REVIEW ARTICLE

Recent Advances in Hydrogel Drug Delivery Systems: Innovations and Applications

Sonwane SM, Ingle RG*

Datta Meghe College of Pharmacy, Datta Meghe Institute of Higher Education & Research (DMIHER), Deemed to be University, Sawangi (M), Wardha (India).

Received: 11th Aug, 2024; Revised: 15th Sep, 2024; Accepted: 8th Nov, 2024; Available Online: 25th Dec, 2024.

ABSTRACT

The drug delivery systems of hydrogels presented themselves with a very versatile platform by virtue of their capability for encapsulating therapeutic agents and controlled release. Recent efforts limiting hydrogel-based drug delivery aim at developing systems more responsive toward a change in external stimuli like pH, temperature, or light for targeted and on-demand drug release. Recent advances in polymer chemistry have fabricated hydrogels with improved biocompatibility, mechanical strength, and degradation profiles, thereby yielding a wide range of biomedical applications. Moreover, the combination of nanotechnology with hydrogels has rendered new opportunities not only for drugs but also for the delivery of complex drugs such as proteins, peptides, and nucleic acids, which are difficult to administer by traditional drug delivery methods. These novel systems are being explored also for localized and sustained drug delivery, especially in cancer therapy and wound healing, and in tissue engineering. The flexibility of the hydrogels for different routes of administration, namely, injectable formulations and implantable devices, underlines further their potential for application as next-generation drug delivery vehicles. More ongoing research is done in optimizing the drug loading efficiency, release kinetics, and targeting capabilities of the hydrogel system, while increasing therapeutic outcomes and limiting side effects. This review reflects recent trends within hydrogel-based drug delivery but focuses on the role in personalized medicine.

Keywords: Hydrogel, Drug delivery, Applications, Recent advances

How to cite this article: Sonwane SM, Ingle RG. Recent Advances in Hydrogel Drug Delivery Systems: Innovations and Applications. International Journal of Drug Delivery Technology. 2024;14(4):2457-66. doi: 10.25258/ijddt.14.4.67

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Hydrogels represent one of the most important achievements in drug delivery systems due to their elastic and innovative tool for therapeutic administration. Hydrogels are three-dimensional networks of hydrophilic polymers that are capable of absorbing and retaining significant water volumes.[1] These characteristics can be used to provide a peculiar matrix for the encapsulation and subsequent release of drugs.[2] The major property of hydrogels is their ability to swell, maintaining a gel-like structure capable of supporting a wide range of therapeutic agents, starting from small molecules and peptides and finishing with proteins and cells.[3] This approach provides not only enhancement of drug stability and bioavailability but also sustained and controlled release, turning hydrogels into one of the most promising tools of contemporary medicine.[4]

One of the most valuable benefits of using hydrogel-based drug delivery systems relates to their potential use for controlled drug release. The use of traditional drug delivery methods has been associated with fluctuating drug levels within the bloodstream, which tends to reduce efficacy and commonly presents various side effects.[5] On the contrary, hydrogels can be specifically fabricated for steady, sustained drug release over an extended time period. This is achieved through the careful manipulation of the physical and chemical properties of the hydrogel, including the density of cross-linking, composition of the polymer, and functionality.[6] Given the broad range of hydrogel classifications in Figure 1 that could help to design hydrogel which can release drugs at such a rate as to decrease dosing frequency and thereby increase patient compliance. Hydrogels play a pivotal role in the field of controlled drug release, offering a sophisticated platform that addresses the challenges of traditional drug delivery systems.[7] Conventional drug delivery often results in fluctuating drug levels in the bloodstream, leading to inconsistent therapeutic effects and an increased likelihood of side effects.[8] It considerably improves the therapeutic effect by maintaining drug levels within a small therapeutic window. This may be considered important because most drugs have a small difference between their therapeutic and toxic doses. Sustained release systems minimize the chances of drug concentrations falling below minimum effective levels during treatment, thus preventing suboptimal dosing and hence possible failures in treatment.[9] Besides, controlled release reduces the incidence of side effects related to peak drug concentrations.[10] By avoiding high levels of the drug that are likely to cause adverse effects, hydrogels make the treatment much safer and more comfortable for the patients. Hydrogels can be designed to respond against different physiological conditions, which makes them highly variable for certain medical uses. For instance, in gastrointestinal drug delivery, pH-sensitive hydrogels are designed to release their payload in response to changes in the pH value.[11] This comes very handy in delivering drugs

