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DESIGN GUIDELINES FOR HYDROGELS MADE FROM PLANTS: AN OVERVIEW

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ABSTRACT

A class of polymeric materials known as hydrogel products can retain a lot of water in its three-dimensional networks due to its hydrophilic structure. It is thought to be crucial to use these products extensively in a variety of industrial and environmental application areas. Hydrogel applications adhere to logical structure and functional design by modifying its physicochemical properties (e.g., stiffness, pore size, viscoelasticity, microarchitecture, degradability, ligand presentation, stimulus-responsive properties, etc.) through material engineering. Numerous groundbreaking studies have been conducted in the last few decades to investigate the interactions between cells and hydrogel matrixes and determine the underlying mechanisms, opening the door for translating hydrogel-based therapies from the lab to the clinic. To date, hydrogels have significantly influenced a variety of biomedical fields, including drug screening, tissue engineering, cancer treatment, and cosmetic medicine. The in-depth understanding of how cells respond to the physicochemical and structural characteristics of the hydrogel matrix in terms of behavior and signal transmission helps to enhance material approaches to better regulate cell destiny and biology for desired needs. Generally speaking, the cell would take in material cues from its surroundings and convert them into intracellular biochemical signals that might affect viability, gene expression, and cell lineage commitment. Importantly, to better replicate the intricate native matrix, researchers focus on a broader variety of hydrogel characteristics and dimensions, including three-dimensionality, hydrogel architecture, degradability, and dynamic properties.

This helps to expand and deepen our understanding of how hydrogel physiochemical, mechanical, and structural cues control the phenotype, function, and fate of cells. The clinic transitioning of hydrogel therapeutics is currently limited due to unexpected side effects and issues as well as improper administration strategies, despite the exciting and significant advancements in hydrogel design. These challenges can be addressed by material optimization when a material library has been created and screened.

Keywords: Hydrogel, Hydrophilic, Biomedical Domains, Complex Native Matrix.

I. INTRODUCTION

Hydrogels, also called aqua gels, are a class of soft, wet materials with low volume fraction that consist of three-dimensional porous networks of polymer molecules, fibers, or particles. The dispersion medium in these materials is water or an aqueous phase. Because of their unique three-dimensional crosslinked polymer meshwork structure, hydrogels have a propensity to hold onto a significant amount of water in their interstices and continue to connect it while keeping the network structure inflated. The presence of polar hydrophilic moieties, such as SO_3H, OH, NH_2, COOH, $CONH_2$, etc., along the polymer network as branching groups, explains the presentation of such phenomena in hydrogels. The tendency of hydrogels to absorb water is caused by their swelling character, which is seen by the crosslinked bonding strength, the hydrophilicity of the attached groups, and the swelling medium. In addition to regulating water absorption, crosslinking aids in preserving the network structure when it is swollen. Crosslinkers are essential for secondary interactions with biological tissues, as well as for hydrophilic groups' involvement in water uptake. Hydrogels are essential in biomedical applications because of their unique qualities, which include superabsorbancy, hydrophilicity, biodegradability, biocompatibility, viscoelasticity, softness, and fluffiness. In addition, hydrogels react to a wide range of stimuli, including ionic strength, temperature, electric and magnetic fields, and biological molecules. Hydrogels can be shaped and sized to nearly any desired shape. There are characteristics in hydrogels with lengths ranging from sub-nanometers to centimeters. Based on their diameters, hydrogels can be broadly divided into three groups: macrogels, which are hydrogels that range in size from millimeters to centimeters and take the shape of

