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TRENDS IN THE DEVELOPMENT AND APPLICATION OF HYDROGELS AS INNOVATIVE BIOMATERIALS

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Aim. To summarize and systematize contemporary scientific data on hydrogels as one of the leading classes of biomaterials; to analyze the stages of their historical development, as well as their structural and functional modifications; and to evaluate the prospects for the application of hydrogel systems in biotechnology, pharmacy, medicine, and cosmetology.

Methods. A comprehensive analysis and synthesis of scientific publications on hydrogels was conducted, with particular attention to their classification, structural features, physicochemical properties, and methods of preparation. Current approaches to modifying hydrogel matrices and the main directions of their practical applications across various scientific and industrial fields were analyzed.

Results. The review systematizes data on the main types of hydrogels, their structural characteristics, and functional properties. The key stages in the evolution of hydrogel materials and current trends in their use as innovative platforms for cell therapy, tissue engineering, medicine, pharmacy, and biotechnology are highlighted. Special attention is given to the potential of loading hydrogel matrices with biologically active substances, which enables the development of systems with controlled properties aimed at restoring and improving the functional state of the organism.

Conclusions. The review confirms the leading role of hydrogels among modern biomaterials due to their combination of high hydrophilicity, biocompatibility, and the ability to regulate physicochemical characteristics. Promising directions for further research aimed at the development of multifunctional hydrogels to meet the needs of the pharmaceutical and medical fields are outlined.

Key words: hydrogel, biomaterials, biotechnology, bioactive compounds.

In recent decades, significant advancements have been achieved in the field of biomaterials. Among the various materials developed, hydrogels stand out as a three-dimensional polymer network with substantial potential for applications across diverse scientific and industrial fields [1].

Initially, the use of hydrogels was limited by the toxicity of crosslinking agents and the challenges of their formation under physiological conditions. However, progress in polymer chemistry, combined with an improved understanding of biological processes, has led to the development of versatile and functional materials with enhanced biocompatibility [1].

Today, hydrogel matrices are composed of a broad range of natural and synthetic polymers, with their structure stabilized through physical or chemical crosslinking. These materials possess unique characteristics, such as biocompatibility, the potential for chemical modification, and adjustable physicochemical properties. Additionally, they are known for their relatively simple production processes. These features make hydrogels an ideal platform for both cell-based and acellular therapies, allowing for the customization of specific requirements and significantly enhancing their effectiveness [2, 3].

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Hydrogels hold significant promise as a platform for developing materials that support cell viability and functionality and facilitate controlled drug release. Their ability to incorporate bioactive substances allows for applications in both cell-based and acellular therapies, leading to high therapeutic efficacy *in vivo* while minimizing systemic side effects. This capability expands the therapeutic window of these approaches. Despite their many advantages, there are still challenges that need to be addressed for the successful clinical implementation of these materials [3].

This review summarizes recent studies that assess the current state and prospects of hydrogels as innovative biomaterials. It organizes information on the origin and historical development of hydrogels, their classification, properties, and preparation methods. Additionally, the review explores the incorporation of bioactive substances into hydrogels and discusses their potential applications in biotechnology, pharmacy, medicine, and cosmetology.

History of Hydrogel Development

The concept of "hydrogel" has a history that spans more than a century. The term was first introduced in 1894 to describe colloidal gels made from inorganic salts. Although these early materials were quite different from modern hydrogels, this period established the theoretical foundation for advancing the physical chemistry of gels. It led to the creation of a new class of materials.

The first "true" hydrogel, which is considered the prototype of modern materials, was described in 1949. This hydrogel, composed of polyvinyl alcohol (PVA) crosslinked with formaldehyde, combines hydrophilicity with stability in aqueous environments, marking a significant advancement toward the medical application of hydrogels [4].

A breakthrough in hydrogel development occurred in the 1960s with the synthesis of poly(2-hydroxyethyl methacrylate) (pHEMA). This polymer served as the foundation for the first soft contact lenses, successfully combining essential performance characteristics and effectively defining the contemporary direction of hydrogel materials [5, 6].

The evolution of hydrogel technologies has shown a gradual increase in compositional complexity and functionality, progressing from simple crosslinked polymers to advanced adaptive systems. Based on historical stages and technological features, three main generations of hydrogels can be distinguished.

