electronics, cosmetics, gene delivery, perfume delivery, regenerative medicine, plastic surgery, sealant adhesive, watering beads for plant and water purification.

Keywords: Hydrogel; Polymers; Drug delivery; Contact lenses; Tissue engineering

Graphical abstract



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1. Introduction

Hydrogels are the hydrophilic polyelectrolyte polymeric system of three dimensional which are physically or chemically cross-linked structures that absorb considerable quantity of water with tunable biocompatibility, acute environmental sensing, biodegradability, and mechanical properties [1] [2] [3] [4] [5] [6] [7]. The hydrogels can be proposed by the incorporation of natural or synthetic polymers through physical or covalent cross linking. Thus, hydrogel networks can significantly swell in water media because biological fluid or water serves as the dispersion medium, hence hydrogels are also known as hydrophilic gels. The swelling, softness, elasticity, flexibility, absorbent nature, and capacity to store water are among the crucial characteristics of hydrogels. It is possible to create this polymer synthetically or naturally [5] [6]. The hydrogels can absorb water for nearly 10-20 times its molecular weight [6]. The hydrophilic functional group connected to polymeric support gives hydrogels their capacity to absorb the water in this way, while the crosslinks between the network chains provide them challenge to dissolution [7]. Although the term "hydrogels" indicates that the substance has already swelled in water, another name for dried hydrogels is "Xerogels". After removal of water without disrupting the polymeric network, either by lyophilization or by extraction with organic solvents, then the resulting material is extremely light with a porosity as high as 98 percent; this dehydrated hydrogel is referred to as aero gel. Surface tension produces the breakdown of the gel body during drying procedure. Due of their simplicity in manufacture and self-application, hydrogels are commonly used as medication carriers. One of their main advantages for being widely employed for clinical and basic applications is the generation of a high and continuous surface area. To explore their potential as a medication delivery mechanism, several polymer combinations are synthesized into hydrogel formulations. Combining natural and synthetic polymers may result in mechanical stability and biological acceptability because of materials' complementary qualities. The hydrogels are discovered to be resilient and stable [8] [9] [10]. The polymer acquires multiple negative charges throughout its length because the acid groups are ionized in water. It has two outcomes. First, the polymer is compelled to expand due to the negative charges repelling one another. Second, the negative charges attract polar water molecules. The polymer chain now occupies more space and resists the movement of solvent molecules around it, increasing the viscosity of the resultant mixture. The polymer and the water around it are in equilibrium, but there are several ways that the equilibrium could be upset. Positive ions attach to the negative sites on the polymer when the ionic concentration of solution is raised, for as by adding salt. This effectively neutralizes the charges. Thus the polymer again collapses in on itself. The point of equilibrium shifts to the right when alkali is added and to the left when acid is added, which has the reverse effect. Hydrogels are available in various distinct types, and they all expand and contract at different pH levels, temperatures, and ionic concentrations [7].

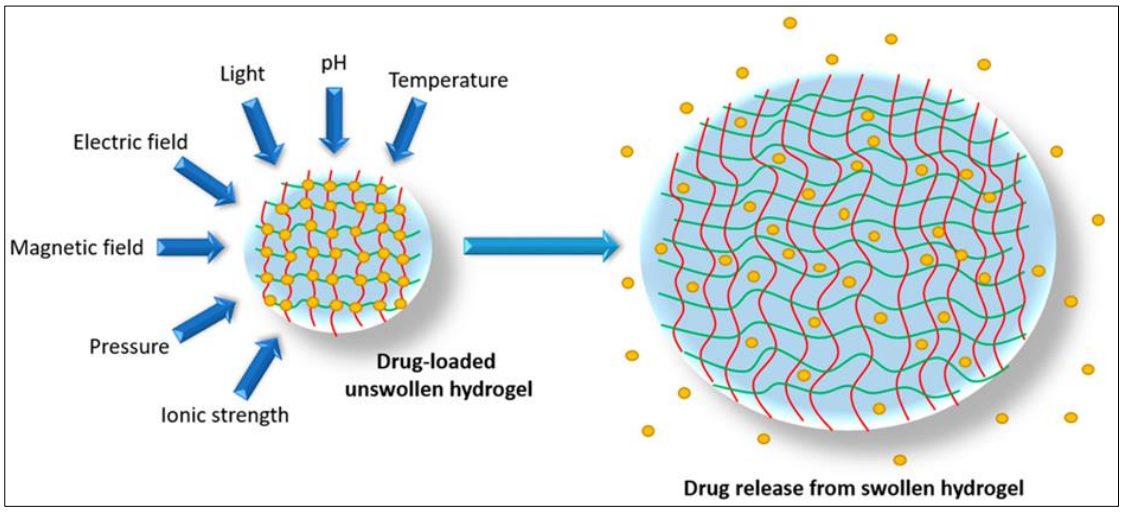

Figure 1 Swelling carried on by various chemical and physical events in a drug delivery hydrogel. The interwoven matrix structure of a hydrogel is represented by red and yellow lines, with yellow spots denoting drug molecules **[11]**.

Physical and chemical hydrogels are the two types of hydrogels which are thus available in the market. Physical hydrogels are not uniform since this would result in the formation of molecular entanglement clusters and domains that are ionically linked. In physical gels, free chain ends, or chain loops reflect momentary network flaws. Ionotropic hydrogels, like calcium alginate hydrogels, are physical hydrogels created when a polyelectrolyte is coupled with a multivalent ion with the opposite charge. In some circumstances, polyelectrolytes with various charges are combined, and poly-ions or complicated coacervates form a gel. Changes in temperature, pH, ionic strength, stress applications, or adding the solute that competes with polymeric ligands for the protein's affinity site can all have an impact on these interactions. Chemical hydrogels are produced by the cross-linking of water-soluble polymers or by the transformation

of hydrophobic polymers into hydrophilic polymers followed by cross-linking to form network. "Permanent" or "chemical" gels are hydrogels which are covalently cross-linked into networks. Chemical hydrogels are not uniform either. They typically have "clusters," or areas of low water swelling and high crosslink density, scattered throughout areas of high swelling and low crosslink density [12]. More than other kind of artificial biomaterials, hydrogels most closely mimic natural living tissue. Thus, it is a result of their high-water content and soft, tissue-like nature. Great attention in use of hydrogels in drug delivery applications has been inspired by their distinctive physical characteristics [3]. Additionally, materials of high-water content enhance their biocompatibility. Therefore, hydrogels are used as materials for artificial skin, contact lenses, biosensor membranes, artificial heart linings, and drug delivery systems. Because they can stay longer at the delivery site, hydrogels are also utilized as carriers that can interact with mucosa lining of the GI tract, colon, vagina, nose, and other regions of the body. It is considered that hydrogen bonds play a key part in the interaction between these carriers and the glycoproteins in the mucosa. Consequently, it seems that materials with high density of carboxyl and hydroxy groups are attractive for this type of application. Acrylic and methacrylic acid are the monomers most frequently utilized in the production of mucoadhesive polymers (MAA) [8].