**Author for Correspondence: rahul.pharmacy@dmiher.edu.in*

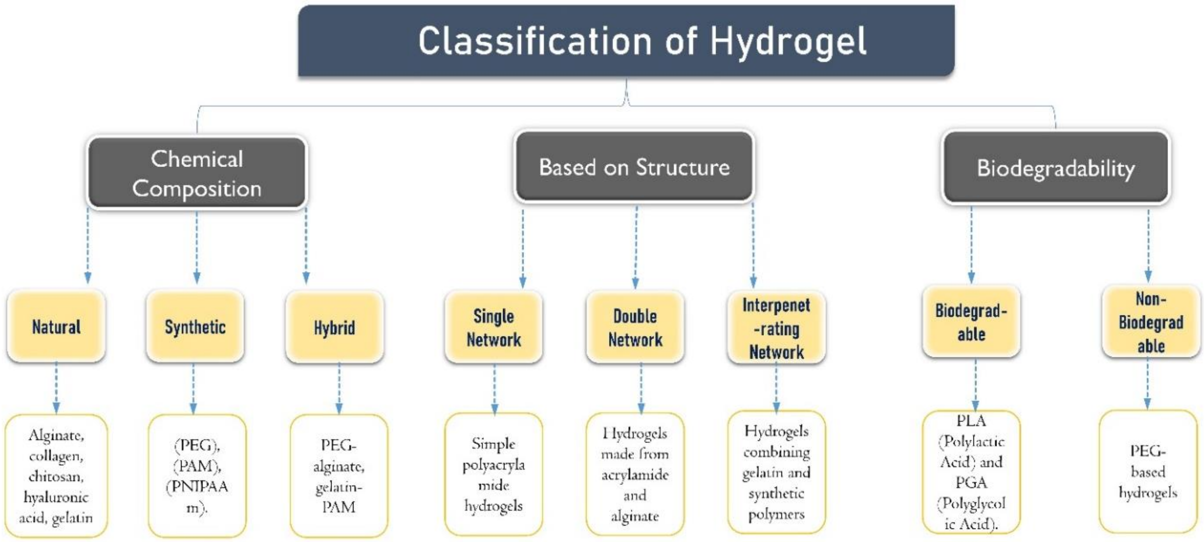

Figure 1: Classification of Hydrogel

in the gastrointestinal environment, where the hydrogels are stable in the acidic pH of the stomach and release their content once it reaches the intestine, where the pH changes to nearly neutral to slightly alkaline.[12] Accordingly, temperature-sensitive hydrogels can be engineered to release drugs upon temperature shift of the body or changes in environmental temperature.[13] This property is of particular value in applications that demand a critical thermal regulatory system in the delivery of a drug, mainly that sensitive to heat, or a biologic. The other important property of hydrogels upon drug delivery is entirely biocompatibility with biological systems and complete biodegradability. Hydrogels native biopolymers include alginate, collagen, and chitosan.[14] All naturally biocompatible and degrade into non-toxic by-products. This makes their application possible in numerous biomedical fields, such as wound healing, tissue engineering, and cell therapy. Even though the synthetic hydrogels do not always fulfill the requirements of biodegradability, by design they are able to mimic the properties of native tissues through support applications in regenerative medicine and tissue repair.[15] However, the work of controlled drug release systems does not end with enhancement of therapeutic efficacy and safety. Such systems also contribute to personalized medicine, in which individual patient needs can be met. Designing hydrogels of specific release profile and responsiveness to conditions specific to the patient can help health professionals provide more tailored and effective therapies.[16] This approach contributes not only to improved outcomes of treatment but also supports the creation of new therapies for diseases of increased complexity and chronicity. Hydrogels offer significant advantages in drug delivery due to their high water content, biocompatibility, and tunable properties.[17] They enable controlled and sustained drug release, improve therapeutic efficacy, reduce side effects, and enhance patient compliance by minimizing dosing frequency, making them highly versatile for various biomedical applications.[18] Some key advantages are shown in Figure 2.

Applications of Hydrogel

Hydrogels have become a highly versatile and innovative platform for drug delivery, providing numerous advantages stemming from their distinct properties, including high water content, adjustable mechanical strength, biocompatibility, and responsiveness to environmental stimuli.[19] Their application in drug delivery encompasses a broad spectrum of therapeutic areas, rendering them essential in the development of advanced treatment modalities. Some key applications of hydrogel are given with the help of Figure 3.

Basic Principles of Hydrogel Preparation

Hydrogels are three-dimensional, hydrophilic polymer networks capable of storing large amounts of water or biological fluids within their structure.[20] Thus, the ability to absorb and retain water in their structures, with maintenance of integrity, places the material in a acquiring position of high value in several fields such as medicine, agriculture, and environmental sciences. Hydrogels are prepared via complex interplays of chemical and physical processes, which, in turn, would dictate the properties and functionalities of the final product.[21]

Polymerization and Cross-Linking Mechanisms

The principle of forming hydrogels is based on the polymerization-cross-linking of monomers or polymers. Polymerization is a process in which small molecules combine chemically to form long chains or networks called polymers. Within the preparation of hydrogels, the polymer network has to be cross-linked in order to get a stable structure with swelling ability in water without dissolving.[22] The method of cross-linking has immense effects on the mechanical properties, swelling behavior, and degradation rate of the hydrogel. For example, covalently cross-linked hydrogels are relatively more stable and less degradable than physically cross-linked hydrogels, which may show reversible or temporary network formation.[23] The formation of hydrogels is influenced by several factors that affect their properties and functionality as summarized in Table 1.[24]

RECENT ADVANCES IN HDDS

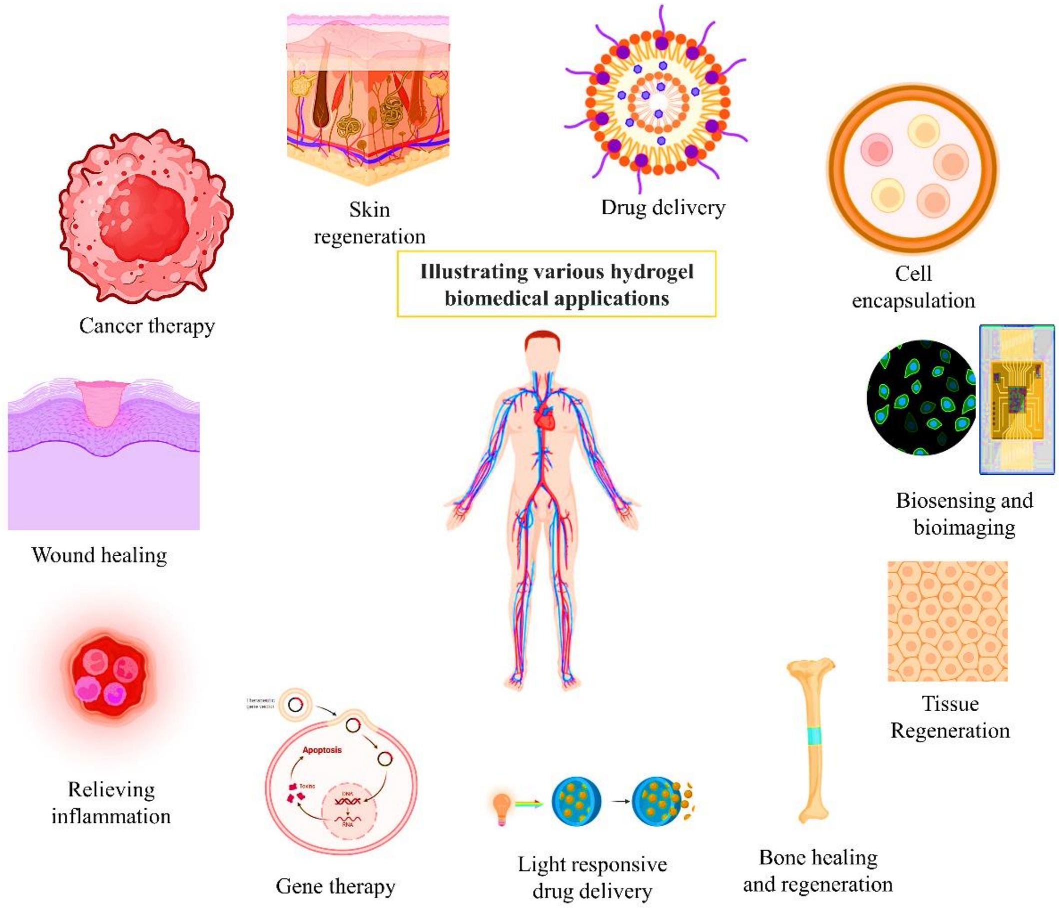

Figure 3: Applications of hydrogel

The unique characteristic to retain water by their three-dimensional network has put hydrogels in the lead for drug delivery purposes for a while. Significant advances in the technology behind hydrogels have placed them as devices exhibiting enhanced efficacy, improved versatility, and higher specificity, leading to breakthroughs in different therapeutic fields.[25] To this end, the current review attempts to outline recent advances in hydrogel-based DDSs and to highlight reports on the development of smart hydrogels, novel materials, advanced manufacturing techniques, and emergent applications.