First-generation hydrogels, developed in the 1960s, are chemically crosslinked polymer networks characterized by high swelling, sufficient mechanical strength, and stability in aqueous environments. These early hydrogels established the foundation for subsequent modifications and advancements in polymer systems [1, 5].

Second-generation hydrogels, developed during the 1970s and 1980s, are stimuli-responsive materials that respond to external factors such as temperature changes, pH changes, or variations in biomolecule concentration. These properties enabled their application in controlled drug release and the creation of adaptive biomaterials [1, 5].

Third-generation hydrogels, emerging since the 1990s, include stereocomplex or physically crosslinked materials. In these hydrogels, intermolecular interactions (such as PEG–PLA complexes or cyclodextrins) provide controlled mechanical, thermal, and biodegradation properties. This generation focuses on enhanced controllability and functionality, significantly broadening their applications in biotechnology and medicine [1, 5].

The evolution of hydrogels — from colloidal gels to advanced adaptive systems — demonstrates the rapid progress of these materials and emphasizes their extensive potential for use in various scientific and industrial fields [5, 7, 8].

Classification of Hydrogels and Their Properties

Hydrogels are three-dimensional crosslinked networks of polymer chains that can absorb and retain large amounts of water within their structural cavities. This high water-retention capacity arises from the presence of hydrophilic groups in the polymer chains, such as -NH_2, -OH, -COOH, and -SO_3H. Additionally, structural features like capillary effects and the osmotic gradient between the polymer phase and the surrounding environment contribute to this property. Furthermore, the spatial structure of hydrogels provides stability and resistance to dissolution, which is crucial for their practical applications [4].

The literature presents a diverse range of hydrogel classifications that highlight their varied structural and functional characteristics. A multifactorial approach to classification enables systematic description

of these materials and identification of key parameters governing their specific applications. Hydrogels are typically classified based on several factors, including the type of crosslinking, their origin, method of preparation, physical properties, and their response to external stimuli, among others [8–9].

Hydrogels can be classified by origin into three categories: natural, synthetic, and semi-synthetic. Natural hydrogels are derived from substances such as cellulose, chitosan, collagen, alginate, hyaluronic acid, gelatin, and fibrin. They are known for their high biocompatibility, bioactivity, and biodegradability. However, they typically have lower structural stability and mechanical strength. Synthetic hydrogels are prepared from polymers such as polyvinyl alcohol (PVA), polyethylene glycol (PEG), polyethylene oxide (PEO), polyacrylamide (PAAM), and poly(2-hydroxyethyl methacrylate) (pHEMA). These materials are more stable and have higher mechanical strength compared to natural hydrogels. Semi-synthetic hydrogels consist of chemically modified natural polymers or a combination of natural and synthetic compounds. This approach allows for an optimal balance between bioactivity and mechanical properties by adjusting various chemical parameters [10, 14].

Hydrogels can be classified based on their network structure into several categories: homopolymeric, copolymeric, and interpenetrating polymer network (IPN) hydrogels. Homopolymeric hydrogels are composed of a single monomer type, which serves as their fundamental structural unit. In contrast, copolymeric hydrogels consist of two or more different types of monomers that can vary in hydrophilicity and spatial arrangement, including random, block, or alternating sequences. Interpenetrating polymer network (IPN) hydrogels are systems formed by two or more independently crosslinked synthetic or natural polymer components [10–12].

The structural organization of hydrogels can range from amorphous to crystalline or semi-crystalline, directly influencing their elasticity, swelling capacity, and permeability. An important aspect of hydrogels is their crosslinking type, which divides them into two categories: physically and chemically crosslinked. Physically crosslinked hydrogels are formed through weak intermolecular interactions, while chemically crosslinked hydrogels are characterized by stable covalent bonds. The method used to fabricate hydrogels determines their macroscopic form, such as matrices, films, or microspheres, which is critical for the delivery of active components in pharmaceutical and cosmetic applications [10, 11].