2. Benefits

- Biocompatible
- Biodegradable
- Can be injected
- Easy to modify
- More elastic and stronger
- Good transparent properties
- Entrapment of microbial cells within polyurethane hydrogel beads with advantage of low toxicity
- Due to the high-water content, they have degree of flexibility remarkably like natural tissues.
- They can sense change temperature, pH, concentration of metabolite and release the load because of such a change.
- Release of medicines and nutrients timely.

3. Limitations

- High cost
- Little mechanical strength
- Challenging to sterilize
- Difficult to load
- Non-adherent, possibly requiring supplementary dressing, and causing sensation from the maggot's movement.
- In contact lens less deposition hypoxia, dehydration, and red eye reactions.
- Inconsistent dehydration and elastic properties
- Poor oxygen permeability
- Inadequate flexibility
- They should be protected by secondary dressing.

4. Properties of the hydrogels

4.1. Swelling Properties [5] [13]

The hydrogel polymer has chains which are crosslinked to each other either chemically or physically. The slight changes in environmental factors may response rapidly to reversible changes in hydrogel. Various types of environmental factors are temperature, pH, electric signal, and enzyme or ionic species, which lead to different physical texture of gels. Experimentally, the weight difference method can be used for calculating the percentage of swelling, as shown by the following equation:

$$\text{Percentage swelling} = [(Ws - Wd)/Wd] \times 100$$

Where,
Ws is weight of swollen gel and
Wd is weight of dry gel.

4.2. Mechanical Strength [5] [7] [14]

This is a crucial characteristic of hydrogel, which is mostly utilized in the biomedical and pharmaceutical industries as a substance for tissue engineering, drug delivery, tendon healing, wound dressing, and cartilage replacement. The mechanical characteristics of a material can be adjusted and changed depending on its intended purpose. Degree of crosslinking can be changed by heating the material to produce a gel with a higher rigidity. Because the changes in mechanical characteristics are related to a wide variety of events and causes, different analyses must be performed depending on the material.

4.3. Biocompatibility [5] [7] [15]

A material's biocompatibility refers to its capacity to function in each application with a favorable host reaction. The hydrogels should be nontoxic and biocompatible, making them particularly useful in biomedical applications. In-vivo toxicity testing and cytotoxicity tests are the concepts that are primarily used in polymers as it comes to these qualities. Essentially, biocompatibility consists of two components: (a) Bio-functionality, or the capacity of a substance to carry out the function for which it is designed. (b) Biosafety, which includes a proper host response that is both systemic and local (in tissue around it), the lack of mutagenesis, and cytotoxicity. It is capacity of polymers that do not produce toxic and immunological response when expose to biological environment.

4.4. Polymers [5] [7]

- Hydrogels are produced from natural and synthetic polymers.
- Natural polymers like chitosan, gelatin, alginates, fibrin.
- Synthetic polymers such as vinyl acetate, acrylic acid, methacrylate-vinyl-2-pyrrolidine.

5. Classification of hydrogels [4] [5] [7] [15] [6] [8] [14]

- Based on Source
  - Natural source
  - Synthetic source
  - Semi synthetic source
- Based on Polymeric Composition
  - Homo polymeric hydrogels
  - Co polymeric hydrogels
  - Multi-polymer interpenetrating polymeric hydrogel
- Based on Biodegradability
  - Biodegradable hydrogels
  - Non-biodegradable hydrogels
- Based on Configuration
  - Amorphous
  - Semi crystalline
  - Crystalline
- Based on Type Of Cross Linking
  - Physical linking
  - Chemical linking
- Based on Physical Appearance
  - Matrix
  - Film
  - Microsphere
- Based on Network Electrical Charges
  - Non-ionic
  - Ionic
  - Zwitter ion
- Based on The Mechanical Controlling The Drug Release
  - Diffusion controlled
  - Swelling controlled
  - Chemically controlled
  - Environmentally responsive release system

5.1. Based on Source

5.1.1. Natural Source

Natural hydrogels have high cell adhesion qualities, are biodegradable, and are biocompatible. Proteins like collagen, gelatin, and lysozyme, also polysaccharides like hyaluronic acid, alginate, and chitosan, are the two important forms of natural polymers that are utilized to create natural hydrogels.

5.1.2. Synthetic Source

They are prepared to form far wider variety of mechanical and chemical properties than their natural counterparts, making them more useful than natural hydrogels. Due of their non-toxicity, compatibility, and low immunogenicity, polyethylene glycol-based hydrogels are one class of the commonly utilized materials in biomedical applications.

5.1.3. Semi Synthetic Source

They are mixture of synthetic and natural polymer hydrogels. Many naturally occurring biopolymers, including dextran, collagen, and chitosan, have been mixed with synthetic polymers, including poly (N-isopropylacrylamide) and polyvinyl alcohol, to combine the benefits of both synthetic and natural hydrogels.

5.2. Based on Polymeric Composition

5.2.1. Homo Polymeric Hydrogels

A homo-polymeric hydrogel is a polymer network composed entirely of single species of the monomer, the basic building block of all polymer networks. Homopolymers have a cross-linked skeletal structure depending on the kind of monomer and the polymerization procedure.

5.2.2. Co Polymeric Hydrogels

Co-polymeric hydrogels are of two or different monomer species that are distributed randomly, in groups, or alternatively along the polymer network's chain. There must be minimum one hydrophilic component per monomer species.

5.2.3. Multi-Polymer Interpenetrating Polymeric Hydrogel (IPN)

A large spectrum of hydrogels with a cross-linked network structure from two different synthetic or natural polymer components. A cross-linked polymer with non-cross-linked polymer both make up the semi-IPN hydrogel.

5.3. Based on Biodegradability

5.3.1. Biodegradable

Hydrogels degrade naturally. Biodegradable polymers include those made by nature like Chitosan, fibrin, and agar. Synthetic biodegradable polymers include poly (aldehyde guluronate), polyanhydrides, and poly (N-isopropyl acrylamide).

5.3.2. Non-Biodegradable

The creation of non-biodegradable hydrogels involves the numerous vinylated monomers or macromers, including 2-hydroxyethyl methacrylate, 2-hydroxypropyl methacrylate, and acrylamide.

5.4. Based on Configuration

5.4.1. Amorphous

They are non-crystalline. They are glycerin and water-based products primarily manufactured for wound hydration.

5.4.2. Semi Crystalline

It is complex mixture of amorphous and crystalline phases.

5.4.3. Crystalline

The crystalline hydrogels have superior tolerance for variety of severe environments and good mechanical strength.

5.5. Based on Type of Cross Linking

5.5.1. Physical Linking

Transient junctions occur in physical networks and can be caused by hydrogen bonds, hydrophobic interactions, or polymer chain entanglements.