Smart Hydrogels

Smart or stimuli-responsive hydrogels represent one of the most interesting fields of investigation in drug delivery. Such hydrogels react to a given physiological or external stimulus with controlled and targeted release of therapeutic agents.[26]

pH-Responsive Hydrogels: Current studies have focused on enhancing the functionality of pH-responsive hydrogels for drug release. Zhu et al., in 2023, developed a pH-responsive, injectable nonapeptide hydrogel as a local chemotherapy reservoir for doxorubicin. The hydrogel, formed through hydrophobic and electrostatic interactions, demonstrated high drug encapsulation efficiency, injectability, and sensitivity to acidic conditions. In vivo and in vitro studies showed enhanced therapeutic effects and increased doxorubicin accumulation at tumor sites. It pointed out that this might provide targeted cancer therapy at reduced systemic adverse effects.[27] pH-responsive hydrogels, formulated as ternary hydrogel films, were developed using a polyelectrolyte complex of chitosan, guar gum, and polyvinyl pyrrolidone cross-linked with sodium tripolyphosphate. The characterization showed interactions between polymeric chains, surface morphology, and thermal stability. Swelling decreased with higher crosslinker concentration, and ciprofloxacin hydrochloride release demonstrated the hydrogels' potential for drug delivery in different pH environments.[28]

Temperature-Responsive Hydrogels: Temperature-sensitive hydrogels have great potential for the control of drug release at body temperature.[29] A thermoresponsive graft copolymer, combining poly(N-isopropyl acrylamide) (PNIPAM) side chains and a chitosan (Chit) backbone, was synthesized via RAFT polymerization. The copolymer demonstrated dual functionality, with pH-responsive amino groups and thermoresponsive behavior, as studied through dynamic light scattering (DLS). Additionally, it was capable of binding DNA and forming nanosized polyplexes, suggesting potential for gene delivery applications.[30] Manish K. et al reported nanoscale magnetic hydrogels based on poly(N-isopropylacrylamide) were developed for theranostic applications, incorporating Fe_3O_4 magnetic nanostructures (MNS) with an LCST of ~40°C. The system, with PEG-functionalized 12 nm MNS (HGMNS-PEG-12), showed adequate MR relaxivity and enhanced RF-induced drug release, delivering over twice the doxorubicin compared to room temperature. This hydrogel system is a promising candidate for combined therapy and diagnostic

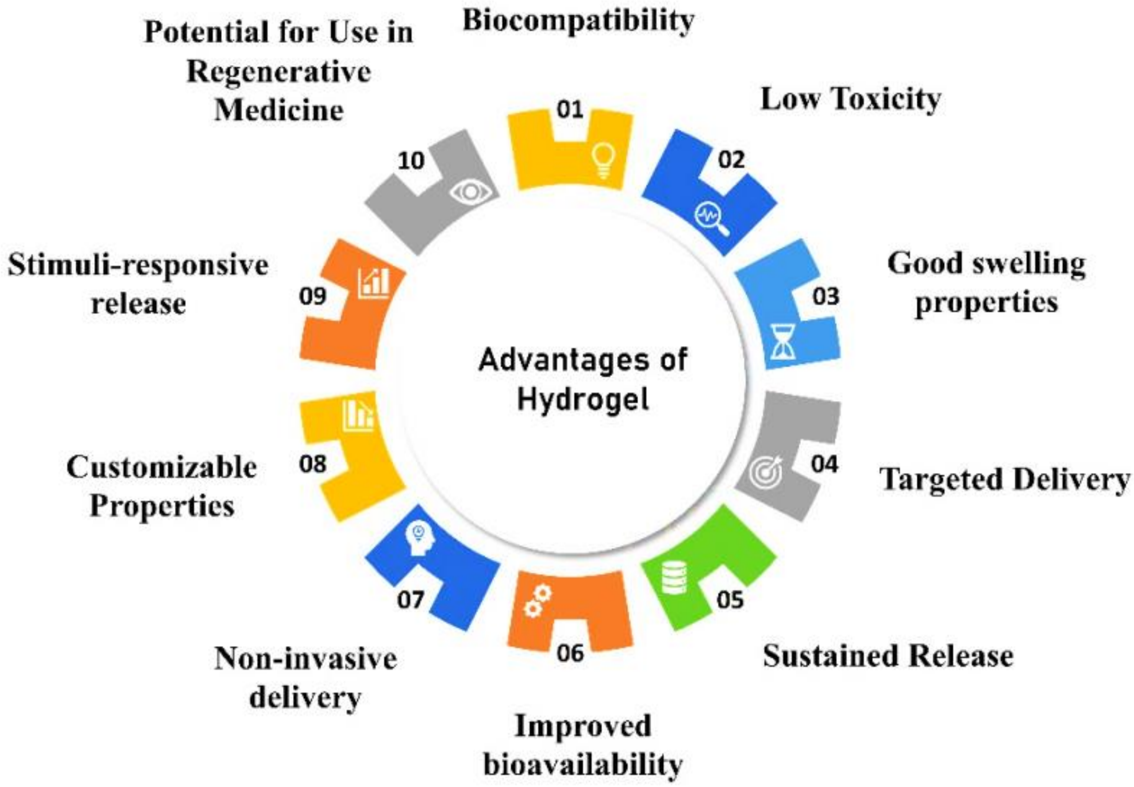

Figure 2: Advantages of Hydrogel

applications.[31] In a study, an injectable chitosan-carbon nanotube (CNT) hydrogel was developed for methotrexate (MTX) delivery in tumor therapy. CNTs were first incorporated into a hydrogel formed by chitosan and β-GP, which was then used to load MTX. The hydrogel containing CNTs showed a reduced MTX release rate compared to the hydrogel without CNTs.[32]