An important way to classify hydrogels is by whether their polymer chains carry an electric charge. Hydrogels can be categorized into four types: neutral (non-ionic), ionic (anionic or cationic), polyampholytic (ampholytic electrolytes), and zwitterionic. The charge state of a hydrogel network affects not only its hydrophilicity but also its ability to interact with biomolecules and its sensitivity to changes in the surrounding ionic strength [10–12].

Significant research attention has been devoted to stimuli-responsive, or “smart” hydrogels. These hydrogels can respond to various types of stimuli, which are generally classified as physical, chemical, or biological. Physical stimuli include changes in temperature, pressure, light, or exposure to electric and magnetic fields. Chemical stimuli involve variations in pH, ionic strength, or solvent composition. Biological stimuli arise from interactions with biological agents such as antigens, ligands, or enzymes. Based on the responsiveness to external conditions, hydrogels are commonly classified into two main categories: conventional and smart hydrogels. Conventional hydrogels typically exhibit only minor responses, such as moderate swelling, when exposed to external stimuli and often possess limited mechanical strength. In contrast, smart hydrogels are highly sensitive to even slight environmental changes and can rapidly adjust their physical properties, including mechanical strength and degree of swelling. Owing to this adaptive behavior, smart hydrogels are particularly promising for applications in cell engineering, tissue platform development, and the targeted delivery of active components [10–13, 15].

The diversity of hydrogels reported in the literature showcases a wide range of physicochemical and functional properties. One of the key parameters characterizing these materials is their swelling behavior, which occurs through a multistage mechanism. Initially, water molecules interact with the most polar and hydrophilic functional groups of the polymer, forming what is referred to as primary bound water. As these groups become saturated, the polymer network expands, revealing hydrophobic regions that also interact with water molecules, leading

to the formation of secondary bound water. The combination of these two types of water (primary and secondary) constitutes the total bound water and initiates the swelling process. After all functional groups have been hydrated, excess water accumulates in the interchain spaces and macropores of the polymer network, thereby forming free (bulk) water. Network expansion continues until equilibrium is reached between the osmotic pressure driving water into the hydrogel and the elastic forces of the polymer network that oppose further deformation. The degree of swelling at equilibrium is a crucial parameter, as it is related to the crosslinking density, degradation rate, and mechanical properties of the material. The ratio of free to bound water can be assessed using various techniques, including nuclear magnetic resonance (NMR) spectroscopy, differential scanning calorimetry (DSC), and molecular probe methods. From a practical standpoint, parameters such as the swelling ratio, gel fraction, and mass loss upon drying are also significant, as they provide rapid and reproducible means for comparing different hydrogel systems [16–18].

The mechanical properties of hydrogels are critical characteristics for their applications in biotechnology, pharmaceutical sciences, and biomedicine. Key characteristics such as material stiffness, elasticity, and mechanical strength can be intentionally tailored by tuning polymer concentration, the type and amount of crosslinking agents, and by adding different monomers or functional groups to the polymer network. Generally, a higher degree of crosslinking increases mechanical strength but can reduce elasticity and elongation at break, making the material more brittle. Conversely, a lower crosslinking density enhances flexibility and deformability, though it may compromise the hydrogel's structural stability. Therefore, achieving an optimal balance between strength and elasticity is essential, especially in therapeutic delivery systems and tissue engineering applications, where the material must maintain structural integrity while adapting to mechanical stresses. Various experimental techniques are used to assess the mechanical behavior of hydrogels. These techniques include compression and tensile testing, localized indentation measurements, rheological analysis, and dynamic mechanical analysis. Such methods help characterize viscoelastic behavior, resistance to cyclic loading, and the material's ability to recover its original structure after deformation. These parameters are vital for predicting hydrogel performance under practical operating conditions [16–18].

Porosity and the morphology of the internal structure of hydrogels also significantly affect their properties. Pores may form during synthesis as a result of phase separation or arise from the spatial organization of polymer chains within the network. Pore morphology can range from closed and semi-open cavities to complex channel-like structures with constrictions and necks. An integrated parameter describing pore architecture, shape, distribution, and interconnectivity is called tortuosity. The pore size distribution in hydrogels is primarily affected by three key factors: the concentration of chemical crosslinks between polymer chains, the density of physical entanglements within the polymer network, and the overall charge of the polyelectrolyte hydrogel. These parameters can be quantitatively linked to the concentrations of the monomer and crosslinking agent used during synthesis. To investigate hydrogel porosity, researchers employ a combination of theoretical and experimental approaches. The most commonly used experimental methods include the use of labeled molecular probes with different molecular weights or sizes, volume determination techniques such as the Archimedes method and liquid displacement measurements, and optical and electron microscopy. More specialized methods for detailed morphological analysis include mercury intrusion porosimetry and gas pycnometry [16–17].

