Journal of Young Pharmacists, 2024; 16(2):195-203.
https://www.jyoungpharm.org

Review Article

Green Fabrication Approach to Hydrogel Synthesis by Using Natural Polymers, their Characterization, and Applications

Muhammad Abid Mustafa[1,*], Namra Rasheed[1], Seerat Ansar[1], Qadeer Zahid[1], Sadia Arshad[1], Yousra[1], Samia Naz[1], Sana Javed[1], Syed Hammad Ali Shah[1], Sehrish[1], Fatima Imran[1], Minahil Arif[1], Muhammad Zahid Iqbal[2]

[1]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Lahore University of Biological and Applied Sciences, Lahore, PAKISTAN.
[2]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Lahore University of Biological and Applied Sciences, Lahore, PAKISTAN.

ABSTRACT

Background: Cross-linked networks of polymers are referred to as hydrogels because they possess the ability to retain water within the interstitial spaces of the polymer chains. The fundamental building block of life is a polymer. Researchers' interest in polymers has expanded due to the widespread availability of polymers exhibiting desirable characteristics, a key factor in the development of contemporary healthcare products. The synthesis of hydrogels involves the integration of various natural polymers. In the realm of biomedical applications, hydrogels can be employed to deliver drugs or cells, regenerate both hard and soft tissues, adhere to moist tissues, halt bleeding, provide contrast during imaging, shield tissues or organs from radiation, and enhance the biological adaptability of therapeutic implants. These attributes render hydrogels advantageous for a diverse array of distinct and critical diseases and medical scenarios, as well as in less conventional fields such as environmental engineering. **Objectives:** The primary objective of this review is to explore the literature related to hydrogels. This includes the classification of hydrogels, examination of natural polymers such as collagen, inulin, pectin, alginate, tragacanth, lignin, and chitosan, which are employed in hydrogel synthesis. The review also covers the general preparation of hydrogels, the methodologies involved in their preparation, common techniques used in characterization, release kinetics, and the diverse applications of hydrogels. **Conclusion:** This research covers the study of natural polymers such as inulin, alginate, lignin, pectin, collagen, chitosan, and tragacanth, employed in the synthesis of hydrogels. The key areas of focus encompass the classification of hydrogels, procedures for hydrogel preparation, various methods for hydrogel characterization, *in vitro* and *in vivo* release kinetics of hydrogels, and the application of hydrogels prepared from specific natural polymers across diverse fields.

Keywords: Green approach, Natural polymers, Hydrogel, Free radical polymerization, Biocompatibility, Eco-friendly.

Correspondence:
Dr. Muhammad Abid Mustafa
Department of Pharmaceutics, Faculty of Pharmacy, Lahore University of Biological & Applied Sciences, Lahore, PAKISTAN.
Email: abidbhatti222@gmail.com
ORCID ID: 0009-0009-2851-3047

Received: 31-12-2023;
Revised: 28-02-2024;
Accepted: 05-03-2024.

INTRODUCTION

Hydrogels are hydrophilic, three-dimensional polymeric matrixes that absorb water and resemble biological tissues. Researchers choose them for specific projects, with synthetic hydrogels offering longer service life and improved strength, while natural hydrogels are preferred for biocompatibility and biodegradability. Conventional hydrogels have low mechanical strength.[1] Polymers, made from organic sources, are versatile building blocks used in medical devices, pharmaceuticals, culinary, and cosmetic industries due to their affordability and potential biodegradability.[2] A polymer hydrogel is a network of hydrophilic polymers that can expand in water or biological fluids, holding significant amounts up to thousands, 20%, or 400 times their original weight.[3] Hydrogels can be synthesized using various natural polymers. Hydrogels can be developed through physical, chemical, or irradiation methods, with quality influenced by factors like topologies, cross-linking patterns, end densities, polymer manufacturing method, pH, temperature, and ionic strength. Some commonly used natural polymers in hydrogel synthesis include alginate, chitosan, collagen, inulin, pectin, lignin, etc. The characterization of hydrogels involves a combination of these techniques to elucidate their physical, chemical, mechanical, and biological properties, which are critical for optimizing their performance in various applications. These natural polymers offer advantages such as biocompatibility, biodegradability, and tunable properties, making them suitable for a wide range of applications in areas such as drug delivery, tissue engineering, wound healing, and regenerative medicine.[4]

OPEN ACCESS

EPUBL editing. publishing. technology

DOI: 10.5530/jyp.2024.16.26

Publishing Partner : EManuscript Tech. [www.emanuscript.in]

NATURAL POLYMERS IN HYDROGEL SYNTHESIS

Collagen

Collagen, a natural polymer, is used in hydrogels for articular cartilage strength and structure. However, its low adsorption capacity has disadvantages. Collagens are essential for tissue scaffolding, cell adhesion, malignancy, angiogenesis, and morphogenesis. Collagen bioink, a type of collagen, could revolutionize 3D printing for animal body support.[5]

Collagens are three polypeptide chains with a broadened polyproline-II shape, a straight-handed supercoil, and a residue stumble between adjacent chains. Polypeptide chains consist of a repeating triplet Gly-XY, containing glycyl residues and proline or 4-hydroxyproline, held together by interchain hydrogen bonding and encircled by organized hydration networks as shown in Figure 1. [6]

Collagen, derived from natural sources like animal tissues or recombinant protein synthesis, can be synthesized. It's primarily found in Achilles tendon, bone, and skin, with skin being the sole source for research purposes.[7] Collagen extraction removes non-collagenous material, while skin rejuvenation involves pretreatment stages like cold water bathing, skin slicing, and periodic water changes.[8]

Pectin

Superabsorbent hydrogels, made from sodium polyacrylates, are water-soluble polymers used in biotechnology and pharmaceutical industries. Pectin, a naturally occurring polysaccharide found in fruits, is considered an environmentally safe alternative to synthetic polymers. Its carboxylic group makes it suitable for drug delivery and can reduce cholesterol and serum glucose levels.[9]

Pectin, a complex compound of 17 monosaccharides with 20 linkages, is found in dicotyledons' primary cell wall and central lamella, as displayed in Figure 2. Its structure diversity is influenced by its basic structure, with the Degree of Methylation tool used.[10]

Pectin, a plant-based polysaccharide found in fruits like sunflower heads, sugar-beet, and mango waste, serves various food industry purposes and is suitable for drug delivery.[10] Thermal hydrolysis of citrus peels, lemons, limes, apple pomace, and sugar-beet plum is used for pectin extraction, but high waste and energy consumption demand green technology. [11]

Alginate Polymer

Alginate, a long-chain hydrophilic polysaccharide derived from seaweed, was first used in cuisine around 600 B.C. and refined in 1896 by Krefting. It is used in food, medicine delivery, tissue engineering, wound dressings, and more.