5.5.2. Chemical Linking

Chemically cross-linked networks have permanent junctions.

5.6. Based on Physical Appearance

Hydrogels are film, matrix and microsphere which depends on the polymerization techniques.

5.6.1. Matrix

5.6.2. Film

5.6.3. Microsphere

5.7. Based on Network Electrical Charges

5.7.1. Non-Ionic – Neutral

5.7.2. Ionic - Anionic or cationic

5.7.3. Zwitter Ionic - Polybetaines containing both anionic and cationic groups.

5.7.4. Amphoteric Electrolyte – Ampholytic which has both acidic and basic groups.

6. Synthesis of hydrogels

A critical step in developing new structures with beneficial properties for drug administration is the production of hydrogels. The hydration of the hydrophilic groups and domains of the relevant polymers determines the hydrogel structure. Thus, to prevent their dissolution in the aqueous phase, these groups, and their linked chains crosslink to form three-dimensional networks [1]. In general, hydrogels can be prepared from synthetic or natural polymers. Synthetic polymers are chemically more powerful and naturally hydrophobic than natural polymers. Its mechanical strength contributes to their durability while also causing a slow rate of deterioration. The greatest design should strike a compromise between these two competing characteristics. If they have the proper functional groups or have been functionalized with radically polymerizable groups, it can also be utilized to create hydrogels from natural polymers [4]. There are several ways to prepare hydrogels, including the cold method, the fusion method, and the dispersion method [15]. Physical cross-linking, chemical cross-linking, grafting polymerization, and radiation cross-linking are some of the formation procedures used [8]. Two well-known methods are frequently used to create polymeric hydrogels: (a) the polymerization of hydrophilic monomers, and (b) the modification or functionalization of pre-existing polymers [16]. Some of the preparation techniques employed include physical cross-linking, chemical cross-linking, grafting polymerization, and radiation cross-linking. For applications in the biological and pharmaceutical fields, these modifications can enhance the mechanical properties and viscoelasticity [17]. Most hydrogels are grafted starch-acrylic acid polymers and slightly cross-linked copolymers of acrylate with acrylic acid created through solution polymerization, emulsion polymerization, and inverse suspension [18]. The monomer, cross-linker, and initiator are the three primary elements used to produce hydrogels. Water and other diluents are used for regulating reaction temperatures [19]. Physical cross-linking, chemical cross-linking, grafting polymerization, and radiation cross-linking are various preparation procedures used. These alterations can enhance the mechanical characteristics and viscoelasticity for applications in the biomedical and pharmaceutical areas [17]. The following methods are described below.

6.1. Physical cross linking [20] [4]

Physical or reversible gels have become more common because of the convenience of production and basic advantage of rarely requiring cross-linking agents. These chemicals affect the integrity of items to be entrapped, such as cells and proteins, and the necessity of removing them before application. The given below are the numerous techniques described in the literature for producing physically cross-linked hydrogels [17] [7].

6.1.1. Heating or cooling a polymer solution

Helix formation, helix association, and junction zone formation are all responsible for the gel's formation. Above the melting transition temperature, carrageenan is found in hot solutions as a randomly shaped coil. As it cools, it solidifies into helical rods. Double helices additionally combine to make stable gels as result of sulphonic group's (SO-3) screening of repulsion in presence of salt.

6.1.2. Ionic interaction

Di- or tri-valent counterions may be used to cross-link ionic polymers. The principle of this method is to combine a multivalent ion with opposing charges, such as Ca2+ + 2Cl-, with a polyelectrolyte solution, such as Na+ alginate-. More examples include chitosan-glycerol phosphate salt, chitosan-polylysine, and chitosan-dextran hydrogels [17].

6.1.3. Complex coacervation

Combining a polyanion and polycation can result in complex coacervate gels. Polymers with diametrically opposed charges will attract one another and combine to form soluble or insoluble complexes depending on concentration and pH of corresponding solutions. The aggravation of polycationic chitosan with polyanionic xanthan is one such instance. Polyion complex hydrogels are more likely to form when anionic hydrocolloids interact with positively charged proteins below their isoelectric point [17] [7].

6.2. Chemical cross linking [4]

In chemical cross-linking, a cross-linking agent joins two polymer chains together or grafts monomers onto the polymer's backbone. By reaction with cross-linkers like aldehydes (such glutaraldehyde and adipic acid dihydrazide), which have functional groups like OH, COOH, and NH2, natural and synthetic polymers may be cross-linked. Glutaraldehyde and epichlorohydrin, among other cross-linkers, were used to create cross-linked hydrogel. Hydrogel, which is formed by crosslinking maize starch, polyvinyl alcohol, and glutaraldehyde, is a good example. Hydrogels can be formed by mixing cellulose in NaOH/urea aqueous solutions with the cross-linker epichlorohydrin, heating, and freezing processes [21] [7] [17].

6.3. Grafting cross linking

Hydrogels created by bulk polymerization typically have a weak structural base. A hydrogel may be surface coated onto a more durable support to improve its mechanical qualities. By first generating free radicals on a surface that is more powerful than the support and polymerizing monomers directly onto it, this technique creates a chain of monomers that are covalently attached to support. Hydrogel have been prepared on various polymeric supports using grafting techniques. Use of N-vinyl-2-pyrrolidone to graft acrylic acid onto starch is an example of process [17] [7] [22].

6.4. Polymerization through irradiation

Two types of ionizing high energy radiation, gamma rays and electron beams, were used for producing unsaturated compound hydrogels. Irradiating an aqueous polymer solution causes radicals to form on polymer chains. Finally, a crosslinked structure is produced through the macro-radicals on various chains recombining to form covalent bonds [7] [17] [8] [16].
It involves stepwise procedure as given below:

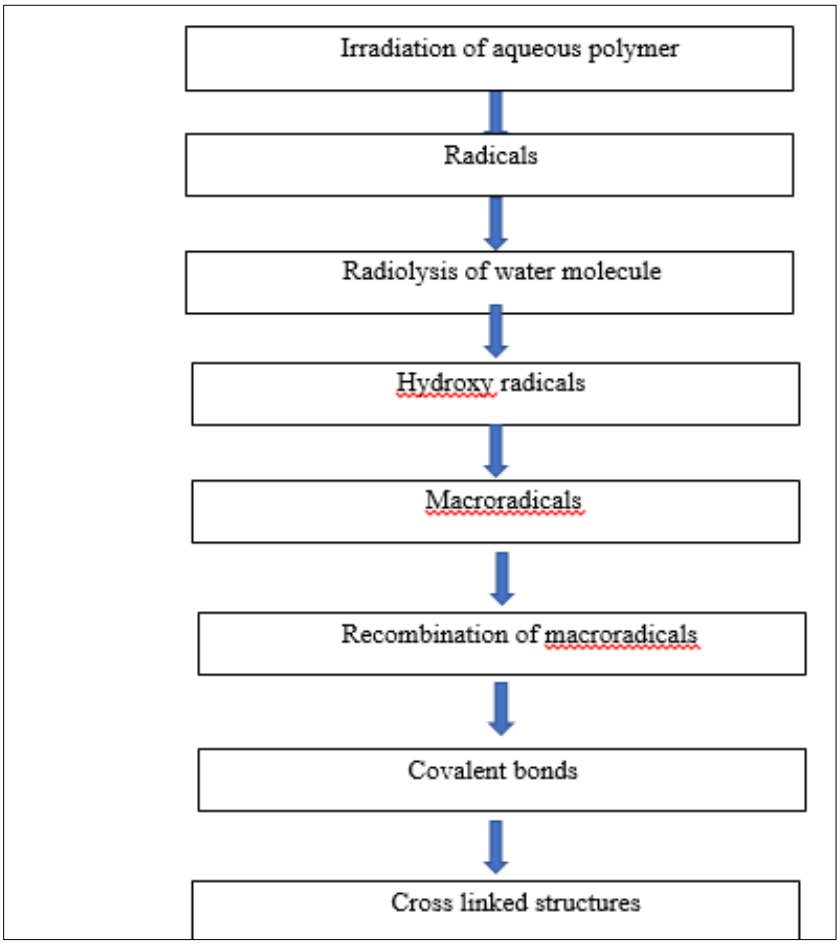

Figure 2 Flowchart for polymerization through irradiation.

7. Applications of hydrogels

7.1. Drug delivery

7.1.1. Drug delivery in oral cavity

Drug administration to the oral cavity can be very beneficial for the local treatment of oral problems like periodontal disease, stomatitis, fungal and viral infections, and oral cavity cancers [23]. For instance, a bio adhesive tablet known as Aftachw had been developed and is being sold. A lactose-free, non-adhesive backing layer and a bio adhesive layer made of hydroxypropyl cellulose and polyethylene make up this product's two layers (acrylic acid). It is a way of treating ulcers locally with triamcinolone [5] [17]. Medication is incorporated into hydrogels and administered to the oral cavity for the local treatment of mouth ailments like stomatitis, fungal diseases, periodontal disease, viral infections, and oral cavity cancers [7]. For the oral administration of various active constituents, such as non-steroidal anti-inflammatory medications, hydrogel delivery systems were proposed (NSAIDs) [2]. They may be used to safeguard medications or proteins (like insulin) that are vulnerable to the stomach's proteolytic breakdown [24]. The P(MMA-g-EG)-containing pH-responsive nanoparticle offers the potential to exploit as an oral delivery system for cancer chemotherapeutics [25]. Application of hydrogels through oral, nasal, buccal, rectal, vaginal, ocular, injection, and other delivery routes has a great deal of potential [26].

7.1.2. Drug delivery in GI tract

Since it happens in numerous specific or diseased body sites, the pH change is the key environmental factors for DDS. Numerous areas of the human body, including the digestive system and specific tissues like tumoral regions and subcellular compartments, have different pH levels. Both acidic and basic polymers are used in pH-sensitive DDS. For gastrointestinal tract medication administration, the most used acidic polymers include PAA, PMAA, poly (L-glutamic acid), and polymers containing sulfonamide [27]. Using hydrogel-based devices, drugs may be administered locally to specific regions of the GI tract, like buccal delivery. For instance, stomach-specific antibiotic medicine delivery devices

while treating Helicobacter pylori infection in peptic ulcer disease. For targeted antibiotic administration in the stomach's acidic environment, they developed cationic hydrogels with pH-sensitive swelling and by drug release characteristics. Oral insulin delivery utilizing pH-responsive complexation hydrogels was recently brought to light. Using PMAA copolymers with graft chains of polyethylene glycol, such hydrogels were cross-linked to safeguard the insulin in harsh, acidic atmosphere of stomach before delivering the medication in small intestine [17]. Because of their capacity to extend their resident length at the delivery site, hydrogels are used as carriers that can react with mucosa lining in GI tract, colon, vagina, nose, and some other parts of the body. The reaction between these carriers and the glycoprotein in the mucosa has been significantly influenced by hydrogen bonding. Consequently, it is seen that materials with high density of carboxyl and hydroxy groups are attractive for this kind of application [8]. Hydrogels delivers drugs to specific site in GIT [7]. Due to micro flora, they are intended to swell to a great extent or degrade [6].

7.1.3. Rectal drug delivery

Hydrogels have advantages in rectal drug delivery since this route can increase patient compliance over injections and improve bioavailability over oral delivery, although being less frequently utilized than certain other routes. For instance, hydroxypropyl methylcellulose hydrogels are used to give anti-seizure medications to children, a key target population for rectal delivery formulations due to children's inability to swallow pills. Additionally, mucoadhesive hydrogels for treatment of colitis, such as chitosan-catechol, have shown effective [20]. Application of hydrogels by oral, nasal, buccal, rectal, vaginal, ocular, injection, and other delivery routes is broadly used [26]. For the local treatment of conditions like hemorrhoids, which are rectum-related, numerous different drug types have been supplied via the rectal route. Since this method skips first pass metabolism and enables drugs absorbed from the lower part of the rectum to enter the bloodstream directly, it is more practical. Traditional suppositories are altered for rectal delivery due to solidification at room temperature thus dissolve or soften at body temperature. It is challenging for medications to be appropriately retained at a specific spot in the rectum when they are delivered from typical suppositories in an irregular manner; additionally, they may travel upward to the colon. This frequently causes bioavailability of medications to vary [17]. For rectal drug distribution, hydrogels with bio adhesive characteristics are used [7]. The usage of xyloglucan gel with a thermal gelling property as drug delivery matrices was investigated by Miyazaki *et al* [6]. Numerous benefits of rectal administration include controlled compound release in the setting of the stable environmental conditions found in rectum, quick compound absorption, avoidance of gastrointestinal tract, and fewer adverse reactions to medicines [1].

7.1.4. Ocular drug delivery

Additionally, hydrogels were being injected into the vitreous humor or implanted in the subconjunctival area before being delivered to the back of the eye. Anti-vascular endothelial growth factor (VEGF) inhibitors are being delivered via injectable hydrogels based mostly on hyaluronic acid, a key component of vitreous humor, to increase effectiveness of intravitreal injections for treatment of acute macular degeneration [20]. Hydrogel contact lenses to be comfortable to wear, have adequate oxygen permeability, and maybe aid in the treatment of eye illnesses, hydrogels are significant contact lens manufacturing materials [26].

7.1.5. Protein drug delivery

Nowadays, instead of being injected, interleukins are supplied as hydrogels, which have better compliance, create in-situ polymeric networks, and release proteins gradually [6]. By offering long-lasting sustain release of proteins after administration, hydrogel carriers may be useful improvements for stabilizing protein therapeutics during shipment, storage and reducing treatment frequency. Frequently the proteins larger than 100 kDa may be designed into hydrogels to control their release primarily through gel degradation and diffusion and are reasonably good at providing a sustained release of cargo. This strategy shows promise for significant therapeutic protein classes as antibodies, large enzymes, and modified proteins [28].