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columns, spheres, porous sponges, matrices, films, and fibers; microgels; and nanogels. Hydrogels' various sizes and shapes, or their multiscale features, can result in a wide range of applications and even entirely distinct functional traits. Certain limitations were revealed by hydrogels, including fatigue and cracking under prolonged load and exposure to harsh climatic conditions. These restrictions are ascribed to the hydrogel network's architecture and chemical makeup. Double crosslinked networks can be created to get around these restrictions. Low conductivity might occasionally present an unforeseen difficulty when using hydrogels in real-time applications. Because conducting elements like nanofillers have a higher surface area and work in concert with other components to produce hybrid hydrogel networks, they can reinforce the conductivity, mechanical strength, and optoelectronic properties of hydrogels. Conducting polymers, metal oxide, sulfide, phosphate, carbon nanotubes, carbon dots, and graphene are examples of nanofillers that are utilized to increase conductivity. Numerous industries have found extensive use for hydrogels: drug delivery systems, agriculture, pharmaceuticals, diagnostics, bio-medication, wound healing, biosensors, food industry, hygienic products, microelectronics industry, electrode production, optoelectronic and photovoltaic devices, environmental science, cosmetics, etc.[1, 2. 3, 4]

II. PLANT EXTRACTS FOR HYDROGEL PREPARATION

Saurabh Kulshrestha et al. (2022) evaluated the efficacy of formulated wound-healing hydrogel based on 5% and 10% hydroalcoholic extract of Moringa oleifera seeds. The DPPH method was used to study in vitro antioxidant activity, while the agar well diffusion method was used to study antimicrobial activity. Povidone-iodine (5%) was used as the standard. Using excision and incision wound models, the wound healing efficiency of a hydrogel formulation was investigated. In the excision model, assessments were conducted on days 1, 4, 6, 9, 12, 13, and 14; in the incision model, they were conducted on day 8. To bolster the findings, histopathological evaluations were also conducted. The hydroalcoholic extract showed the minimum zone of inhibition (mm) of 11.167±0.235 against P. aeruginosa, 16.167±0.235 against S. aureus, and 18.233±0.205 against E. coli proving to be a potent agent for wound healing by inhibiting the microorganisms. In excision wounds, the hydrogels that were created utilizing the shown noteworthy wound healing activity when compared to the control group and the conventional treatment group up until the thirteenth day. The topical use of prepared hydrogel considerably enhanced the breaking strength in the incision model. Furthermore, a histopathological analysis explained the favorable outcomes.[5]

Xiangyu Zhang et al. (2021) reported rose bengal/graphene oxide/PVA hybrid hydrogel with enhanced mechanical properties and light-triggered antibacterial activity for wound treatment. A modified graphene oxide network (β-GO) and a mixed polyvinyl alcohol (PVA) solution of rose bengal (RB) encapsulated with chitosan microspheres (CM) are frozen and thawed to create graphene oxide/rose bengal/polyvinyl alcohol hybrid hydrogel (β-GO/RB/PVA HD). A thorough assessment is conducted on the mechanical characteristics and light-induced antibacterial efficacy of hydrogel. The PVA porosity structure allows the β-GO inorganic network to interpenetrate, significantly improving the mechanical properties of the hydrogel. According to the in vitro and in vivo tests, the combination of β-GO hyperthermia caused by 808 nm light irradiation and RB's production of reactive oxygen species (ROS) under 550 nm light irradiation results in excellent antibacterial activity against S. aureus and E. coli using the spread plate method. using the spread plate method. that requires only 10 minutes of irradiation. β-GO/RB/PVA HD, on the other hand, demonstrates remarkable water-absorbing efficiency and biocompatibility. More crucially, the hybrid hydrogel can greatly speed up wound healing that is aided by bacteria. The outcomes showed that the hybrid hydrogel might make a good wound dressing to stop bacterial infections.[6]

Nair VV et al. (2019) investigated Azadirachta indica extract microbeads using a hydrogel system for wound healing. Polyionic complexation, the medication, and polymers were mixed to create the microbeads. Pharmaceutical criteria, including solubility, drug release, water holding capacity, percentage of drug entrapped, bead diameter measurement, and antimicrobial work against Staphylococcus aureus, were assessed for the formulation. The optimized batch evaluation revealed a drug entrapment percentage of 5.61%, drug release of 65.688% in phosphate buffer pH 8 in 5 hours, and water absorption of 80%. These results were comparable to the solutions produced by the DX7 Statease program, a design expert. This implied the validation of the optimization model. The improved batch's microbeads were about 80 µm in diameter. β-GO/RB/PVA HD, on the other hand, demonstrates exceptional water-absorbing ability and biocompatibility. What's more, the hybrid