Alginate is a monomeric compound consisting of two units, β-(1,4)-linked d-mannuronic acid (ManAp) and α-(1,4)-linked l-guluronic acid (GulAp), with free hydroxyl and carboxyl groups forming hydrogen bonds. The structure is shown in Figure 3.[12]

Brown marine algae, treated with alkali solutions, produce alginate, a commercially available product. It is derived from various species and bacteria, including *Pseudomonas* and *Azotobacter.*[13] Alginate extraction involves proton exchange, solubilization with alkali, filtering, precipitation, drying, and milling, leaving certain cytotoxic impurities unsuitable for biomedical applications. [14]

Inulin

Inulin, a naturally occurring fructan polysaccharide from Asteraceae plants, mimics fats, acts as a low-calorie sweetener, and alters texture. It's used in pharmaceutical and food industries due to its flexible backbone and stability in the gastrointestinal tract. Inulin's solubility changes with chain length, making it suitable for colon targeting.[15]

The structure as shown in Figure 4 shows that primary constituents are (2-1) fructofuranosyl units and a terminal glycopyranose unit (1-2), making it a member of the fructans family. Insulin properties are influenced by polymerization and branching. High-performance inulin, with a DP greater than 23, forms a gel structure, alters texture, and mimics fat. Branched molecules and lower DP inulin improve flavor and are used as sucrose replacements in foods.

Fructans are found in 15% of flowering plant species, while inulin is derived from fruits, vegetables, cereals, roots, rhizomes, and bacteria, primarily found in Jerusalem and Chicory. Inulin can be obtained from various plants like dandelion roots, chicory roots, burdock roots, and dahlia bulbs. Inulin is produced through extraction and purification of chicory roots, followed by liming, carbonation, filtering, demineralization, sterilization, filtration, evaporated, and drying processes.[16]

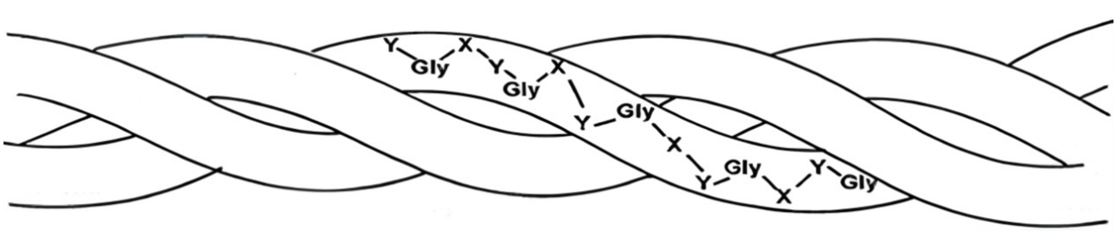

Figure 1: Structure of Collagen.

Lignin

Lignin, the second most abundant polymer, accounts for 10-30% of organic carbon in the biosphere. Found in vascular plants and angiosperms, it is a carbon and methoxyl-rich material.[17] Lignocellulosic biomass, a renewable carbon source, offers sustainable biorefinery options due to its role in plant growth, nutrient transportation, and mechanical support.

Lignin, a complex aromatic heteropolymer, consists of three monomers: p-coumaryl alcohol, guaiacyl aclochol, and sinapyl alcohol, with hardwood lignin having a lower molecular weight as shown in Figure 5. Its functional groups form linkages during biosynthesis.[18]

This led to the increase in plant size, resulting in their dominance in the terrestrial environment Lignin is a bioproduct used in pretreatment and separation processes for lignocellulosic biomasses, including pulp and second-generation ethanol production, generated by agro-industrial activities.[19] The LignoBoost process is an efficient and cost-effective method for lignin extraction from black liquor, involving CO_2 injection,

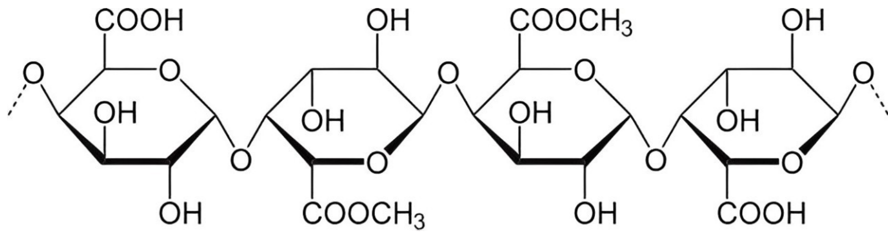

Figure 2: Structural representation of Pectin.

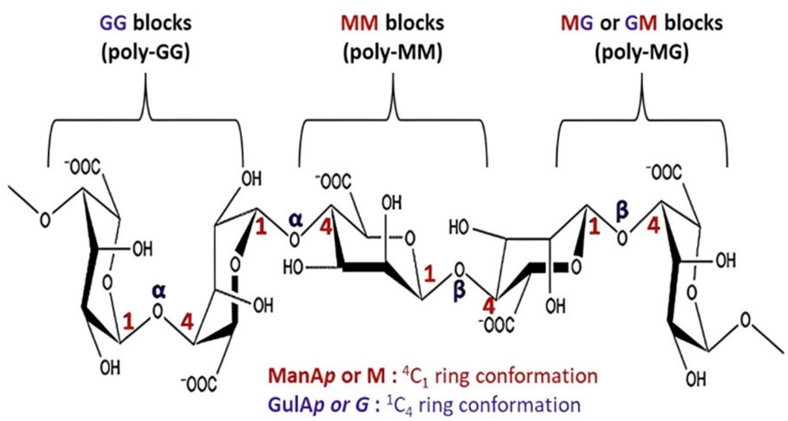

Figure 3: Chemical structure of alginate.