Light-responsive hydrogels have received great interest in drug delivery for the simple irradiation at a certain wavelength of light may provide a way of drug release.[33] In this regard, Lim S. et al. developed a light-responsive hydrogel-based system for controlled epidermal growth factor (EGF) release in wound healing. A photocleavable linker attached EGF to a hyaluronic acid (HA) hydrogel, allowing UV light to trigger its release. In vitro and in vivo experiments showed that this system enhances EGF's therapeutic effect on wound healing.[34] In another study PASP-SS hydrogel and ProK-PtNPs were synthesized, achieving injectability through redox reactions and rapid sol-to-gel conversion. The photothermal effect of PtNPs under NIR irradiation enhanced ProK activity, accelerating hydrogel degradation and controlling drug release. Cytotoxicity tests showed the carrier materials and drugs were non-toxic to NIH3T3 cells, while the drug inhibited MCF7 cell proliferation. This study successfully developed an injectable, in situ gel-forming drug delivery system with NIR-controlled degradation for on-demand drug release, advancing the design of novel controlled drug delivery systems.[35] This study developed a hydrogel with photoswitchable cross-linkers that allows reversible stiffness changes upon light irradiation, without affecting cell behavior. The hydrogel was used to study bone-marrow-derived mesenchymal stem cells (MSCs), showing that increased substrate stiffness from blue light exposure led to characteristic cell spreading and higher aspect ratios. The hydrogel is noncytotoxic and provides a platform for studying mechanosignaling in response to dynamic stiffness changes, offering insights into mechanotransduction and biological processes like development, aging, and fibrosis.[36]

Novel Materials in Hydrogel Drug Delivery

Novel Materials in Hydrogel Drug Delivery reviews the development of advanced materials to improve hydrogel-based drug delivery. Innovations like stimuli-responsive polymers, nanocomposites, and biohybrid hydrogels enhance drug release control, biocompatibility, and targeting. Supramolecular hydrogels offer precise release through dynamic assembly, while injectable hydrogels enable localized, minimally invasive treatments.[37] These materials promise more efficient, precise, and convenient drug delivery solutions.

Biodegradable and biocompatible polymers are of growing interest in the formulation of hydrogels.[38] The addition of nanoparticles, such as gold, silver, or magnetic particles in nanocomposite hydrogels, results in a material with even greater functionality. These may enhance mechanical strength for the hydrogel, increase drug loading, and even develop responsiveness to external stimuli-for example, magnetic fields or light.[39] The incorporation of magnetic nanoparticles in hydrogels may be used for directing the drug-loaded hydrogel through specific sites in the body, thus enhancing targeting and reducing systemic exposure.[40]

Table 1: Factors influencing the properties and functionality of hydrogels

Factor	Description	Influence on Hydrogel Formation
Monomer Concentration	The concentration of monomers or cross-linkers in the solution.	Higher concentration generally leads to increased gel density and stiffness.
Cross-Linking Agent	Substances used to link polymer chains together.	Affects the mechanical strength and stability of the hydrogel.
Polymer Type	The type of polymer used, such as natural (e.g., alginate, collagen) or synthetic (e.g., polyacrylamide).	Influences the hydrogel's properties, including biocompatibility and swelling behavior.
Solvent	The liquid in which the polymerization occurs, often water.	Determines the swelling behavior and gel formation process.
Temperature	The temperature at which polymerization occurs.	Affects the rate of polymerization and the final hydrogel's properties.
pH Level	The acidity or alkalinity of the solution.	Influences the solubility of the monomers and the stability of the hydrogel.
Polymerization Method	The method used to initiate polymerization, such as chemical, thermal, or UV-induced polymerization.	Impacts the rate and uniformity of gel formation.
Ionic Strength	The concentration of ions in the solution, often affecting hydrogels based on ionic interactions (e.g., alginate).	Affects the gelation process and final hydrogel properties.
Degree of Hydrophilicity	The affinity of the polymer for water.	Determines how much water the hydrogel can absorb and retain.
Time	The duration of polymerization.	Affects the extent of cross-linking and the final structure of the hydrogel.
Additives	Presence of other substances, such as plasticizers or surfactants.	Can modify the hydrogel's mechanical properties, swelling, and stability.

Besides, the addition of a nanomaterial can often confer duality in functionality, and in those cases, hydrogels can work as therapeutic-diagnostic tools-theranostics.[41]

Biohybrid hydrogels result from a simple combination of synthetic polymers with natural biopolymers such as chitosan, alginate, or collagen.[42] This provides features of both individual materials. Such hydrogels can simulate the natural ECM and are hence especially valuable in tissue engineering and regenerative medicine. While the natural constituents improve their biocompatibility and cell proliferation/differentiation, structural stability and tunable properties are provided by the synthetic constituent.[43]

The supramolecular hydrogels self-assemble through non-covalent interactions and are dynamic in nature owing to their reversible self-assembly process.[44] Therefore, this makes them ideal candidates for the purpose of on-demand drug release. Hydrogels can also respond to changes in environmental conditions-for example, changes in pH-or the presence of certain molecules, through which drugs could be released at exactly the right time.[45] Injectable hydrogels, which are formatted for in situ gelation, represent a minimally invasive method for drug delivery directly to the target site. Upon injection, they would form a gel that could release drugs over a prolonged period of time.[46]

Advanced Fabrication Techniques

Advanced fabrication techniques have turned hydrogels into extremely functional and precisely engineered materials, tailored for specific biomedical and industrial applications. Since the dawn of their history, the excellent biocompatibility, tunable mechanical properties, and versatility of hydrogels as a network of hydrophilic polymers have been appreciated for their capability to hold large amounts of water.[47] Various fabrication techniques developed, especially 3D printing methods[48], microfluidics[49], electrospinning[50], and photolithography[51], have extended the capabilities of hydrogels toward the design of complex structures with precisely controlled physical and chemical properties.

3D printing, otherwise stated as additive manufacturing, has turned into one of the powerful approaches in hydrogel fabrication. This technique enables the layer-by-layer assembly of hydrogels into complex architectures, therefore allowing the realization of tailor-made shapes and structures which were hitherto unreachable or highly difficult to achieve.[52] Three-dimensional printing of hydrogels is eminently useful in tissue engineering, wherein the biomimicking of complicated geometries of tissues and organs matters a great deal.[53] The precise control of hydrogel material deposition can fabricate scaffolds that truly mimic the structure of the extracellular matrix, encouraging cell growth and tissue regeneration.[54] In addition, this technique also offers 3D printing with different materials in one structure and enables the preparation of hydrogels that will be multifunctional, possessing regionally distinct areas for different biological functions, including drug delivery, mechanical support, and bioactive signaling.[55]