7.1.6. Subcutaneous drug delivery

Administering a subcutaneous injection to mice is the most effective ways to evaluate their response to medication and determine their toxicity in real time. A minimal reaction to foreign substances is anticipated because the subcutaneous area is vascularized, and the implanted hydrogels or other biomaterials have immunological privilege [1]. Hydrogel formulations for Anti-cancer medications are being administered subcutaneously ready with viz applying crosslinked PHEMA to cytarabine (Ara-c). For now, implantable hydrogels developing the formation of biodegradable systems that don't need to be detached surgically after the medication has been given [6].

7.1.7. Controlled drug delivery

Hydrogels can potentially been used to control release of drugs reversible gel formations that can change in reaction to environmental factors. The category of environmentally sensitive polymer systems has most likely attracted the most

attention in drug delivery research is hydrogels that vary with temperature. The hydrophobic groups like methyl, ethyl, and propyl, are typically found in the networks of temperature-sensitive polymers. The hydrogel contracts because of stronger connections between polymer chains made through hydrophobic interactions between hydrophobic segments as the temperature rises. When grafting N-vinyl caprolactam (NVCL) or n-isopropylacrylamide (NIPA Am) on drug release that is negatively thermosensitive from cellulose or chitosan systems with hydrogels are obtained. These gels exhibit a lower swelling ratio as the temperature rises and consequently, they are used as "on-off" release mechanisms, with "on" (swelling) at Low temperature and "off"(shrinking) at High temperature [29]. HYPAN is a new hydrogel with useful controlled drug delivery features. HYPAN hydrogels are distinct from others because of physical complex of crystalline clusters [6].

7.1.8. Transdermal drug delivery

Hydrogels has been used in two situations for skin distribution even though the stratum corneum's hydrophobic layer prevents their direct usage for transdermal delivery. First, by using hydrogels to deliver nanoparticles into the skin via cellular transport pathways, the time a medicine is delivered and the retention of nanoparticles at the target site are both lengthened. Second, by increasing the viscosity of continuous phase, hydrogels can be used in the reservoir of a transdermal patch to prolong the time that a medication is released into the skin through the porous membrane and enhance the suspension of an insoluble substance inside the patch [3]. When used topically, hydrogels have various benefits, including the capacity to circumvent hepatic metabolism, thus boosts drug bioavailability and effectiveness. To provide a consistent drug release, transdermal drug delivery systems are employed. Hydrogels are removed more easily than other dose forms like patches and ointments because they are swollen and like live tissues [17]. To produce improved penetration of substances like hormones and nicotine, hydrogel-based formulations for transdermal iontophoresis are being studied [7].

7.2. Contact lenses

Ophthalmology, particularly contact lenses, is a crucial field in application of synthetic hydrogels of bio applications. A contact lens is a tiny optical device that is placed directly on the cornea to alter corneal power. Since direct contact with cornea prevents the exchange of ambient oxygen, interrupting the physiological metabolism of the cornea known as hypoxic stress, a good contact lens must have highest possible oxygen permeability. The hydrogels used to prepare contact lenses thus satisfy the bulk of requirements needed when using in a variety of physiological circumstances. To prepare contact lenses that are comfortable to wear, a hydrogel material must meet a few specifications. There must be enough water present, adequate mechanical properties, permeability toward oxygen, surface wetness, good optical facilities, and stability against hydrolysis, among other conditions [27]. By thermal or photopolymerizing HEMA solutions using ethylene glycol Di methacrylate as the cross-linker and various ratios of N-vinyl-2-pyrrolidone or methacrylic acid as comonomers, poly (2-hydroxyethyl methacrylate) (p(HEMA)) soft contact lenses are developed. Based on adjustment of the hydrogel composition and microstructural alterations using water during the polymerization process, the drug loading capacity and release properties of soft contact lenses based on p(HEMA) were enhanced [26]. Due to their broad range of properties, hydrogels based on poly (2-hydroxyethyl methacrylate) are utilized for soft contact lenses [5]. The first silicon hydrogels that were sold commercially used two separate strategies. Bausch & Lomb's initial strategy was a logical progression from its creation of silicon monomers with improved compatibility in hydrogel forming monomers. The formation of siloxy monomers with hydrophilic polyethylene oxide segments and oxygen permeable polysiloxane units was Ciba's second vision [6]. Soft contact lenses can be produced using a range of methods, including spin casting, mould casting, and lathe cutting. A little amount of a liquid monomer mixture is poured into specialized optical moulds that are "concave" to spin and create cast lenses. The concave mould rotates to produce the lens during spin-casting, forcing the liquid monomer to flow out uniformly and coat the whole surface [24].

7.3. Wound healing

An effective wound gel dressing should permit gaseous exchange, keep the wound bed at the right moisture level and temperature, eliminate excess exudates, safeguard the wound by bacteria and pollution, hasten healing, and reduce discomfort. Additionally, it must be non-toxic, non-allergenic, non-adherent, and trauma-free when removed [29]. Hydrogels can stimulate skin regrowth. It might be loaded with the medication needed to treat wounds [15]. A hydrogel thus maintains the system's moisture levels, absorb exudate and inflammatory media (high swelling ratio), have enough mechanical strength to remain intact over the required period, resist the applied stresses faced (including physical handling), allow proper gas exchange, and shorten the healing time compared to normal physiological procedures (low protein adsorption). Hydrogels often have lower adhesive strength than synthetic adhesives, but they also reduce irritation and have improved exudate absorption and/or active agent delivery capabilities to support with wound healing procedure [20]. In addition to being non-adhesive, hydrogels are resistant to attack from hydrophilic surfaces. This characteristic relates to wound dressings where hydrogels do not adhere to wound and reduce patient discomfort

[18]. Hydrogels can protect the wound through bacterial violations, reducing bacterial development, and so increasing overall wound healing. It can also give oxygen to the wound to speed up the growth of epithelial cells and the proliferation of new capillaries [26]. Hydrogels consisting of gelatin and sodium alginate are used to guard and shield a wound against bacterial infection [17]. To treat cartilage abnormalities, hydrogels made from modified polysaccharides present in cartilage are used [6]. Depending on the type of injury, hydrogels can be applied as an elastic, solid sheet, or film, as an amorphous gel, or both. The polymer components are crosslinked for gels or sheet fabrication to trap water [30]. A mechanism for releasing energy usually exists in natural systems that are repairing fissures. Sacrificial bonds, which can break and repair dynamically before or during the failure occurring, can simplify the self-healing process. Both covalent and non-covalent interactions is used in the development of self-healing hydrogels [25]. Hydrogels are frequently used as moist dressings, debriding agents, and ingredients in pastes for treatment of wounds. However, they are appropriate for dry wounds and do not require additional wound fluids to be the gels [24]. Since non-covalent interactions in self-healing hydrogels are so weak and reversible in nature, self-healing hydrogels have poor mechanical characteristics. In contrast, strong self-hydrogels that can endure deformation have been created by utilizing various crosslinking mechanisms, such as those present in interpenetrating polymer networks [31].