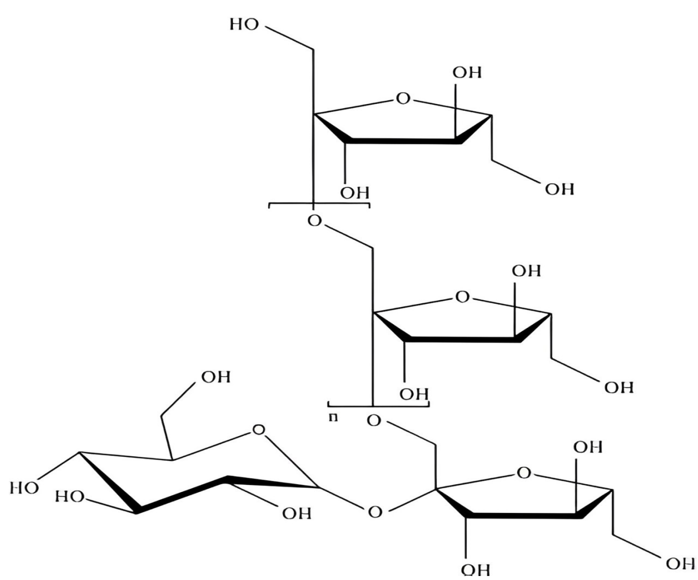

Figure 4: Inulin structure.

precipitation, filtering, acid filtration, crushing, and drying to form lignin powder, with higher pH decreases increasing precipitated yield but increasing CO_2 gas consumption and operational costs.[20]

Chitosan

Chitosan, a natural linear bio-polyaminosaccharide found in crustaceans' exoskeletons and shellfish shells, is used as a fat magnet, cheap, biodegradable, non-toxic, and ideal for hydrogel structures due to its hydrophilic nature, biodegradability, and biocompatibility.[21]

Chitosan is a random copolymer with a molar fraction of beta-(1à4)-N-acetyl-D-glucosamine and a fraction (1-DA) of beta-(1à4)-D-glucosamine, characterized by its degree of acetylation.[22] Chitin, unlike cellulose, shares an acetamide group at the carbonyl group, making it nearly identical to cellulose due to its chemical backbone. The structure is shown in Figure 6.

Chitin, a chitosan compound, is found in crustaceans, fungi, insects, and cell walls, with 15-30% content in crab cuticles, exoskeletons, and fungi cell walls.[23] Chitosan is a natural product of decomposing chitin in shells, obtained by collecting, demineralizing, washing, and de-proteinizing prawn shell waste. It forms a chitin cake when excess water is removed, then treated with NaOH.[24]

Gum Tragacanth

Researchers are developing hydrogels with high water absorption rates and enhanced wet strength for various applications, including drug entrapment, personal hygiene, agriculture, construction, food packaging, electronics, and cosmetics. Tragacanth, a water-soluble Asian gum component, is used in pharmaceuticals, cosmetics, adhesives, and more. Graining gum tragacanth with vinyl monomers produces diverse polymers with varying properties and applications.[25]

GT, a thick gel made of soluble tragacanthin and insoluble bassorin as shown in Figure 7, is diverse in quality and functional features due to the ratios of TGSW and BIW.

Tragacanth gum, a high-molecular-weight polysaccharide from Astragalus gummifer stems, is a popular natural emulsifier and thickener in food, pharmaceuticals, cosmetics, textiles, and food thickening due to its effective emulsifying abilities, long shelf life, heat stability, and pH range, as well as its water-insoluble, gel-like component, bassorin.[26]

Tragacanthin, a gel made of tragacanthic acid, arabinogalactan, and sugars, dissolves in water and forms a thick hydrosol. It contains varying amounts of fucose, glucose, galacturonic acid, galactose, xylose, arabinose, and rhamnose, with varying ratios in different species.[27] Astragalus tree wound sap is collected using tap roots with central gum cylinders, with poor-quality gum often produced due to dry conditions. The gummosis process releases soft gum and dries on the trunk using vertical, horizontal, and diagonal incision methods. Raw gum is sorted into color, ribbon, or flake morphologies.[28]

PREPARATION OF HYDROGEL BY USING NATURAL POLYMERS

Preparation of hydrogel by using collagen

The hydrolyzed collagen was dissolving, and the insoluble phosphate salt was removed. The mixture was stirred in a three-neck reactor at 80°C, supplemented with initiator solution, and then added with a weight ratio of AAM/AA and MBA.

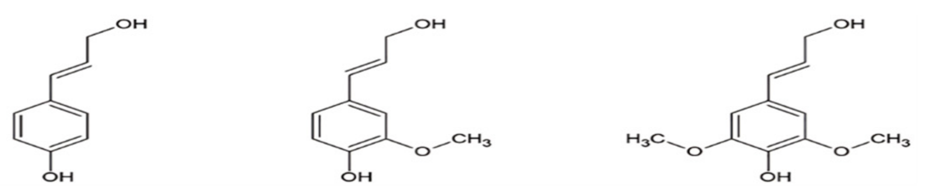

Figure 5: The three monolignols considered as building block of lignin.

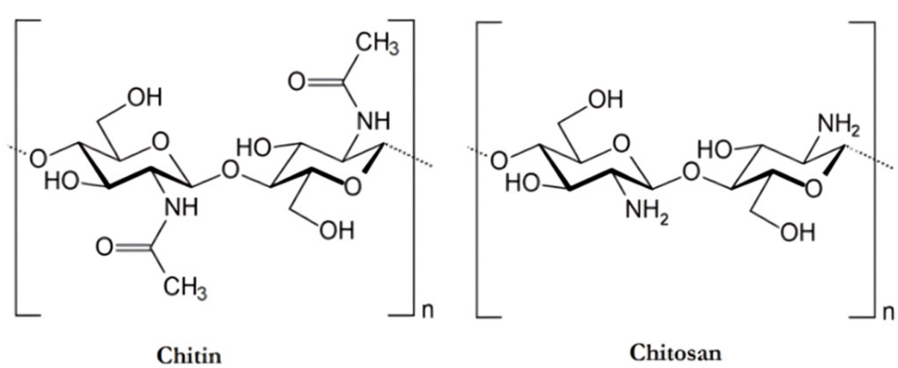

Figure 6: Chemical structure of chitin and chitosan.