Another most revolutionary advanced technique to change the face of hydrogel fabrication is microfluidics. This approach mainly incorporates small-volume fluid handling within microchannels to generate hydrogels that have very controlled properties. These hydrogel particles, fibers, and capsules, prepared by microfluidic fabrication, must be of uniform size and shape in drug delivery and cell encapsulation.[56] The outstanding control over fluid flow in microfluidic devices allows fabricating hydrogels with gradient properties, in fact, composition, stiffness, or concentration of bioactive molecules can change in space within the material. Such hydrogels are a great tool to explore the cell behavior in artificial conditions of gradients of tissue oxygen, nutrients, or growth factors.[57] The technique of electrospinning exploits an electric field to draw fine fibers out of a polymer solution. This has been modified into fabricating hydrogel-based nanofibers.[58] Electrospun hydrogel fibers have a high surface area-to-volume ratio for such applications that demand rapid drug release or enhanced cell attachment.[59] The fibrous architecture of the electrospun hydrogels also closely resembles the natural extracellular matrices, hence suiting them for tissue engineering and wound healing applications.[60] The adjustment in the electrospinning parameters allows regulation of hydrogel fibers in diameter and alignment, hence the mechanical properties and degradation rates in the resulting material.[61]

Photolithography has now adapted to the wide use from the semiconductor industry for the precise patterning of hydrogels. The process selectively cross-links or degrades regions of a hydrogel precursor with the use of light, yielding well-defined micro-structures.[62] Photolithography allows for complex shapes and patterns in hydrogels at the microscale, which proves highly instrumental in several applications, such as microfluidic devices, biosensors, and cell culture platforms.[63] High-resolution patterning of hydrogels opens the route to microenvironments able to direct cell behavior and for performing studies on cell-material interactions, thus opening the way toward advanced biomedical devices.[64]

Emerging Applications

In this regard, the versatility of the drug delivery systems has made hydrogels applied in a wide range of medical and therapeutic fields. Recent advancements increase these applications in various ways by solving complicated medical challenges with novelty.

In biomedicine, hydrogels are being used in the development of novel drug delivery systems and tissue engineering. Due to the encapsulation properties of hydrogels, many avenues have opened up in targeted drug delivery systems.[65] Hydrogels can be engineered to respond against physiological conditions, pH, or temperature-specific for releasing drugs at a specific site to reduce side effects and enhance the therapeutic action of drugs.[66] Hydrogels are also being used in developing scaffolds that are applied in tissue engineering. Most of these scaffolds are said to successfully mimic tissues' extracellular matrices.[67] This is due to the fact that they provide an appropriate environment for the growth and differentiation of cells. This has been considered relevant in the regeneration of damaged tissues or organs.[68] Injectable scaffolds in hydrogel form are also being researched for minimally invasive surgery; they may be delivered in a liquid state at the site of the injury and then allowed to solidify in situ, thus offering new prospects for wound healing and regenerative medicine.[69]

Hydrogels are being investigated for various applications in the field of environmental engineering, including water purification and environmental remediation.[70] Given the high absorbing capacity of water and the possibility of their functionalization with specific chemical groups, they can work effectively as adsorbents in water purification from pollutants.[71] Additionally, hydrogels can be designed to trap heavy metals, dyes, and contaminants of that sort, hence making them useful in solving water pollution.[72] In addition, environmentally responsive smart hydrogels, responding to environmental stimuli like a change in temperature or pH, will be elaborated on for controlled release or adsorption of substances to further raise the effectiveness of different environmental remediation processes.[73] Moreover, hydrogels are under research as conditioners for agricultural soil. It can enhance water retention in soil to reduce frequency of irrigation, hence improving growth and development in places with low availability of water.[74] This application is particularly relevant in the context of global climate change, where water scarcity and desertification are becoming increasingly prevalent.

The potential of hydrogels is also being recognized in the fields of robotic and wearable devices.[75] Hydrogels can be prepared so that their mechanical properties resemble those of biological tissues; hence, they are ideal for soft robotics applications in actuators and sensors.[76] These soft robots, sometimes referred to as biohybrids, are capable of performing delicate tasks-lifting fragile objects, interacting with humans-Impossible with more traditional rigid robots.[77] Furthermore, the flexibility and stretchability of hydrogels enable the development of wearable devices to monitor physiological signals, such as heart rate or glucose levels in real time.[78] These hydrogel-based wearables offer a friendly interface to the human body, for which integration in more integrated and less-invasive health monitoring systems is foreseen.[79]

FUTURE PERSPECTIVES

Hydrogel drug delivery systems are set for transformative advancements, with innovations in stimuli-responsive technologies, personalized medicine, and nanotechnology. Future hydrogels could be engineered to respond to a wide range of biological and external stimuli, making them highly targeted and precise in drug release. Personalized hydrogels, informed by genomics, will be tailored to individual patients' genetic profiles, optimizing therapeutic outcomes. Nanotechnology will enhance hydrogels through hybrid systems with multifunctional nanoparticles, improving drug loading and targeting. The future will also focus on sustainability with degradable, renewable hydrogels and real-time monitoring systems for dynamic drug delivery adjustments, expanding their use in gene therapy, regenerative medicine, and hybrid therapies.

CONCLUSION

In that respect, hydrogel drug delivery systems represent one of the marvels in modern drug delivery and continue to promise boldly for the any overcome of drawbacks associated with conventional drug therapies. The current review has discussed the recent trends and developments concerning hydrogel drug delivery systems, emphasizing how they have transformed therapeutic modalities and augmented patient outcomes. Hydrogels have received significant interest due to their distinct properties, which include a high water content, excellent biocompatibility, and controlled encapsulation and release of active therapeutic agents. Recent progress has widened their application from mere conventional uses to encompassing high-tech specialized techniques, including stimuli-responsive mechanisms, personalized medicine, and even nanotechnology.