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hydrogel can greatly quicken wound healing that is aided by bacteria. According to the findings, the hybrid hydrogel shows promise as a wound dressing that can stop bacterial infections.[7]

Judyta Cielecka-Piontek et al. (2022) evaluated Hydrogel from Lyophilisates of the Aloe arborescens Aqueous Extract. The gel preparation generated from the aqueous lyophilised extracts of A. arborescens leaves did not change the composition of aloins A and aloenin A content. Using DPPH and CUPRAC methods, the lyophilisate ability was investigated to counteract free radicals, and the findings confirmed its anti-radical properties. It was carried out to check for enzyme inhibition since their hyperactivity is linked to unfavorable pro-inflammatory skin alterations. Crucially, it was demonstrated that certain extract components might potentially penetrate the skin utilizing the PAMPA SKIN model. Following that, two formulations based on hydroxypropyl methylcellulose (HPMC) and sodium alginate were created, and the hydrogels were characterized using rheological analysis, drug release profiles, permeability, and stability investigations. The hydrogel based on HPMC exhibited a more stable and tailored release of active ingredients. Based on "green technology," the hydrogel matrices appear to be a potential therapy option for surface damage caused by inflammation at the extraction and drug form development stages for topical administration.[8]

David Julian McClements et al. (2016) reported the encapsulation of curcumin in polysaccharide-based hydrogel beads. Three distinct delivery strategies were used to incorporate curcumin: lipid-loaded carrageenan beads, lipid-loaded alginate beads, and free lipid droplets. Alginate or carrageenan polysaccharides were used to create hydrogel beads by combining an injection process with potassium or calcium ion gelation, respectively. The mouth, stomach, and small intestine phases of a simulated gastrointestinal tract (GIT) were traversed by the delivery systems. Carrageenan beads' rather brittle structure was revealed by light scattering and microscopy to be readily broken down in the GIT, releasing the curcumin and containing lipid droplets. On the other hand, the lipid droplets and curcumin were maintained by alginate beads, which exhibited a strong structure that held up well throughout the GIT. The following was the decline in the pace and amount of lipid digestion: alginate beads, carrageenan beads, and free lipid droplets. Similar trends were seen in the sequence of curcumin bioaccessibility: free lipid droplets (73%) > carrageenan beads (33%) > alginate beads (16%). These findings imply that lipase digestion is necessary for the release of the curcumin that has been encapsulated and the development of mixed micelles capable of dissolving the curcumin that has been released.[9]

Nidhi Chaurasiya et al. (2014) reported Formulation and Evaluation Of Herbal Hydro Gel From Hibiscus rosa-sinensis. The formulation's physical characteristics—such as viscosity, color, appearance, pH, spreadability, and skin irritation—were compared. 20% of the three created formulations were determined to be more successful in terms of spreadibility, viscosity, and other criteria. The findings suggested that the formulations made with gel in cooperation had good visual quality since there was no sedimentation. There was no evidence of lump development, indicating that the preparation was transparent and clear with a homogeneous mass. It was discovered that the spreadibility and viscosity were within the ranges recommended by common pharmacopeias. As a result, these preparations made using herbal medications are less expensive than the products that are sold commercially. In the comparison with the other two formulations (10 and 30%), certain factors such as pH and viscosity did not have as much relevance.[10]

Baodong Zhu et al. (2016) investigated multi-responsive hydrogel based on lotus root starch. The hydrogel made of lotus root starch was created by the process of free radical copolymerization in the presence of initiator $K_2S_2O_8$ and crosslinker MBA. It was shown by Fourier Transform Infrared Spectroscopy (FTIR) that the target product was formed. The analysis of X-ray diffraction (XRD) revealed the modification of starch crystallization. A field emission scanning electron microscope (FESEM) and a biomicroscope were used to evaluate the hydrogel's pore structure and form. The higher heat stability of hydrogel was confirmed by thermogravimetric measurement. Additionally, the swelling in solutions containing $CaCl_2$ and $AlCl_3$ at temperatures When the swelling duration was prolonged, the "overshooting phenomenon" swelling-deswelling events were seen between 25 and 65°C. Furthermore, the hydrogel reacts rapidly to varying pH levels.[11]