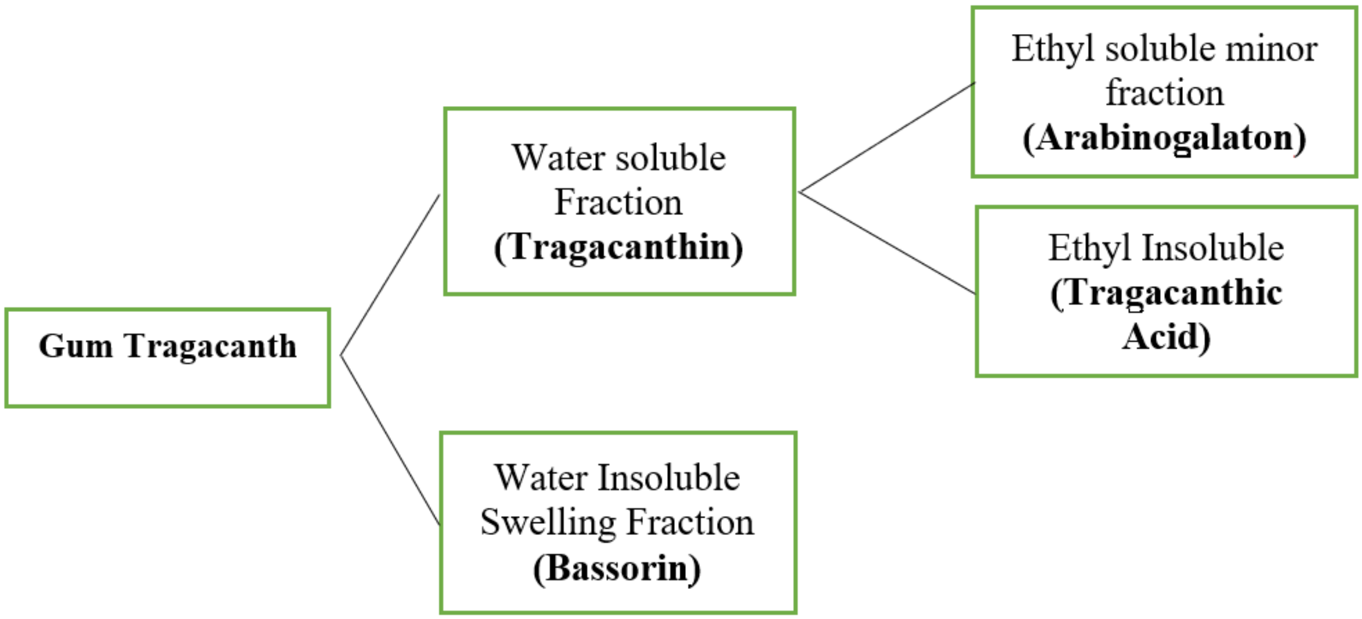

Figure 7: The precise and accurate nomenclature of the GT fraction.

After 60 min, 1 N NaOH solution was added, followed by an additional non-solvent ethanol. The mixture was stirred for 2 min to dewater, and the hydrogel was cut into small pieces. After 24 hr, the hydrogel was kept in new ethanol. The hydrogel was then baked for 10 hr at 60°C to dry.[29]

Preparation of hydrogel by using pectin

Pectin with varying esterification degrees was used for free radical polymerization to developed an adsorbent hydrogel, which was analyzed using FTIR, SEM, and XPS. The mixture of water and pectin was mixed, homogenized with glutaraldehyde and HCl, heated at 50°C for 24 hr, then diluted with NaOH and methanol. The precipitate was filtered, dried, and finely chopped to produce off-white granules, which were then screened through a 16-mesh sieve.[30]

Preparation of hydrogel by alginate polymer

Ionic crosslinking is the most effective method for creating alginate hydrogels, which can be achieved through chemical and physical crosslinking procedures. Alginate gelation and crosslinking involve the exchange of sodium ions from glucuronic acid units with divalent cations like calcium, strontium, and barium. These hydrogels have varying degrees of stability, permeability, and strength, and their mechanical properties can limit their application for long-term cell investigations. Stability depends on the exchange between monovalent cations from the environment and divalent cations from the hydrogel and is affected by alginate characteristics, concentration, source, crosslinking intensity, and molecular weight. *In vitro* stability varies, with calcium-crosslinked hydrogels losing stability in solutions containing chelators. However, in cell culture media, calcium alginate hydrogels can remain stable for weeks.[31]

Preparation of hydrogel by using inulin

The inulin hydrogel was developed by repeating units of monomer in the Inulin-Divinylsulfone Derivative (INUDV). The INUDV derivative was dissolved in Phosphate-Buffered Saline (PBS) and degassed under vacuum. The mixture was mixed and kept for 4 hr for crosslinking. After treating with acetone, a fine powder was produced, which was dried in P_2O_5 to achieve a consistent weight. The microparticles were mixed with a concentrated ethanolic solution of flutamide and stirred for three days. The sample was then washed with acetone to remove externalized flutamide.[32]

Preparation of hydrogel by using lignin

Lignin can be employed as biomass when it is immobilised inside a polymer matrix, and a physical combination is simply lignin dispersed or blended with one or more other polymers. This strategy aims to enhance the mechanical characteristics of already prepared polymeric networks by taking use of lignin's fundamental function in nature, which is to provide plants with structural strength. Nevertheless, very little research has been done on the semi-Interpenetrating Polymeric Networks (IPNs) that are so produced. For instance, in the presence of lignin, Peñaranda *et al.* used a free radical reaction to polymerize and crosslink Acrylamide (AAm) with the crosslinking agent N,N′ -methylene-bis-acrylamide (NMBA) (other combinations with starch and peat were also analysed).[33]

Preparation of hydrogel by using chitosan

One approach that is seen to be promising is the development of hydrogel using components from natural products. Using this method, Yu and colleagues produced a hydrogel for food packaging applications based on chitosan. After being well stirred to dissolve the different weight percentages of chitosan in acetic acid, the mixture was moved to a Petri dish and kept at 70°C. After being removed, the clear layer that resembled a thin film was employed for more research (Figure 1). The hydrogel film produced by this process has a thin sheet with excellent toughness and antiadhesion properties. It is based on polysaccharides and has exceptional mechanical and antiadhesion properties.[34]

Preparation of Hydrogel by using tragacanth

Gum tragacanth's active-OH group-containing arabinose units undergo graft copolymerization with acrylic acid, starting with lipase. A homogenous mixture is developed, adjusted for water absorption, and the hydrogel is extracted using water. The hydrogel is dried at 55°C.[35]

CHARACTERIZATION OF NATURAL POLYMER CONTAINING HYDROGEL

Percentage swelling

Hydrogels' water holding capacity is primarily due to hydrophilic groups in polymer chains, varying from 10% to thousands of times its weight. The % age swelling, a measure of water imbibed within a hydrogel, is crucial for biomedical applications, as it directly influences solute diffusion properties. Experimentally, it can be determined using the weight difference method.