REFERENCES

1. Thang NH, Chien TB, Cuong DX. Polymer-based hydrogels applied in drug delivery: An overview. Gels. 2023;9(7):523.DOI: 10.3390/gels9070523
2. Pérez-Luna VH, González-Reynoso O. Encapsulation of biological agents in hydrogels for therapeutic applications. Gels. 2018;4(3):61.DOI: 10.3390/gels4030061
3. Ho TC, Chang CC, Chan HP, Chung TW, Shu CW, Chuang KP, Duh TH, Yang MH, Tyan YC. Hydrogels: Properties and applications in biomedicine. Molecules. 2022;27(9):2902. DOI: 10.3390/molecules27092902
4. Liu B, Chen K. Advances in hydrogel-based drug delivery systems. Gels. 2024;10(4):262. DOI: 10.3390/gels10040262
5. Adepu S, Ramakrishna S. Controlled drug delivery systems: Current status and future directions. Molecules. 2021;26(19):5905.DOI: 10.3390/molecules26195905
6. Gila-Vilchez C, Rodriguez-Arco L, Mañas-Torres MC, Álvarez de Cienfuegos L, Lopez-Lopez MT. Self-assembly in magnetic supramolecular hydrogels. Current Opinion in Colloid & Interface Science. 2022;62:101644.DOI: 10.1016/j.cocis.2022.101644
7. Li J, Mooney DJ. Designing hydrogels for controlled drug delivery. Nature Reviews Materials. 2016;1(12):16071.DOI: 10.1038/natrevmats.2016.71
8. Wen H, Jung H, Li X. Drug delivery approaches in addressing clinical pharmacology-related issues: Opportunities and challenges. American Association of Pharmaceutical Scientists Journal. 2015;17(6):1327-1340.DOI: 10.1208/s12248-015-9814-9
9. Buwalda S, Vermonden T, Hennink WE. Hydrogels for therapeutic delivery: Current developments and future directions. Biomacromolecules. 2017;18(2):316-330.DOI: 10.1021/acs.biomac.6b01604
10. Powell G, Saunders M, Rigby A, Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database Syst Rev. 2016;12(12).DOI: 10.1002/14651858.CD007124.pub5
11. Raina N, Pahwa R, Bhattacharya J, Paul AK, Nissapatorn V, de Lourdes Pereira M, Oliveira SMR, Dolma KG, Rahmatullah M, Wilairatana P, Gupta M. Drug delivery strategies and biomedical significance of hydrogels: Translational considerations. Pharmaceutics. 2022;14(3):574.DOI: 10.3390/pharmaceutics14030574
12. Rizwan M, Yahya R, Hassan A, Yar M, Azzahari AD, Selvanathan V, Sonsudin F, Abouloula CN. pH sensitive hydrogels in drug delivery: Brief history, properties, swelling, and release mechanism, material selection and applications. Polymers (Basel). 2017;9(4):137.DOI: 10.3390/polym9040137
13. Fan R, Cheng Y, Wang R, Zhang T, Zhang H, Li J, Song S, Zheng A. Thermosensitive hydrogels and advances in their application in disease therapy. Polymers (Basel). 2022;14(12):2379.DOI: 10.3390/polym14122379
14. Tsung TH, Tsai YC, Lee HP, Chen YH, Lu DW. Biodegradable polymer-based drug-delivery systems for ocular diseases. International Journal of Molecular Sciences. 2023;24(16):12976.DOI: 10.3390/ijms241612976
15. Revete A, Aparicio A, Cisterna BA, Revete J, Luis L, Ibarra E, Segura González EA, Molino J, Reginensi D. Advancements in the use of hydrogels for regenerative medicine: Properties and biomedical applications. International Journal of Biomaterials. 2022;2022:3606765.DOI: 10.1155/2022/3606765
16. Puccetti M, Pariano M, Schoubben A, Giovagnoli S, Ricci M. Biologics, theranostics, and personalized medicine in drug delivery systems. Pharmacological Research. 2024;201:107086.DOI: 10.1016/j.phrs.2024.107086
17. Jacob S, Nair AB, Shah J, Sreeharsha N, Gupta S, Shinu P. Emerging role of hydrogels in drug delivery systems, tissue engineering and wound management. Pharmaceutics. 2021;13(3):357.DOI: 10.3390/pharmaceutics13030357
18. Martins CF, García-Astrain C, Conde J, et al. Nanocomposite hydrogel microneedles: A theranostic toolbox for personalized medicine. Drug Delivery and Translational Research. 2024;14:2262-75.DOI: 10.1007/s13346-024-01533-w
19. Sytze J. Buwalda, Tina Vermonden, and Wim E. Hennink. Hydrogels for Therapeutic Delivery: Current Developments and Future Directions. Biomacromolecules. 2017;18(2):316-330.DOI: 10.1021/acs.biomac.6b01604
20. Chai Q, Jiao Y, Yu X. Hydrogels for biomedical applications: Their characteristics and the mechanisms behind them. Gels. 2017;3(1):6.DOI: 10.3390/gels3010006
21. Bashir S, Hina M, Iqbal J, Rajpar AH, Mujtaba MA, Alghamdi NA, Wageh S, Ramesh K, Ramesh S. Fundamental concepts of hydrogels: Synthesis, properties, and their applications. Polymers (Basel). 2020;12(11):2702.DOI: 10.3390/polym12112702
22. Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. Journal of Advanced Research. 2015;6(2):105-121.DOI: 10.1016/j.jare.2013.07.006
23. Mashabela LT, Maboa MM, Miya NF, Ajayi TO, Chasara RS, Milne M, Mokhele S, Demana PH, Witika BA, Siwe-Noundou X, Poka MS. A comprehensive review of cross-linked gels as vehicles for drug delivery to treat central nervous system disorders. Gels. 2022;8(9):563.DOI: 10.3390/gels8090563