Mohamed Gomaa et al. (2023) reported macroalgal-derived alginate/wastepaper hydrogel to alleviate sunflower drought stress. To support sunflower growth under mild (75% FC) and high (50% FC) water deficiency stress, the hydrogel was created and tested as a soil additive. Wastepaper and alginate made from brown algae were used to construct the hydrogel. The hydrogel swelled quickly in water and followed pseudo-

first-order dynamics. Furthermore, it improved the soil's water-holding capacity, presented excellent phosphate adsorption in the soil (37 mg PO4− g−1 hydrogel after 6 days), and after 20 days, over 67% of the adsorbed phosphate had desorbed. As a result, after four episodes of over-irrigation, the phosphate leaching from the hydrogel-amended soil decreased to 2.77 mg in a column experiment, compared to 11.91 mg in the hydrogel-free soil. When hydrogel was applied under the same circumstances as the no-hydrogel treatments, several root parameters increased, such as fresh and dry biomass, area, and length by >2-, >1.6-, >1.35, and >1.3-folds under both water regimes. Moreover, the sunflower shoots showed proline concentrations that were comparable to the well-watered control (100% FC), with a reduction of more than 50% when compared to the plants that were stressed by dryness in the same circumstances. Malondialdehyde concentrations were also decreased by more than 15%. The examination of the antioxidant enzymes also revealed a significant decrease in the specific activity of ascorbate peroxidase and catalase at 75 and 50% FC in comparison to the corresponding controls. Furthermore, the hydrogel encouraged sunflower roots to absorb phosphate. These findings suggested that the biodegradable hydrogel that was developed could be effectively added to soil to help crops that are stressed by drought.[12]

Jaiganesh Ramamurthy et al. (2023) investigated the Formulation and evaluation of Ocimum sanctum containing carboxymethylcellulose and sorbitol-based hydrogel. Atomic force microscopy was used to analyze the formulation surface and assess its swelling index, contact angle, and in vitro release characteristics. According to the swelling index, weight increased significantly between the first and 84th hours, by 11.1% and 15.8%, respectively. The results of the contact angle test were 72.81° and 75.99°, respectively. Drug release in vitro exhibited a burst release until day six and a steady release until day twenty. By using atomic force microscopy, the hydrogel matrix's surface topography was found to be uniformly smooth and 51µm in diameter, indicating that the particles are evenly distributed throughout. According to data, a hydrogel comprising sorbitol, carboxymethyl cellulose, and extract from Ocimum sanctum could be a cost-effective, natural, non-toxic steroid replacement that is designed for clinical use.[13]

Zhi Qin Zhou et al. (2014) reported the Sodium hydroxide-mediated hydrogel of citrus pectin for the preparation of fluorescent carbon dots for bioimaging. In addition to lowering the hydrothermal reaction's temperature to 100 °C, the addition of hydrogel can prevent visibly carbonized precipitates from forming throughout the synthesis process, even at temperatures as high as 180 °C. The as-synthesized CDs have an average size of 2.7 nm, are widely distributed in water, and exhibit good biocompatibility and cyan fluorescence. Moreover, the CDs may serve as a possible fluorescent probe for imaging cells. Citrus pectin offers a new strategy for the effective future use of citrus germplasm as a non-toxic carbonaceous precursor for the creation of luminous CDs.[14]

Yan Zhao et al. (2020) evaluated injectable Blueberry anthocyanins-loaded hydrogel based on carboxymethyl chitosan and oxidized hyaluronic acid for promoting full-thickness wound healing. The hydrogel mechanical characteristics and gelation kinetics were examined. The hydrogel's mechanical properties (76.0 kPa compression stress at the strain of 80%) and appropriate gelation time (~70 s) were attributed to oxidized hyaluronic acid with an oxidation degree of 38.1%. In a full-thickness skin wound model in rats, the injectable Blueberry anthocyanins (BA)-loaded hydrogel dramatically sped up the healing process, encouraged tissue and epithelial regeneration, reduced inflammation, and encouraged collagen deposition and angiogenesis. Furthermore, the hydrogel has the potential to increase the expression of VEGF and IL-10 proteins, decrease NF-κB activity, and facilitate the transition of macrophages from M1 to M2 phenotype. The biological effects of BA-loaded hydrogel, such as its anti-inflammatory and antioxidant properties, and its ability to regulate several variables associated with wound healing, are primarily responsible for the hydrogel's stimulation of wound healing.[15]