Equation

$$\% S = Ws - \frac{Wd}{Wd} x\, 100$$

where Ws is the (weight of swollen gel) and Wd is (the weight of dry gel).[36]

Microbe penetration test

The hydrogel film is sterilized, cut into 22 cm squares, and placed on cultured tryptose soy agar. Bacteria are sprayed, and the films are incubated at 30°C for two weeks. The hydrogel film is sterilized, cut into 22 cm squares, and placed on cultured tryptose soy agar. Bacteria are sprayed, and the films are incubated at 30°C for two weeks.[37]

Biocompatibility test

A biocompatibility test is crucial for medical technology and products to ensure user safety and patient safety. Cytotoxicity assessment is essential for hydrogels used in wound dressing applications. The test involves placing the substance near host cells and incubating at 37°C or immersing it in a physiological solution. Hydrogels are sterilized, seeded with host cells, and incubated for 1 hr to promote cell growth. Microscopy or the MTT assay can be used to observe cell growth and proliferation.[38]

Bulk gel mechanical measurement

Hydrogels' network architecture allows for nutrient, compound, and cell-signaling diffusion while retaining cells as a scaffold. Crosslinking density influences diffusion properties. Evaluation methods like differential scanning calorimetry and mid-IR spectroscopy are challenging due to high water content.[39]

Chemical/Physical Analysis

Hydrogels facilitate diffusion of nutrients, compounds, and cell signals, retaining cells as a scaffold. Evaluation methods like differential scanning calorimetry and mid-IR spectroscopy are challenging due to high water content.

FTIR spectroscopy

The study uses FTIR analysis to characterize hydrogels and hybrid networks, demonstrating the effectiveness of a proposed method for creating nanostructured materials. The method uses diffuse reflectance spectroscopy (DRIFTS-FTIR) and ATR crystals, with 32 scans obtained at 2 cmK1 resolution.[40]

X-ray Diffraction (XRD)

X-ray Diffraction (XRD) is a technique used to identify a substance's crystal structure, revealing properties like crystallite dimension, orientation, and stresses. It uses monochromatic X-rays to diffract rays, calculates interplanar atomic spacing, and can characterize materials quantitatively and qualitatively. XRD can also describe semi-crystalline polymers with both amorphous and crystalline components.[41]

Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) is a technique used to analyze the morphological properties of hydrogels, enabling the detection of their microscale porosity with varying diameters. Low vacuum mode of a high-resolution scanning electron microscope allows for the identification of hydrogel surface morphology and monitoring of biological material surface topography without sputter-coating.[42]

Degradability

The study examines the biodegradability of hydrogel materials, specifically nanoemulsion-functionalized hydrogels, to determine their impact on enzyme activity, which is tested by mixing the hydrogel with a dissolved enzyme in PBS.[43]

Rheology Analysis

Scientists are using rheological attributes to characterize food-related products like yogurt as hydrogels, based on the correlation between molecular weight and zero shear viscosity in the food sector. This technique involves testing dynamic viscoelasticity in a humidity chamber at 37°C to minimize water evaporation.[44]

Thermal Analysis

Thermal analysis, thermogravimetry, and differential scanning spectroscopy are essential tools in the pharmaceutical sector for characterizing polymeric materials, understanding properties like stability and polymorphism, and ensuring product quality control. These methods reveal degradation events, particularly when produced from multiple monomers.[45]

In vitro drug release studies

Hydrogels are effective drug delivery systems for administering immunoglobulins and proteins, with *in vitro* studies frequently conducted to determine their release. The medium was diluted to 900 mL, stored at 37±0.5°C, and the desired dosage form was packed in muslin cloth and placed in a dissolution basket. A 5cm diameter, 4 cm height cylinder was used as a sample holder to place the desired dosage form, preventing it from sticking to the vessel's bottom.[46] Samples were replaced with fresh medium every hour to maintain sink conditions and maintain temperature at 37°C. The desired drug concentration was measured using a UV-vis spectrophotometer.[47] Calibration curves of desired drug was obtained for estimation of amount of released drug.

In vivo drug release studies

In vivo drug release investigations use HPLC and radioactivity measurement to determine residual drug contents. *In vivo* imaging techniques track fluorescently labeled materials' behavior, improving data quality and reducing animal requirements. A study using mice anesthetized with ketomin and xylazine found that drug release from hydrogel disks occurs due to reduced fluorescence intensity at the implantation site. Unloaded hydrogel drugs also produce fluorescence signals, indicating sustained drug entrapment in polymeric networks. The study highlights the importance of *in vivo* imaging techniques in determining drug contents and improving data quality.[48]

Kinetic Modeling

Hydrogel discs dissolve in water due to osmotic pressure gradient, swelling, and drug release. The most effective model for best release data was found to be close to 1.

The study examined drug release kinetics using various models including the 1st order model, zero order model, Higuchi model, Korsemeyer Peppas model, and Hamilton-Crowell model.[49] The Weibull model, Baker Lonsdale model, Hopfenberg model, and Gompertz model are all statistical models used to analyze data.[50]

APPLICATIONS OF NATURAL POLYMER CONTAINING HYDROGEL

Collagen-based hydrogel

In the field of treating skin injuries, collagen-based hydrogel is frequently employed.[51] Collagen-based hydrogel films, infused with metal nanoparticles like Ag and Cu, are utilized as drug delivery devices, exhibiting antibacterial properties against common bacteria.[52] The ubiquitous use of the designed collagen-based substitutes is because of the extensive distribution of collagen within all organs and tissues.[53] Collagen and doxycycline, combined for tissue recovery and bacteriostatic effects against bacteria, are expected to create a more effective local drug delivery system for treating skin infections and tooth decay.[54]

Pectin-based hydrogel

Hydrogels have various applications in drug delivery, peptides, proteins, hormones, agriculture, horticulture, biotechnology, cell construction, pharmaceuticals, and biomedical fields.[55] Composite hydrogels, made from polysaccharide biopolymers and natural pectin, enhance hemostasis properties, antibacterial activity, and degradability, while maintaining anti-inflammatory and antioxidant benefits in medicine.[56] Pectin, a structural polysaccharide derived from plant cell walls, is being utilized for skin repair and regeneration due to its water solubility, biocompatibility, biodegradability, and anionic nature. Its branching polymer offers multiple target areas for chemical modification and can degrade both *in vitro* and *in vivo*.