The degree of crosslinking is a crucial parameter that determines the functional properties of a hydrogel. The polymer network can be formed through physical mechanisms, such as hydrogen bonding, hydrophobic interactions, and ionic complexes, or through chemical mechanisms involving covalent bonds. By controlling the degree of crosslinking, it is possible to deliberately tailor the material's properties and optimize it for a variety of applications. In principle, this approach allows a single-base polymer to exhibit a wide range of functionalities, from soft, highly elastic hydrogels to rigid structures that can withstand mechanical stress [16–18].

Hydrogels have a wide range of applications in biotechnology and medicine, making biocompatibility a crucial factor in determining their suitability for biomedical applications [18]. Biocompatibility refers to a material's ability to perform its intended

function without inducing adverse local or systemic effects while maintaining an appropriate host response. The biological safety of hydrogels is commonly evaluated according to standardized protocols, including those outlined in ISO 10993 series, which assess cytotoxicity, sensitization, irritation, systemic toxicity, genotoxicity, implantation compatibility, and hemocompatibility. *In vitro* studies typically involve cell viability assays (e.g., MTT or Live/Dead assays) and monitoring changes in cell morphology, proliferation, and metabolic activity. In contrast, hemocompatibility is evaluated using hemolysis and blood coagulation tests. *In vivo* assessment includes histological examination of the implantation site to identify inflammatory cell infiltration, fibrous capsule formation, tissue integration, and immune responses, thereby providing essential information on the hydrogel's biological performance under physiological conditions. Equally important is the assessment of the long-term stability of hydrogels *in vivo*, which determines their ability to maintain structural integrity and therapeutic functionality throughout the intended period of application. This includes monitoring degradation kinetics, changes in mass, mechanical properties, structural integrity, swelling behavior, and the biological effects of degradation products [19, 20].

Key considerations in the evaluation of hydrogel safety include potential risks such as chronic inflammatory responses, foreign-body reactions, premature or excessively slow degradation, accumulation of degradation by-products, and the loss of mechanical integrity, all of which may compromise therapeutic efficacy and patient safety [2, 21]. Therefore, the degradation profile of hydrogels should be carefully tailored to match the rate of tissue regeneration while minimizing prolonged material persistence and preventing the release or accumulation of potentially harmful degradation products.

Although most recently developed hydrogel systems have demonstrated favorable short-term biocompatibility and promising degradation profiles, evidence of their long-term biological performance remains limited. Most available studies are based on short-term *in vitro* experiments or small-animal models, whereas comprehensive long-term preclinical and clinical investigations are still scarce. Further research should therefore prioritize standardized long-term assessments of immune responses, degradation-product safety, mechanical durability, and functional performance under physiologically relevant conditions. Such studies will be essential for improving the predictability, safety, and successful clinical translation of hydrogel-based biomaterials.

Methods of Hydrogel Preparation

Hydrogel fabrication methods are generally categorized into chemical and physical approaches. The choice of method determines the resulting structure, functional properties, and potential applications of the materials. Most approaches use hydrophilic monomers as a base; however, incorporating hydrophobic monomers enables targeted control of mechanical strength, stability, and swelling rate. The composition of the reaction mixture depends on the selected monomers, initiators, and crosslinking agents. Controlling the degree of monomer conversion and ensuring thorough purification are critical for obtaining a final material that is stable and safe [22–23].

Technological parameters, such as the sequence and intensity of mixing, temperature, and degassing, significantly affect the quality of the final material. Air inclusions can affect mechanical strength and transparency, while improper addition of components may lead to uneven crosslinking. These factors are particularly crucial when encapsulating therapeutic agents or plant extracts [24].