Kai Liu et al. (2018) investigated ultra-flex Self-Healing Guar Gum-Glycerol Hydrogel with Injectable, Antifreeze, and Strain-Sensitive Properties. A compact three-dimensional dynamic cross-linked net composed of glycerol, water, and borax was developed by chelation cross-linking between glycerol and borax, which was motivated by the strong hydrogen bonding between glycerol and water. The dynamic interactions between the glycerol, water, and borax net under stress serve as sacrificial bond energy for efficient dissipation, allowing the hydrogel to attain excellent stretchability, injectability, and flexibility. More significantly, the gel's moisturizing and antifreeze qualities are enhanced by the glycerol content. Additionally, the hydrogel demonstrated an

incredibly quick 15-second self-healing time. The outcomes also demonstrate the hydrogel's strain sensitivity and self-adhesive qualities. The hydrogels could be utilized to create flexible, wearable, and 3D-printable electronic skin and strain-sensitive sensors.[16]

Bernal-Chávez et al. (2023) evaluated unique cationic guar gum hydrogel made of crosslinked poly (ethylene oxide) that is ultra-stretchable and self-healing. It investigated how adding PolyOX [poly (ethylene oxide)] affected the mechanical properties and the connection to cationic guar gum for potential tissue engineering applications. Variations in pH and PolyOX concentrations have an impact on the mechanical properties of cationic guar gum hydrogels. Through optimization studies, a unique hydrogel that was 33 times more extensible than the hydrogel before it was stretched was prepared. It was semi-crystalline, extremely stretchable, and had an extensibility area of about 400 cm^2. In addition, the hydrogel demonstrated a viscosity of 153,347±4,662 cP and a recovery of 96.8% during the self-healing process. As a result, this unique hydrogel demonstrated ideal mechanical and chemical qualities and may find use in a variety of fields, including tissue engineering, medication delivery, and food storage.[17]

Sung Soo Han et al. (2022) reported the Effect of Grape Seed Extract (proanthocyanidins, PC) on the physicochemical and biological functions (bovine satellite muscle cell (BSC) growth and adhesion) of an edible gelatin (GL)-based hydrogel for Cultured Meat Application. The freeze-dried hydrogels with pore diameters ranging from 100 to 300 μm showed good compressive properties. BSCs were able to proliferate and adhere to GL-PC hydrogels with pores. These investigations revealed that the produced hydrogels Muscle cell growth for applications involving cultured meat may be facilitated by the use of edible components produced utilizing an inexpensive technique.[18]