Alginate-based hydrogel

The success of a therapeutic factor encapsulation system is significantly influenced by the coating material, with alginate being a promising option due to its non-toxic, biocompatible, and biodegradable properties.[57] Oxidized alginate-based hydrogels, being biodegradable materials, are widely utilized in tissue engineering due to their faster degradation rate compared to native alginate.[58] The preparation of thin hydrogel films made of alginate and aloe vera gel demonstrated enhanced absorption and swelling properties.[59] Alginate and carrageenan, in various forms like beads and fibers, have shown significant potential as cell-carrier materials for tissue engineering and regenerative medicine applications.[60]

Inulin based hydrogel

Inulin, a biodegradable polysaccharide, is widely used in food and pharmaceutical industries due to its biocompatibility, non-toxicity, and adaptability, making it versatile for medical applications. Longer chain inulin is suitable for drug delivery systems due to its non-solubility at normal body temperature, while shorter chain inulin is soluble and suitable for renal function tests. Inulin, a hydrophobic domain in polymeric micelles, is utilized in the administration of hydrophobic drugs like curcumin. It contributes to pH-sensitive lysosome-triggered drug delivery systems, improves drug efficacy, and can enhance drug solubility in solid dispersion.[61]

Lignin-based hydrogels

Lignin-based hydrogels are widely used in agriculture and industry for water treatment, serving as smart biomaterials for water retention and treatment. Lignin-based hydrogels are widely used for absorption of organic and inorganic materials due to their ability to swell water, with their absorption capacity varying depending on the hydrogel's structure. Lignin-based hydrogels are widely used for controlled release of functional materials and water, extending soil retention and absorbing significant amounts for plant growth in sandy soils. Smart materials with stimuli response capabilities, such as pH, thermos, and mechanical responses, have increased potential for controlled release of drugs and pesticides.[62]

Chitosan based hydrogel

Chitosan-based hydrogels, like HemCon bandage, are widely used as homeostatic and wound dressing agents to promote wound healing. Chitosan-based hydrogels are extensively utilized in tissue engineering due to their significant impact on cell adhesion, proliferation rate, and swelling properties. Chitosan-based hydrogels are utilized for oral drug delivery to the stomach, intestine, and colon, specifically for treating inflammatory bowel disease and preventing irritability.[63]

Gum tragacanth-based hydrogel

TG is ideal for encapsulation in food processing, cosmetics, and medication manufacturing due to its non-toxic and biocompatibility properties, ensuring material protection against oxygen, light, moisture, and extreme temperatures. Industrial waste production is influenced by pollution and effluent, with plant-based chemicals like GT providing high safety, low cost, and simple processing for removing dyes and heavy metals. The soil-release capacity of an interpenetrating polymer network based on GT for spreading fertilizer across the ground, finding a progressive release profile and 79% biodegradability under burial conditions. A progressive release profile and 79% biodegradability of an interpenetrating polymer network based on GT for spreading fertilizer across the ground.[64]

CONCLUSION

This study delves into the utilization of natural polymers in hydrogel synthesis, preparation methods, and characterization. This study explores both physical and chemical cross-linked hydrogels, including their kinetic modeling, and investigates their diverse applications across various fields. Additionally, the research scrutinizes drug release studies, kinetic modeling, and the wide-ranging applications of hydrogels. By combining original research papers and review articles, the study aims to offer a comprehensive insight into hydrogels as a noteworthy drug delivery system.

ACKNOWLEDGEMENT

We would like to extend our sincere gratitude to the Deanship of the Faculty of Pharmaceutical Sciences at Lahore University of Biological & Applied Sciences (UBAS) for providing the essential resources and support that made this research possible. Their commitment to fostering academic excellence has been invaluable.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

DP: Degree of Polymerization; **B.C.:** Before Christ; **AAM:** Acrylamide; **AA:** Acrylic Acid; **MBA:** N,N'-Methylenebisacrylamide; **FTIR:** Fourier-transform Infrared Spectroscopy; **XPS:** X-ray Photoelectron Spectroscopy; **MTT:** Mean Transit Time; **HPLC:** High-performance Liquid Chromatography.

REFERENCES

1. Zhang YS, Khademhosseini A. Advances in engineering hydrogels. Science. 2017;356(6337):eaaf3627.
2. Varghese SA, Rangappa SM, Siengchin S, Parameswaranpillai J. Natural polymers and the hydrogels prepared from them, in Hydrogels based on natural polymers. Elsevier. 2020;17-47.
3. Laftah WA, Hashim S, Ibrahim AN. Polymer hydrogels: A review. Polym Plast Technol Eng. 2011;50(14):1475-86.
4. Gibas I, Janik H. Synthetic polymer hydrogels for biomedical applications. 2010.
5. https://scholar.google.com/citations?user=vYeJXigAAAAJ&hl=en&oi=sraA Sionkowska. Collagen blended with natural polymers: Recent advances and trends. Prog Polym Sci. 2021;122:101452.
6. Bella J, Liu J, Kramer R, Brodsky B, Berman HM. Conformational effects of Gly–X–Gly interruptions in the collagen triple helix. J Mol Biol. 2006;362(2):298-311.
7. Rupert Timpl, Robert W. Glanville, Hans Nowack, Hanna Wiedemann, Peter P. Fietzek, Klaus Kühn, *et al.* Isolation, chemical and electron microscopical characterization of neutral-salt-soluble type III collagen and procollagen from fetal bovine skin. 1975.
8. Omar El Blidi, Nasreddine El Omari, Abdelaali Balahbib, Rokia Ghchime, Naoual El Menyiy, Azeddine Ibrahimi, *et al.* Extraction methods, characterization and biomedical applications of collagen: A review. Biointerface Res Appl Chem. 2021;11:13587-613.
9. Mishra R, Banthia A, Majeed A. Pectin based formulations for biomedical applications: a review. Asian J Pharm Clin Res, 2012;5(4):1-7.
10. Cortés-Camargo S, Román-Guerrero A, Alpizar-Reyes E, Pérez-Alonso C. New Sources of Pectin: Extraction, Processing, and Industrial Applications, in Utilization of Pectin in the Food and Drug Industries. 2023, IntechOpen.
11. Escalante-Garcia JI, Borges PC, Duran-Herrera A. Proceedings of the 75th RILEM Annual Week 2021: Advances in Sustainable Construction Materials and Structures. Springer Nature. 2023;40.
12. https://scholar.google.com/citations?user=4bOr_SIAAAAJ&hl=en&oi=sraR Abka-Khajouei, L Tounsi, N Shahabi, AK Patel, S Abdelkafi, P Michaud. Structures, properties and applications of alginates. Mar. Drugs. 2022;20(6):364.
13. Hasnain MS, Nayak AK. Alginates in Drug Delivery. 2020: Academic Press.
14. Pawar SN, Edgar KJ. Alginate derivatization: A review of chemistry, properties and applications. Biomater Res. 2012;33(11):3279-305.
15. Afinjuomo F, Abdella S, Youssef SH, Song Y, Garg S. Inulin and its application in drug delivery. J.Pharm, 2021;14(9):855.
16. Giri S, Dutta P, Giri TK. Inulin-based carriers for colon drug targeting. J Drug Deliv Sci Technol. 2021;64:102595.
17. dos Santos Abreu H, do Nascimento AM, Maria MA. Lignin structure and wood properties. Wood Fiber Sci. 1999: p. 426-33.