7.4. Tissue engineering

In regenerative medicine, tissue engineering (TE) is important. It is divided into three categories: implantation and/or grafting, scaffold and cell/tissue, and. Scaffolds have >80um-sized pores are coupled with ceramics or polymers. It oversees angiogenesis, cell augmentation, and cell migration into the scaffold's central region. Hydrogel sterilization alters the property of scaffold [15]. The native extracellular matrix (ECM) of cells has served as a major source of inspiration for design of hydrogel tissue engineering scaffolds. Natural ECM contains numerous vital cells signaling molecules, fibrous proteins (mainly based on collagen, elastin, and laminin), and proteoglycans in addition to providing mechanical support to cells (glycosaminoglycans) [3]. One of the common types of hydrogels used in tissue engineering is hydrogel scaffolds, a different type based on self-assembly peptides (SAPs). SAPs are made up of polypeptides that self-assemble when given certain conditions, such as a hydrophilic environment and nanostructures. The long-chain alkyl tail and cell adhesion ligand can be self-assembled by amphiphilic molecules. While amphiphilic revealed a hydrophobic nature with a long-chain alkyl tail, the polypeptide demonstrated a hydrophilic character [18]. To enhance or replace organic organs, tissue engineering combines materials, engineering, and cells. Finding the right cell types and cultivating them in right circumstances in suitable scaffold are required for this. Due to their structural resemblance to extracellular matrix found in many tissues, the ease with which they can be manufactured, and potential for minimally invasive delivery, hydrogels make attractive scaffold materials [27]. For several reasons, hydrogels are frequently used as scaffold materials in tissue engineering. First, hydrogels resemble soft tissues in vivo in which they are flexible and soft. Second, liquid hydrogels that have been injected into the body can quickly fill tissue defects by becoming amorphous, non-flowing semisolids [26]. Another naturally occurring substance, fibrin, has recently demonstrated promise as scaffold that has been injected and used to carry cells. A clot forms when fibrinogen and thrombin solutions are combined, and this is how it has traditionally used in medicine. Fibrin glue is widely used in surgery to stop bleeding and bind tissues. Additionally, it has shown improved outcomes for skin grafts, especially those that were challenging, and introduction of exogenous growth factors to decrease the time it takes for wounds to heal [32]. To transfer macromolecules to the cytoplasm of antigen-presenting cells, micronized hydrogels are utilized. A natural hydrogel made of agarose, methylcellulose, or another naturally produced substance is utilized in tissue engineering [7]. The repair of cartilage also makes use of this property [6]. Processability, biodegradability (through hydrolysis or enzymatic cleavage), biocompatibility (i.e., excellent cell viability/proliferation, without inflammatory response), bioactivity (i.e., biomineralization), cell adhesion ability, etc. are just a few of the design criteria that hydrogel scaffolds in tissue engineering must satisfy. The qualities of the scaffolds are improved by hybridizing the matrix (cellulose or chitin) with a second component. For example, hydroxyapatite (HA) and silica increase mechanical strength, calcification, and speed up biodegradation, while collagen and gelatin boost strength and cell adhesion [29]. Because of the crosslink density of hydrogels, large objects like cells cannot, in principle, move or grow within gel. It is a potential problem which needs to be carefully considered when employing hydrogels in cell culture. One method calls for gels to be biodegraded by the cells as they develop. This is frequently accomplished by including protein segments in polymer that exoproteomes generated by the cells can break down [30]. The various properties for hydrogels to be used are non-degradable, injectable, easy to use, water content, pores, chemical, added bioactive components and sterilizability [23]. The synthetic substances poly (ethylene oxide), poly (vinyl alcohol), poly(acrylic acid), poly(propylene fumarate-co-ethylene glycol), and polypeptides are efficient of creating hydrogels appropriate for tissue engineering. Natural polymers of a natural origin, such as agar, alginate, chitosan, collagen, fibrin, gelatin, and hyaluronic acid, could also be utilized for this [24]. A hydrogel network containing magnetic nanoparticles can deform in a magnetic field, and existence of macropores causes a large and rapid deformation of the scaffold that significantly improves release of drug molecules [33]. The injectable devices can fill irregularly shaped defects and provide a way to minimize surgical intrusion. Due to their benefit of reduced rejection rates, significant current research approaches have been

documented on use of autografts in bone implantation therapy. Recently, efforts have been undertaken to improve biomimetic capacity of cell-based therapeutics using injectable bio hydrogels (collagen, chitosan, gelatin, and cellulose) [1]. The best option for bone repair is still autologous bone grafting, but its use is severely constrained by its limited availability and tendency to create lesions at the donor site. Therefore, the best materials for bone repair are anticipated to be tissue engineering scaffolds that enable minimally invasive surgery, adapt to irregular bone lesions, and encourage bone regeneration [34].

7.5. Biosensing

A biosensor is created by combining chemical and physical sensors. A biosensor is regarded of as a tool that can detect and report biophysical characteristic of system being studied or as a tool that can offer relevant analytical information by changing biochemical data. A biological recognition component that enables the analysis of biological data is a feature shared by all biosensors [27]. In most cases, biomolecules are fixed to hydrogels' exterior or interior, linking to the physical components of the biosensors. The hydrogel film serves as connecting point for the physical and biological elements. Alginate, alginic acid in conjunction with chitosan, acrylamide, or N-isopropyl acrylamide are frequently found in hydrogels created for sensors [26]. Biosensor hydrogels, which serve as supports for the immobilization of enzymes, may be used to produce biosensors. The enzyme D-fructose dehydrogenase is employed to immobilize the hydrogel polycarbamoylsulphonate [5]. A hydrogel that might provide an anti-fouling layer for the diffusion of glucose was physically crosslinked using the PVA/PEG method and thus modified with 4-boronobenzaldehyde (4-BBA) [34].

7.6. Bacterial culture

Spirulina and chlorella are two utilizing microorganisms, the contaminants are removed from water resources, a chemical. During bacterial the substrate culture agar is common in use of biotechnology [15]. A vast number of microorganisms can be retained inside the matrix of hydrogels for use in production of biomolecules, the filtration of water, or the simple cultivation of bacteria on their own. It offers the ideal environment for their culture on a solid substrate because it is indigestible to many bacteria and microorganisms [7].