Physical crosslinking relies on reversible, noncovalent interactions, such as hydrogen bonding, crystallization, ionic interactions, or protein-polymer interactions. Hydrogels formed through physical crosslinking do not require additional chemical reagents, providing advantages such as the absence of toxic residues and high biocompatibility. This category includes systems based on ionic gelation (e.g., alginate), thermoresponsive polymers, and pH-responsive polymers. Due to the simplicity and safety, physical crosslinking is widely used in pharmaceutical applications, especially in sustained-release systems based on hydroxypropyl methylcellulose or other semi-synthetic polysaccharides [25–27].

Chemical crosslinking involves the formation of stable covalent bonds between polymer chains, enhancing mechanical strength and enabling controlled porosity. Hydrogels can be prepared via radiation-induced crosslinking, free-radical polymerization, enzymatic reactions, or highly selective click reactions. One of the most controllable approaches is photopolymerization, which uses

photosensitive initiators. This method allows for precise regulation of the gelation rate, the formation of desired porous structures, and *in situ* application (directly at the site of use), making it particularly advantageous for medical and engineering applications [25–27].

Current trends in hydrogel materials science emphasize "green" synthesis approaches and the minimization of the use of low-molecular-weight chemical agents. There is a special focus on physical crosslinking processes and combined (hybrid) methods, such as chemo-physical crosslinking. This approach enables the production of materials with enhanced safety, which is critically important for their biomedical applications [25–27].

Applications of Hydrogels and Future Perspectives

The historical development of hydrogels as materials, along with the current state of research, demonstrates their transformation from simple polymeric matrices to advanced, high-tech systems with customizable properties and expanded applications. Based on an analysis of the literature, it can be concluded that contemporary studies encompass a wide range of hydrogels synthesized from both synthetic and natural polymers, providing the potential for targeted use in specific fields.

Hydrogels are characterized by their biocompatibility, high water-retention capacity, and structural flexibility, making them essential materials in tissue engineering, biotechnology, pharmaceutical sciences, and biomedicine. Practical applications of hydrogels include ophthalmic formulations, wound dressings, drug delivery systems, transdermal and dental materials, implants, and injectable platforms. Additionally, certain types of hydrogels are commonly used in hygiene products, cosmetics, agriculture, and hybrid biosystems that incorporate encapsulated living cells. This wide range of applications highlights the versatility and significance of hydrogels as next-generation materials [28–31].

Ophthalmology, especially the production of contact lenses, represents the most established and technologically advanced application of hydrogels. For hydrogels to be suitable for this purpose, they must fulfill several crucial requirements. These include sufficient mechanical strength, optimal oxygen diffusion (or gas permeability), excellent optical properties and transparency, resistance to hydrolysis, the ability to undergo sterilization, and non-toxicity and biocompatibility. The combination of these characteristics is vital for ensuring the safety of the material and the comfort of the user. The clinical reliability of hydrogel materials is evidenced by the widespread use of FDA-approved silicone hydrogel formulations (e.g., senofilcon A, lotrafilcon A), which provide superior oxygen transmission and reduced corneal hypoxia compared with conventional hydrogel lenses. In addition, preclinical and clinical studies have demonstrated the potential of therapeutic hydrogel contact lenses as sustained ocular drug delivery platforms amв as supportive materials for corneal wound healing and ocular surface regeneration. These findings further emphasize the importance of continuous optimization of hydrogel formulations for ophthalmic applications [32–33].

Hydrogels hold significant potential for biomedical research due to their ability to create three-dimensional hydrated matrices that replicate the complexity of the natural extracellular matrix. These characteristics make hydrogels an ideal material for scaffolds in three-dimensional cell cultures, which are extensively used to study cellular behavior, conduct toxicological assessments, screen pharmacological agents, and support tissue engineering applications.

In pharmaceutical technology, hydrogel-based polymers have proven to be versatile platforms for developing controlled drug delivery systems. Depending on the polymer's chemical structure and architectural organization, it can form various nanostructures, such as polymeric micelles or vesicles. These systems effectively protect labile active pharmaceutical ingredients (APIs) and bioactive compounds from enzymatic or hydrolytic degradation while enabling their sustained and site-specific release. The therapeutic potential of hydrogel-based drug delivery systems has been demonstrated in numerous preclinical and clinical studies, particularly in oncology, localized drug delivery, and regenerative medicine. For example, stimuli-responsive hydrogels (e.g., pH-, thermo-, and redox-sensitive systems) have shown promising efficacy in preclinical tumor models by providing spatiotemporally controlled release of chemotherapeutic agents such as doxorubicin and paclitaxel, thereby enhancing antitumor activity and reducing systemic toxicity [34–37].