24. Chamkouri H, Chamkouri M. A review of hydrogels, their properties and applications in medicine. American Journal of Biomedical Science & Research. 2021;11(6).DOI: 10.34297/AJBSR.2021.11.001682
25. Farasati Far B, Isfahani AA, Nasiriyan E, Pourmolaei A, Mahmoudvand G, Karimi Rouzbahani A, Namiq Amin M, Naimi-Jamal MR. An Updated Review on Advances in Hydrogel-Based Nanoparticles for Liver Cancer Treatment. Livers. 2023;3(2):161-189. DOI:10.3390/livers3020012
26. El-Husseiny HM, Mady EA, Hamabe L, Abugomaa A, Shimada K, Yoshida T, Tanaka T, Yokoi A, Elbadawy M, Tanaka R. Smart/stimuli-responsive hydrogels: Cutting-edge platforms for tissue engineering and other biomedical applications. Materials Today Bio. 2022;13:100186.DOI: 10.1016/j.mtbio.2021.100186.
27. Zhu J, Gao R, Wang Z, Cheng Z, Xu Z, Liu Z, Wu Y, Wang M, Zhang Y. Sustained and targeted delivery of self-assembled doxorubicin nonapeptides using pH-responsive hydrogels for osteosarcoma chemotherapy. Pharmaceutics. 2023;15(2):668.DOI: 10.3390/pharmaceutics15020668
28. Ghauri ZH, Islam A, Qadir MA, et al. Development and evaluation of pH-sensitive biodegradable ternary blended hydrogel films (chitosan/guar gum/PVP) for drug delivery application. Scientific Reports. 2021;11:21255.DOI: 10.1038/s41598-021-00452-x
29. Aljeboree AM, Fared RW, Al-wahed HMA, Jawad MA, Alkaim AF. Role of SA-g-(PAA-co-AM)/ CdS Hydrogel: As Photocatalytic for Decolonization Methyl Red Dye as a Pollutant from Aqueous Solution. International Journal of Pharmaceutical Quality Assurance. 2023;14(1):171-174.DOI: 10.25258/ijpqa.14.1.29
30. Zaharia MM, Bucatariu F, Karayianni M, Lotos E-D, Mihai M, Pispas S. Synthesis of thermoresponsive chitosan-graft-poly(N-isopropylacrylamide) hybrid copolymer and its complexation with DNA. Polymers. 2024;16(10):1315.DOI: 10.3390/polym16101315
31. Jaiswal MK, De M, Chou SS, Vasavada S, Bleher R, Prasad PV, Bahadur D, Dravid VP. Thermoresponsive magnetic hydrogels as theranostic nanoconstructs. ACS Applied Materials & Interfaces. 2014;6(9):6237-6247.DOI: 10.1021/am501067j
32. Saeednia L, Yao L, Cluff K, Asmatulu R. Sustained releasing of methotrexate from injectable and thermosensitive chitosan–carbon nanotube hybrid hydrogels effectively controls tumor cell growth. ACS Omega. 2019;4(2):4040-4048.DOI: 10.1021/acsomega.8b03212
33. Xing Y, Zeng B, Yang W. Light responsive hydrogels for controlled drug delivery. Frontiers in Bioengineering and Biotechnology. 2022;10:1075670.DOI: 10.3389/fbioe.2022.1075670
34. Lim S, Kim JA, Chun YH, Lee HJ. Hyaluronic acid hydrogel for controlled release of heterobifunctional photocleavable linker-modified epidermal growth factor in wound healing. International Journal of Biological Macromolecules. 2023;253(1):126603.DOI: 10.1016/j.ijbiomac.2023.126603
35. Zhao J, Liang X, Cao H, et al. Preparation of injectable hydrogel with near-infrared light response and photo-controlled drug release. Bioresources and Bioprocessing. 2020;7:1. DOI: 10.1186/s40643-019-0289-x
36. Lee I-N, Dobre O, Richards D, Ballestrem C, Curran JM, Hunt JA, Richardson SM, Swift J, Wong LS. Photoresponsive hydrogels with photoswitchable mechanical properties allow time-resolved analysis of cellular responses to matrix stiffening. ACS Applied Materials & Interfaces. 2018;10(9):7765-76.DOI: 10.1021/acsami.7b18302
37. Bernhard S, Tibbitt MW. Supramolecular engineering of hydrogels for drug delivery. Advanced Drug Delivery Reviews. 2021;171:240-56.DOI: 10.1016/j.addr.2021.02.002
38. Hu B, Gao J, Lu Y, Wang Y. Applications of degradable hydrogels in novel approaches to disease treatment and new modes of drug delivery. Pharmaceutics. 2023;15(10):2370. DOI: 10.3390/pharmaceutics15102370
39. Karchoubi F, Afshar Ghotli R, Pahlevani H, Baghban Salehi M. New insights into nanocomposite hydrogels: A review on recent advances in characteristics and applications. Advanced Industrial and Engineering Polymer Research. 2024;7(1):54-78.DOI: 10.1016/j.aiepr.2023.06.002
40. Singh R, Pal D, Chattopadhyay S. Target-specific superparamagnetic hydrogel with excellent pH sensitivity and reversibility: A promising platform for biomedical applications. ACS Omega. 2020;5(34):21768-21780.DOI: 10.1021/acsomega.0c02817
41. Zhu W, Wei Z, Han C, Weng X. Nanomaterials as promising theranostic tools in nanomedicine and their applications in clinical disease diagnosis and treatment. Nanomaterials (Basel). 2021;11(12):3346.DOI: 10.3390/nano11123346
42. Vasile C, Pamfil D, Stoleru E, Baican M. New developments in medical applications of hybrid hydrogels containing natural polymers. Molecules. 2020;25(7):1539.DOI: 10.3390/molecules25071539
43. Krishani M, Shin WY, Suhaimi H, Sambudi NS. Development of scaffolds from bio-based natural materials for tissue regeneration applications: A review. Gels. 2023;9(2):100.DOI: 10.3390/gels9020100
44. Telrandhe UB, Shete VS, Vaidya SN. Exploring the Pharmacological Potential of Fisetin: A Comprehensive Review. International Journal of Pharmaceutical Quality Assurance. 2024;15(2):1048-1055.DOI: 10.25258/ijpqa.15.2.76
45. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Advanced Drug Delivery Reviews. 2012;64(Suppl):49-60.DOI: 10.1016/j.addr.2012.09.024
46. Dimatteo R, Darling NJ, Segura T. In situ forming injectable hydrogels for drug delivery and wound repair. Advanced Drug Delivery Reviews. 2018;127:167-84.DOI: 10.1016/j.addr.2018.03.007