18. Yao Lu, Yong-Chao Lu, Hong-Qin Hu, Feng-Jin Xie, Xian-Yong Wei, Xing Fan Structural characterization of lignin and its degradation products with spectroscopic methods. Int J Spectrosc. 2017; 2017:1-15.
19. Yu O, Kim KH. Lignin to materials: A focused review on recent novel lignin applications. Appl. Sci. 2020;10(13):4626.
20. Souza R, Gomes F, Brito E, Lelis RC. A review on lignin sources and uses. J Appl Biotechnol Bioeng. 2020;7(3):100-5.
21. Ahmadi F, Oveisi Z, Samani SM, Amoozgar Z. Chitosan based hydrogels: characteristics and pharmaceutical applications. Pharm Res. 2015;10(1):1.
22. Younes I, Rinaudo M. Chitin and chitosan preparation from marine sources. Structure, properties and applications. Mar Drugs. 2015;13(3):1133-74.
23. Pellis, A., G.M. Guebitz, G.S. Nyanhongo. Chitosan: Sources, processing and modification techniques. Gels. 2022;8(7):393.
24. Biswas, A., C. Gargi. Extraction of chitosan from prawn shell wastes and examination of its viable commercial applications. Int J Theor Appl Res Mech Eng, 2013;2(3):17-24.
25. Sharma, H.K., S. Lahkar, L.K. Nath. Formulation and *in vitro* evaluation of metformin hydrochloride loaded microspheres prepared with polysaccharide extracted from natural sources. Acta Pharm. 2013;63(2):209-22.
26. Khoylou, F., F. Naimian. Radiation synthesis of superabsorbent polyethylene oxide/ tragacanth hydrogel. Radiat. Phys Chem. 2009;78(3):195-8.
27. Balaghi, S., M.A. Mohammadifar, A. Zargaraan, H.A. Gavlighi, M. Mohammadi. Compositional analysis and rheological characterization of gum tragacanth exudates from six species of Iranian Astragalus. Food Hydrocoll. 2011;25(7):1775-84.
28. Boamah, P.O., N.A. Afoakwah, J. Onumah, E.D. Osei, G.K. Mahunu. Physicochemical properties, biological properties and applications of gum tragacanth-A review. Carbohydr Polym. 2023: p. 100288.
29. Pourjavadi, A., M. Kurdtabar. Collagen-based highly porous hydrogel without any porogen: Synthesis and characteristics. Eur Polym J. 2007;43(3):877-89.
30. Mishra, R.K., M. Datt, K. Pal, A. Banthia. Preparation and characterization of amidated pectin based hydrogels for drug delivery system. J Mater Sci.: Materials in Medicine, 2008;19:2275-80.
31. Bidarra, S.J., C.C. Barrias, P.L. Granja. Injectable alginate hydrogels for cell delivery in tissue engineering. Acta Biomater. 2014;10(4):1646-62.
32. https://onlinelibrary.wiley.com/authored-by/Pitarresi/GiovannaGiovanna Pitarresi, Daniela Triolo, Mario Giorgi, Calogero Fiorica, Filippo Calascibetta, Gaetano Giammona. Inulin-Based Hydrogel for Oral Delivery of Flutamide: Preparation, Characterization, and *in vivo* Release Studies. Macromol Biosci. 2012;12(6):770-8.
33. Diana Rico-García, Leire Ruiz-Rubio, Leyre Pérez-Alvarez, Saira L. Hernández-Olmos, Guillermo L. Guerrero-Ramírez, José Luis Vilas-Vilela. Lignin-based hydrogels: Synthesis and applications. Polym. 2020;12(1):81.
34. H. Nagahama, H. Maeda, T. Kashiki, R. Jayakumar, T. Furuike, H. Tamura. Preparation and characterization of novel chitosan/gelatin membranes using chitosan hydrogel. Carbohydr Polym. 2009;76(2):255-60.
35. Saruchi, B.S. Kaith, R. Jindal, G. Kapur. Enzyme-based green approach for the synthesis of gum tragacanth and acrylic acid cross-linked hydrogel: its utilization in controlled fertilizer release and enhancement of water-holding capacity of soil. Iran Polym J. 2013;22:561-70.
36. Das, S., V. Kumar, R. Tiwari, L. Singh, S. Singh. Recent advances in hydrogels for biomedical applications. Asian J Pharm Clin Res. 2018;11:62-8.
37. Tomić, S.L., M.M. Mićić, S.N. Dobić, J.M. Filipović, E.H. Suljovrujić. Smart poly (2-hydroxyethyl methacrylate/itaconic acid) hydrogels for biomedical application. Radiat Phys Chem. 2010;79(5):643-9.
38. Nuno Alexandre, Jorge Ribeiro, Andrea Gartner, Tiago Pereira, Irina Amorim, Joao Fragoso, *et al.* Biocompatibility and hemocompatibility of polyvinyl alcohol hydrogel used for vascular grafting—*In vitro* and *in vivo* studies. J. Biomed. Mater. Res., 2014;102(12):4262-75.
39. Kloxin, A.M., C.J. Kloxin, C.N. Bowman, K.S. Anseth. Mechanical properties of cellularly responsive hydrogels and their experimental determination. Adv. Mater, 2010;22(31):3484-94.
40. Mansour, L.M., B.M. Taj, M. Mokhtari. Synthesis and swelling characterization of cross-linked PVP/PVA hydrogels. 2005.
41. JONES, J.R.Scaffolds for tissue engineering, in Biomaterials, artificial organs and tissue engineering., Elsevier, 2005, p. 201-14.