7.7. Agriculture

60% of the water used annually worldwide is used for agriculture, and by 2050, 40% of the world's population is likely to reside in regions with significant water scarcities [28]. There are numerous ways that hydrogels are used for horticulture and agriculture. The simplest of these examples is addition of active agrochemicals to hydrogels, either directly (e.g., drug loading and gel synthesis simultaneously) or indirectly (e.g., passive diffusion, solvent evaporation, or centrifugation after gel formation). Polysaccharides, which promote high water retention and degradability, and superabsorbent polymers (SAPs), such as poly(acrylamide) or poly(butadiene), are most extensively used starting ingredients to produce agricultural hydrogels (acrylic acid) [3].

7.8. Electronics

In electronics, hydrogels like potassium poly(acrylate), poly (vinyl alcohol), poly (ethylene oxide), and gelatin are employed as matrixes to confirm the utmost tunability and precision of capacitors [5]. As a result of mobile ion transport in electric field, which effects in bending towards one electrode, CMC/chitosan and cellulose/alginate hybrid hydrogels are possible electroactive sensors or actuators in electronic devices [29]. It is possible to create high-performing, low-cost capacitors by altering polymer and solution used. In contrast to properties of inorganic hydrogels, organic polymers appear to have lesser properties [7].

7.9. Cosmetics

A personal care product is anything used for personal hygiene and grooming, while a cosmetic is something that is "intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance," according to the US Food and Drug Administration (FDA) [3]. Because of comparatively low cost of preparation, businesses are able to introduce novel cosmetic items based on hydrogels, such as so-called "beauty masks," to the market. These masks, which are typically manufactured with polyvinyl pyrrolidone (Pecogel), hyaluronic acid, or engineered collagen (Masque ology by SEPHORA USA Inc., Bio Collagen Cosmeceuticals by NOVOSTRATA UK Ltd.), promise to hydrate the skin, restore its suppleness, and promote anti-aging effects [7].

For long-lasting effects in cosmetics industry, hydrogel mechanical properties are crucial. Yu et al. created an elastic cross-linked polymer layer that approximated the mechanics of young skin through this way. In this case, hydrogel structure made it possible for the topically applied substance to be breathable without irritating the skin and possess

the elastic qualities of young skin [28]. To improve their appearance, hydrogels are implanted in breast tissue. These implants are prepared from silicon elastomer and filled with gel made of hydroxypropyl cellulose polysaccharide [6].

7.10. Miscellaneous

Various other applications of hydrogel are Gene delivery, Watering beads for plants, Diapers preparation, Perfume delivery, Plastic surgery, Sealant and adhesive, Water purification, Regenerative medicine, Dyes and heavy metal ion removal, Colon specific hydrogels, etc.

8. Conclusion

This review comprises of various properties like its material involved its introduction, synthesis procedure, advantages and disadvantages, classification, it's application in various fields and conclusion based on its classification and application. Three-dimensional crosslinked polymeric networks called hydrogels should be seriously considered as carriers or matrices for cells in tissue engineering, self-healing materials, and delivery systems for pharmaceuticals and biomolecules. One of the possible applications for high-intensity hydrogels is high-end medicine, particularly targeted cancer treatment, in vitro organ culture, and human tissue repair. Hydrogels are having a substantial therapeutic influence on ophthalmic medication delivery. Applications in eye care range from pleasant contact lenses to biodegradable medication delivery. They deliver small molecules or large proteins, are 90% water, offer constant medication release over days or months, are completely absorbed after delivery, and remain visible during monitoring. The use of injectable hydrogels for drug delivery and tissue engineering-based applications would be even increased by the utilization of new physicochemical techniques (or combinations of existing cross-linking techniques) to instantaneously control not only the gelation process but also the interactions between the gel and the native tissues. The use of hydrogels in the markets for contact lenses, hygiene products, and wound dressings is well-known. Commercial hydrogel products are also used in tissue engineering and drug delivery, food, agriculture, cosmetic. Hydrogels made by heating exhibited macro porous structure, but hydrogels made by freezing exhibited fiber-like structure. There are various methods through which hydrogels can be prepared. Some of them are discussed in this article.

Compliance with ethical standards

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References

[1] Hydrogels Based Drug Delivery Synthesis, Characterization and Administration. Anca Onaciu 1, Raluca Andrada Munteanu 1 , Alin Iulian Moldovan 1,2 , Cristian Silviu Moldovan 1,2,3 and Ioana Berindan-Neagoe 1,3,4,*. 432, 2019, MDPI, Vol. 11.

[2] Hydrogels and Their Applications in Targeted Drug Delivery. *, Radhika Narayanaswamy and Vladimir P. Torchilin. 603, 2019, MDPI, Vol. 24.

[3] Hydrogels in drug delivery: Progress and challenges. Todd R. Hoare a, Daniel S. Kohane b,*. 2008, SCIENCEDIRECT, pp. 1993-2007.

[4] Enas M. Ahmed. Hydrogel: Preparation, characterization, and applications. Journal of Advanced Research. JULY 2013.

[5] Polymer Hydrogels and Their Applications. Anamica, P.P.Pande. 1, 2017, International Journal of Materials Science, Vol. 12, pp. 11-14.

[6] HYDROGELS: A REVIEW. Anisha Singh1 *, Pramod Kumar Sharma1 , Vipin Kumar Garg1 , Garima Garg1. 2, 2010, International Journal of Pharmaceutical Sciences Review and Research, Vol. 4, pp. 97-105.

[7] A Review On- Hydrogel. Prashant S. Malpure*, Shital S. Patil, Yashpal M. More, Priti P. Nikam. 3, 2018, AMERICAN JOURNAL OF PHARMTECH RESEARCH, Vol. 8, pp. 41-61.

[8] A REVIEW ARTICLE ON HYDROGELS. Pulasani Sowjanya*1, Boddu Venkata Komali 1, CH. Ajay Babu1. 5, 2013, International Journal of Research in Pharmaceutical and Nano Sciences, Vol. 2, pp. 548-553.

[9] K. Park, W. S. W. Shalaby and H. Park. Biodegradable Hydrogels for Drug Delivery. pp. 234-235.

[10] Prud'homme, R. A. Harland and R. K. Polyelectrolyte Gels: Properties, Preparation, and Applications. Washington, DC : American chemical society, 1993, pp. 425-426.

[11] Hydrogels for Atopic Dermatitis and Wound Management: A Superior Drug Delivery Vehicle. *, Ian P. Harrison and Fabrizio Spada. 71, 2018, MDPI, Vol. 10.

[12] HYDROGELS AS A DRUG DELIVERY SYSTEM AND APPLICATIONS: A REVIEW. PRASHANT P. KALSHETTI1*, VIVEK B. RAJENDRA2, DEEPASHREE N. DIXIT2, PRANAV P. PAREKH2. 1, 2012, International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 4, pp. 1-7.

[13] Preparation and Characterization of Polyvinyl Alcohol–Gelatin Hydrogel Membranes for Biomedical Applications. Kunal Pal, 1 Ajit K. Banthia,1 and Dipak K. Majumdar2. 1, 2007, American Association of Pharmaceutical Scientists, Vol. 8.