47. Ali F, Khan I, Chen J, Akhtar K, Bakhsh EM, Khan SB. Emerging fabrication strategies of hydrogels and its applications. Gels. 2022;8(4):205.DOI: 10.3390/gels8040205
48. Li J, Wu C, Chu PK, Gelinsky M. 3D printing of hydrogels: Rational design strategies and emerging biomedical applications. Materials Science and Engineering R Rep. 2020;140:100543.DOI: 10.1016/j.mser.2020.100543
49. Goy CB, Chaile RE, Madrid RE. Microfluidics and hydrogel: A powerful combination. Reactive and Functional Polymers. 2019;145:104314.DOI: 10.1016/j.reactfunctpolym.2019.104314
50. Li Y, Wang J, Wang Y, Cui W. Advanced electrospun hydrogel fibers for wound healing. Composites Part B Engineering.2021;223:109101.DOI: 0.1016/j.compositesb.2021.109101
51. Subramani K. Chapter 11 - Fabrication of Hydrogel Micropatterns by Soft Photolithography. In: Ahmed W, Jackson MJ, editors. Micro and Nano Technologies, Emerging Nanotechnologies for Manufacturing. William Andrew Publishing; 2010. p. 261-276. ISBN: 9780815515838.DOI: 10.1016/B978-0-8155-1583-8.00011-9
52. Kaliaraj GS, Shanmugam DK, Dasan A, Mosas KKA. Hydrogels—A promising material for 3D printing technology. Gels. 2023;9(3):260.DOI: 10.3390/gels9030260
53. Fang W, Yang M, Wang L, Li W, Liu M, Jin Y, Wang Y, Yang R, Wang Y, Zhang K, Fu Q. Hydrogels for 3D bioprinting in tissue engineering and regenerative medicine: Current progress and challenges. International Journal of Bioprinting. 2023;9(5):759.DOI: 10.18063/ijb.759
54. El-Sherbiny IM, Yacoub MH. Hydrogel scaffolds for tissue engineering: Progress and challenges. Global Cardiology Science and Practice. 2013;2013(3):316-342.DOI: 10.5339/gcsp.2013.38
55. Fang W, Yang M, Liu M, Jin Y, Wang Y, Yang R, Wang Y, Zhang K, Fu Q. Review on additives in hydrogels for 3D bioprinting of regenerative medicine: From mechanism to methodology. Pharmaceutics. 2023;15(6):1700.DOI: 10.3390/pharmaceutics15061700
56. Mohamed MGA, Ambhorkar P, Samanipour R, Yang A, Ghafoor A, Kim K. Microfluidics-based fabrication of cell-laden microgels. Biomicrofluidics. 2020;14(2):021501.DOI: 10.1063/1.5134060
57. Rosellini E, Cascone MG. Microfluidic fabrication of natural polymer-based scaffolds for tissue engineering applications: A review. Biomimetics (Basel). 2023;8(1):74.DOI: 10.3390/biomimetics8010074
58. Xue J, Wu T, Dai Y, Xia Y. Electrospinning and electrospun nanofibers: Methods, materials, and applications. Chemical Reviews. 2019;119(8):5298-5415.DOI: 10.1021/acs.chemrev.8b00593
59. Luraghi A, Peri F, Moroni L. Electrospinning for drug delivery applications: A review. Journal of Controlled Release. 2021;334:463-484.DOI: 10.1016/j.jconrel.2021.03.033
60. Balusamy B, Senthamizhan A, Uyar T. Electrospun nanofibrous materials for wound healing applications. In: Advances in Electrospinning. Woodhead Publishing. 2017;147-177, ISBN 9780081010228.DOI: 10.1016/B978-0-08-101022-8.00012-0
61. Haider A, Haider S, Kang I-K. A comprehensive review summarizing the effect of electrospinning parameters and potential applications of nanofibers in biomedical and biotechnology. Arabian Journal of Chemistry. 2018;11(8):1165-1188.DOI: 10.1016/j.arabjc.2015.11.015
62. Tenje M, Cantoni F, Porras Hernández AM, Searle SS, Johansson S, Barbe L, Antfolk M, Pohlit H. A practical guide to microfabrication and patterning of hydrogels for biomimetic cell culture scaffolds. Organs-on-a-Chip. 2020;2:100003.DOI: 10.1016/j.ooc.2020.100003
63. Maji S, Lee H. Engineering hydrogels for the development of three-dimensional in vitro models. International Journal of Molecular Sciences. 2022;23(5):2662.DOI: 10.3390/ijms23052662
64. Cao H, Duan L, Zhang Y, et al. Current hydrogel advances in physicochemical and biological response-driven biomedical application diversity. Signal Transduction and Targeted Therapy. 2021;6:426.DOI: 10.1038/s41392-021-00830-x
65. Sonule M, Devhare LD, Babu MN, Gunjal SD, Varalaxmi S. Microemulgel-based Hydrogel of Diclofenac Sodium using Lipidium sativum as a Gelling Agent. International Journal of Drug Delivery Technology. 2023;13(4):1235-1239.DOI: 10.25258/ijddt.13.4.19
66. Zhang Y, Wu BM. Current advances in stimuli-responsive hydrogels as smart drug delivery carriers. Gels. 2023;9(10):838.DOI: 10.3390/gels9100838
67. Radulescu DM, Neacsu IA, Grumezescu AM, Andronescu E. New insights of scaffolds based on hydrogels in tissue engineering. Polymers. 2022;14(4):799.DOI: 10.3390/polym14040799
68. Ikada Y. Challenges in tissue engineering. Journal of The Royal Society Interface. 2006;3(10):589-601.DOI: 10.1098/rsif.2006.0124
69. Singh, UK, Sudheer, P Hydrogel Beads- A Versatile Dimension in Controlled Oral Delivery. International Journal of Drug Delivery Technology. 2022;12(3):1453-1464. DOI: 10.25258/ijddt.12.3.88
70. Sinha V, Chakma S. Advances in the preparation of hydrogel for wastewater treatment: A concise review. Journal of Environmental Chemical Engineering. 2019;7(5):103295.DOI: 10.1016/j.jece.2019.103295
71. Algarni TS, Al-Mohaimeed AM. Water purification by adsorption of pigments or pollutants via metal oxide. Journal of King Saud University. 2022;34(8):102339.DOI: 10.1016/j.jksus.2022.102339
72. Darban Z, Shahabuddin S, Gaur R, Ahmad I, Sridewi N. Hydrogel-based adsorbent material for the effective removal of heavy metals from wastewater: A comprehensive review. Gels. 2022;8(5):263.DOI: 10.3390/gels8050263
73. Cao J, Yuan P, Wu B, Liu Y, Hu C. Advances in the research and application of smart-responsive hydrogels

in disease treatment. Gels. 2023;9(8):662.DOI: 10.3390/gels9080662

74. Jaramillo-Quiceno N, Duque Carmona AS, Serna Serna J, Carmona DM, Torres-Taborda M, Hincapié-Llanos GA, Santa Marín JF, Álvarez-López C. Enhancing soil water retention and plant growth with thermal crosslinked silk sericin-based hydrogel. Journal of Environmental Chemical Engineering. 2024;12(2):112260.DOI: 10.1016/j.jece.2024.112260
75. Ying B, Liu X. Skin-like hydrogel devices for wearable sensing, soft robotics and beyond. iScience. 2021;24(11):103174.DOI: 10.1016/j.isci.2021.103174
76. Lee Y, Song WJ, Sun J-Y. Hydrogel soft robotics. Materials Today Physics. 2020;15:100258.DOI: 10.1016/j.mtphys.2020.100258
77. Hsiao J-H, Chang J-Y, Cheng C-M. Soft medical robotics: Clinical and biomedical applications, challenges, and future directions. Advanced Robotics. 2019;33:1-13.DOI: 10.1080/01691864.2019.1679251
78. Wang X, Ji H, Gao L, Hao R, Shi Y, Yang J, Hao Y, Chen J. Wearable hydrogel-based health monitoring systems: A new paradigm for health monitoring. Chemical Engineering Journal. 2024;495:153382.DOI: 10.1016/j.cej.2024.153382
79. Lyu X, Hu Y, Shi S, Wang S, Li H, Wang Y, Zhou K. Hydrogel bioelectronics for health monitoring. Biosensors. 2023;13(8):815.DOI: 10.3390/bios13080815