Gianluca Viscusi et al. (2022) reported the Encapsulation of Vitis vinifera Pomace Polyphenols in Soybean Extract-Based Hydrogel Beads as Carriers of Polyphenols and pH-Monitoring Devices. Before the Lambrusco extract was encapsulated in hydrogels made from soybean extract using an ionotropic gelation technique, its phenolic profile and total anthocyanin concentration were evaluated. According to their first results, 5% grape pomace powder in water is the point at which polyphenol extractability reaches saturation. Various groups of phenols, soluble acids (cutaric acid, caftaric acid, and gallic acid), flavonols (catechin and epicatechin), flavanols (quercetin, rutin, quercetin 3-glucosilate, and kaempferol 3-glucosilate), and anthocyanins were identified in this aqueous extract. The extremely dispersed profiles of the SBs suggest that they are rougher than the LSBs, however, the SEM micrograph shows that the LSB surfaces are more uniform with some sharp peaks that belong to the combe-like structure. The analysis of Ra and RMS parameters supports this conclusion. The LSBs have an RMS of 137.1 and a Ra of 113.9, whereas the SBs have an RMS of 152.0 and an RMS of 170.6. In neutral and acidic media, no discernible variations were found. At pH = 2, SBs absorbed water up to SD = 32%, whereas after 4 hours, LSBs experienced a swelling phenomenon up to 28%. Subsequently, the erosion and dissolving processes caused the polymeric matrix to dissolve, resulting in a deswelling phenomenon that showed a weight drop of up to 14% and seemed to be rather stable over time. Therefore, the swelling behavior of beads based on soybean extract was not significantly affected by the presence of Lambrusco extract. Before they experienced deswelling, swelling up to 34% and 32% for SBs and LSBs, respectively, was confirmed in neutral conditions (pH = 7). Finally, an entirely new behavior was found under basic circumstances (pH = 12). The rate of water absorption spiked for brief periods before leveling down. Hydrogen bonds were broken when pH rose, converting -COOH groups into -COO- groups. Acidic amino acids (Glu, pKa = 4.25; Asp, pKa = 3.86) also underwent total ionization. The hydrogel swells more as a result of the electrostatic repulsions present in the test hydrogel beads. As previously stated, the first modest burst release for pH = 2 (10%) and pH = 7 (11%) is thought to be associated with the free functional substances following the gradual increase in volume caused by the swelling phenomena. A noticeable increase in the amount released is seen after 7 hours, and after 24 hours, the amount reaches a plateau regime, releasing 50% at pH = 2 and 65% at pH = 7. There is a noticeable difference in the release in the pH = 12 medium. Increased electrostatic repulsions between the negative charges of the carboxylic groups cause chain relaxation and gel expansion. Thus, after seven hours, a high burst release was seen, with a release of almost 60%. It is possible to relate the 1/A1 and 1/A2 ratios to the kinetic constants of the relaxation and diffusion processes, respectively. Therefore, the kinetic constants for pH = 2 and pH = 7 are quite close, while the 1/A1 ratio for pH = 12 is relatively low, indicating that relaxation phenomena—rather than diffusion ones—are the primary mechanism of release (97.8%). In addition, the 1/A2 ratio exhibits

a trend in opposition, with a greater release constant for basic medium release. The extremely negative value of b1 for pH = 12 further supports this claim by helping to make the diffusion process extremely insignificant.[19]

Cheng-wei Wu et al. (2019) evaluated Onion-structure bionic hydrogel capsules based on chitosan for regulating doxorubicin (DOX) release. The process of ionotropic crosslinking is used to create the bionic multilayer hydrogel capsules. The dense cuticular membranes of the hydrogel capsules can limit the migration and diffusion of DOX, and when compared to monolayer hydrogel capsules, multilayer hydrogel capsules can substantially homogenize the distribution of DOX and suppress the concentration gradient of DOX between the outermost hydrogel layer and the external environment. Consequently, it is possible to significantly block the burst release of DOX. Additionally, the bionic multilayer hydrogel capsules show good biocompatibility to human epidermal keratinocyte (HaCaT) cells and pH sensitivity.[20]

III. CONCLUSION

Numerous hydrogel-based networks have been developed recently to satisfy the demands of various applications. One of these advantages is their capacity to swell in an aqueous solution. The review that is being presented shows the literature that covers the many classifications of hydrogels, the physical and chemical properties of these materials, and the technological viability of using them. It also included block diagrams, ideal preparation conditions, technologies used to produce hydrogels, and the consequences for process design. A detailed presentation of a newly developed category of hydrogel materials from recent generations was also given. Super-porous hydrogels are novel materials that swell quickly to enormous sizes, regardless of their initial size. It is possible to conclude that batch or semi-batch reactors are appropriate reactors for polymerization operations based on the literature review. Temperature, pressure, batch cycle time, reactant volume, and feed addition technique are the variables that affect batch reactors. For a given batch reactor system, optimization variables like reactant amount and batch cycle duration are continuous variables with fixed values that are primarily dependent on material and energy balance. Three types of impellers are known to work well in high viscosity ranges: double ribbon mixer, screw mixer with four baffles, and ribbon mixer with a screw around the axis.

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