42. Kamel Rahali, Ghazi Ben Messaoud, Cyril J.F. Kahn, Laura Sanchez-Gonzalez, Mouna Kaci, Franck Cleymand., *et al.* Synthesis and characterization of nanofunctionalized gelatin methacrylate hydrogels. Int. J. Mol. Sci., 2017;18(12):2675.
43. R. Kadri, G. Ben Messaoud, A. Tamayol, B. Aliakbarian, H. Y. Zhang, M. Hasan, *et al.* Preparation and characterization of nanofunctionalized alginate/methacrylated gelatin hybrid hydrogels. RSC Adv., 2016;6(33):27879-84.
44. Zuidema, J.M., C.J. Rivet, R.J. Gilbert, F.A. Morrison. A protocol for rheological characterization of hydrogels for tissue engineering strategies. J. Biomed. Mater. Res. Part B:ACS Appl. Bio Mater, 2014;102(5):1063-73.
45. Khalid, M., F. Agnely, N. Yagoubi, J. Grossiord, G. Couarraze. Water state characterization, swelling behavior, thermal and mechanical properties of chitosan based networks. Eur. J. Pharm. Sci., 2002;15(5):425-32.
46. Lamberti, G., I. Galdi, A.A. Barba. Controlled release from hydrogel-based solid matrices. A model accounting for water up-take, swelling and erosion. Int. J. Pharm., 2011;407(1-2):78-86.
47. Ekenna, I.C., S.O. Abali. Comparison of the Use of Kinetic Model Plots and DD Solver Software to Evaluate the Drug Release from Griseofulvin Tablets. JDDT, 2022; 12(2-S):5-13.
48. Tulain, U.R., M. Ahmad, A. Rashid, M.Z. Malik, F.M. Iqbal. Fabrication of Ph-responsive hydrogel and its *in vitro* and *in vivo* evaluation. Adv. Polym. Technol., 2018;37(1):290-304.
49. Sadia Ata, Atta Rasool, Atif Islam, Ismat Bibi, Muhammad Rizwan, Muhammad Khalid Azeem, *et al.* Loading of Cefixime to pH sensitive chitosan based hydrogel and investigation of controlled release kinetics. Int. J. Biol. Macromol., 2020;155:1236-44.
50. Dash, S., P.N. Murthy, L. Nath, P. Chowdhury. Kinetic modeling on drug release from controlled drug delivery systems. Acta Pol Pharm, 2010;67(3):217-23.
51. Yuan Zhang, Yong Wang, Ying Li, Yunpeng Yang, Mingyuan Jin Application of Collagen-Based Hydrogel in Skin Wound Healing. Gels, 2023;9(3):185.
52. Sahiner, M., D. Alpaslan, B.O. Bitlisli.Collagen-based hydrogel films as drug-delivery devices with antimicrobial properties. Polym. Bull., 2014;71:3017-33.
53. Sorina Dinescu, Madalina Albu Kaya, Leona Chitoiu, Simona Ignat, Durmus Alpaslan Kaya, Marieta Costache. Collagen-based hydrogels and their applications for tissue engineering and regenerative medicine. Polym. Compos. A Reference Series. Cham: Springer, 2019;10:978-3.
54. Mădălina Georgiana, A., M.V. Ghica, P. Lăcramioara, M. Leca, V. Trandafir. Kinetics of *in vitro* release of doxycycline hyclate from collagen hydrogels. Rev. Roum. Chim., 2009;54(5):373-9.
55. Ullah, F., M.B.H. Othman, F. Javed, Z. Ahmad, H.M. Akil. Classification, processing and application of hydrogels: A review. Adv. Eng. Mater.: C, 2015;57:414-33.
56. Sunghwan Kim, Jie Chen, Tiejun Cheng, Asta Gindulyte, Jia He, Siqian He, *et al.* PubChem in 2021: new data content and improved web interfaces. Nucleic Acids Res., 2021;49(D1):D1388-95.
57. Reig-Vano, B., B. Tylkowski, X. Montané, M. Giamberini. Alginate-based hydrogels for cancer therapy and research. Int. J. Biol. Macromol., 2021;170:424-36.
58. Reakasame, S., A.R. Boccaccini. Oxidized alginate-based hydrogels for tissue engineering applications: a review. BMMJ, 2018;19(1):3-21.
59. Kurakula, M., G.K. Rao, V. Kiran, M.S. Hasnain, A.K. Nayak. Alginate-based hydrogel systems for drug releasing in wound healing, in Alginates in Drug Delivery. Elsevier. 2020, p. 323-58.
60. Popa, E.G., M.E. Gomes, R.L. Reis. Cell delivery systems using alginate–carrageenan hydrogel beads and fibers for regenerative medicine applications. BMMJ. 2011;12(11):3952-61.
61. Kirtania, M.D., N. Kahali, A. Maity. Inulin-based hydrogel, in Plant and algal hydrogels for drug delivery and regenerative medicine. Elsevier. 2021, p. 261-92.
62. Meng, Y., J. Lu, Y. Cheng, Q. Li, H. Wang. Lignin-based hydrogels: A review of preparation, properties, and application. Int. J. Biol. Macromol., 2019;135:1006-19.
63. Shariatinia, Z., A.M. Jalali. Chitosan-based hydrogels: Preparation, properties and applications. Int. J. Biol. Macromol., 2018;115:194-220.
64. Zare, E.N., P. Makvandi, F.R. Tay. Recent progress in the industrial and biomedical applications of tragacanth gum: A review. Carbohydr. Polym., 2019;212:450-67.

Cite this article: Mustafa MA, Rasheed N, Ansar S, Zahid Q, Arshad S, Yousra, *et al*. Green Fabrication Approach to Hydrogel Synthesis by using Natural Polymers, their Characterization, and Applications. J Young Pharm. 2024;16(2):195-203.