[14] PREPARATION METHODS AND PROPERTIES OF HYDROGEL: A REVIEW. DAS*, NILIMANKA. 3, 2013, International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 5, pp. 112-117.

[15] Hydrogels: A review. Madan, Shikha Yadav* and Jitender. 6, 2020, International Journal of Pharmacy & Life Sciences, Vol. 11, pp. 6711-6717.

[16] Methods for Synthesis of Hydrogel Networks: A Review. Arvind M. Mathur a, Shailender K. Moorjani a & Alec B. Scranton a. 1996, Journal of Macromolecular Science, pp. 405-430.

[17] A REVIEW ON HYDROGEL. Bharskar*, Ganesh R. 7, JULY 2020, WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES, Vol. 9, pp. 1288-1298.

[18] G. Madhumitha, J. Fowsiya and Selvaraj Mohana Roopan. Emerging Technology in Medical Applications of Hydrogel. s.l. : SPRINGER NATURE PRIVATE LIMITED, 2018, pp. 197-218.

[19] Synthesis of Hydrogels. Nishi Panchal, Dhruv Patel, Nimish Shah. 2017, RESEARCH AND SCIENTIFIC INNOVATION SOCIETY, pp. 64-72.

[20] Hoare, Michael J. Majcher and Todd. Applications of Hydrogels. s.l. : SPRINGER NATURE SWITZERLAND, 2019, pp. 453-490.

[21] Structure and properties of hydrogels prepared from cellulose in NaOH/urea aqueous solutions. Chunyu Changa, Lingzhi Zhanga, Jinping Zhoua,⁎, Lina Zhanga, John F. Kennedy. 1, 2010, Elseiver, Vol. 82, pp. 122-127.

[22] Crosslinking and grafting of polyetheretherketone film by radiation techniques for application in fuel cells. J. Chen, D. Li, H. Koshikawa, M. Asano, and Y. Maekawa. 2010, Journal of Membrane Science, pp. 488-494.

[23] Hydrogels for biomedical applications. ⁎, Allan S. Hoffman. 2012, Advanced Drug Delivery Reviews, pp. 18-23.

[24] Biomedical applications of hydrogels: A review of patents and commercial products. Enrica Caló, Vitaliy V. Khutoryanskiy ⇑. 2014, EUROPEAN POLYMER JOURNAL.

[25] Hydrogels for Biomedical Applications: Their Characteristics and the Mechanisms behind Them. Qinyuan Chai, Yang Jiao and Xinjun Yu *. 6, 2017, MDPI, Vol. 3.

[26] Functional Hydrogels and Their Application in Drug Delivery, Biosensors, and Tissue Engineering. Ke Wang, 1 Yuting Hao,2 Yingna Wang,3 Jinyuan Chen,2 Lianzhi Mao,2 Yudi Deng,2 Junlin Chen,2 Sijie Yuan,4 Tiantian Zhang ,5 Jiaoyan Ren ,1 and Wenzhen Liao 2. 2019, International Journal of Polymer Science.

[27] Morteza Bahram, Naimeh Mohseni and Mehdi Moghtader. An Introduction to Hydrogels and Some Recent Applications. s.l. : INTECH, pp. 9-38.

[28] Translational Applications of Hydrogels. Santiago Correa, Abigail K. Grosskopf, Hector Lopez Hernandez, Doreen Chan, Anthony C. Yu, Lyndsay M. Stapleton, and Eric A. Appel*. 2021, American Chemical Society, Vol. 121, p. 11385−11457.

[29] Hydrogels Based on Cellulose and Chitin: Fabrication, Properties, and Applications. Xiaoping Shen, ab Julia L. Shamshina,c Paula Berton,a Gabriela Gurau,cd Robin D. Rogers* ad. 2013, The Royal Society of Chemistry, pp. 1-3.

[30] Hydrogels for biomedical applications. Moratti†1, Jaydee Cabral1 & Stephen Carl. 15, 2011, Future Med. Chem., Vol. 3, pp. 1877-1888.

[31] Fundamental Concepts of Hydrogels: Synthesis, Properties, and Their Applications. Shahid Bashir 1, * , Maryam Hina 1 , Javed Iqbal 2 , A. H. Rajpar 3 , M. A. Mujtaba 4 , N. A. Alghamdi 5 , S. Wageh 6 , K. Ramesh 1 and S. Ramesh 1,*. 2072, 2020, MDPI, Vol. 12.

[32] Hydrogels in Regenerative Medicine. Brandon V. Slaughter, Shahana S. Khurshid, Omar Z. Fisher, Ali Khademhosseini, and Nicholas A. Peppas*. 2009, ADVANCED MATERIALS, Vol. 21, pp. 3307-3329.

[33] Designing hydrogels for controlled drug delivery. J. Mooney, Jianyu Li and David. 2016, NATURE REVIEWS .

[34] Applications of Hydrogels with Special Physical Properties in Biomedicine. Gong Chen 1, † , Wenwei Tang 2,† , Xiaohui Wang 1 , Xueling Zhao 1,3, Cheng Chen 1,* and Zhigang Zhu 1,3,*. 1420, 2019, MDPI, Vol. 11.

[35] Hydrogels as Drug Delivery Systems: A Review of Current Characterization and Evaluation Techniques. Margaux Vigata 1, 2 , Christoph Meinert 1,2,3 , Dietmar W. Hutmacher 1,2,4,5 and Nathalie Bock 1,4,5,6,*. 1188, 2020, MDPI, Vol. 12.

[36] Rational Design of Smart Hydrogels for Biomedical Applications. Yanyu Zhang1, 2 and Yishun Huang1,2*. FEB 2021, Frontiers in Chemistry, Vol. 8.

[37] Ghobashy*, Mohamed Mohamady. The application of natural polymer-based hydrogels for agriculture. s.l. : ELSEVIER, 2020, pp. 329-356.

[38] Hydrogels and Hydrogel-Derived Materials for Energy and Water Sustainability. Youhong Guo, † Jiwoong Bae,† Zhiwei Fang,† Panpan Li,† Fei Zhao, and Guihua Yu*. AMERICAN CHEMICAL SOCIETY.

[39] Degradable and injectable hydrogel for drug delivery in soft tissues. Vincent Pertici, Caroline Pin-barre, Claudio Rivera, Christophe Pellegrino, Jeröme Laurin, Didier Gigmes, and Thomas Trimaille. 2018, American Chemical Society.

[40] Densely crosslinked polymer networks of PEG in trimethylolpropane triacrylate for cell adhesion-resistant surfaces,. Hubbell+, Paul D. Drumhellere and Jeffrey A. 1995, Journal of Biomedical Materials Research, Vol. 29, pp. 207-215.

[41] Influence of molecular structure imaged with atomic force microscopy on the rheological behavior of carrageenan aqueous systems in the presence or absence of cations. 4, June 2007, Food hydrocolloids, Vol. 21, pp. 617-629.