Hydrogel-based wound dressings have gained widespread popularity due to

their combination of moisturizing, anti-inflammatory, hemostatic, and antibacterial properties. Owing to their structure, such dressings create an optimal environment for tissue regeneration by maintaining an appropriate moisture level. Additionally, the use of natural polymers such as cellulose, chitosan, collagen, and hyaluronic acid enhances their biological functions, stimulating angiogenesis and activating tissue repair processes. Commercially available hydrogel dressings such as Purilon and HydroTac have been successfully used to manage burns, chronic wounds, pressure ulcers, and diabetic foot ulcers [38–39].

Tissue engineering is one of the most promising and significant fields in which hydrogels are used as scaffold materials. This is due to their biocompatibility, biodegradability, and elasticity. The structure of hydrogels mimics the extracellular matrix, providing the necessary support for cell adhesion, proliferation, differentiation, and regeneration. Currently, hydrogels are being actively researched for the regeneration of neural, cardiac, cartilage, and bone tissues. In these applications, they serve as cell carriers, matrices for incorporating growth factors, or structural frameworks for building new tissue. Injectable and 3D-bioprinted hydrogels loaded with stem cells or growth factors have demonstrated enhanced tissue regeneration and functional recovery in bone, cartilage, and cardiac repair, while clinically approved hydrogel matrices such as Chondro-Gide and Novocart Basic further confirm their therapeutic potential [37, 40–41].

In addition to biomedical uses, stimulus-responsive hydrogels have garnered increasing attention for their potential in selective separation and purification processes. Hydrogel-based porous membranes function as semipermeable barriers, with separation occurring primarily via sieving. The efficiency of separation depends on factors such as pore size, the chemical composition of the material, and specific interactions between the polymer network and the substances passing through it. Due to these characteristics, hydrogel membranes have found widespread applications in bioseparation technologies, particularly for the purification of proteins, biomolecules, and cellular products. In particular, thermo-responsive (e.g., poly(N-isopropylacrylamide)-based) and pH-sensitive hydrogel membranes enable reversible control over pore architecture and surface hydrophobicity in response to minor environmental triggers. The practical feasibility has been demonstrated in advanced bioprocessing, including continuous purification of monoclonal antibodies, size-selective isolation of extracellular vesicles and exosomes, and ultrafiltration of plasma proteins, thereby offering high selectivity without prote.

In addition to biomedical applications, hydrogels have attracted considerable attention in agriculture and agronomic practices. As effective soil conditioners and moisture-retention agents, superabsorbent hydrogels can improve soil structure and physical properties, increase water-holding capacity, and alleviate drought-induced stress in crops. Functionalized hydrogel networks can act as controlled-release systems for agrochemicals, fertilizers, and micronutrients, promoting more efficient nutrient utilization while reducing leaching losses and potential environmental toxicity. Recent advances in hydrogel processing and the development of biodegradable polymer matrices have further facilitated their application in agriculture, providing environmentally sustainable approaches to improving crop productivity and enhancing the resilience of agricultural systems to climate-related stresses [43–44].

One of the most innovative directions in modern hydrogel technology is the integration of natural biologically active compounds into polymer matrices. Due to their hydrophilicity and high absorption capacity, hydrogels provide ideal conditions for incorporating plant extracts, retaining them, and allowing for their gradual release. This approach leads to the development of multifunctional systems that are already being used in sustained-release pharmaceutical formulations, anti-inflammatory cosmetic products, and biomedical materials [3, 45–46].

Enhancing the efficiency of plant extract utilization aligns with the principles of sustainable development, as secondary metabolites are an accessible, renewable, and safe source of bioactive molecules. In clinical practice, there is a growing number of patients with dermatological lesions, trophic ulcers, and purulent wounds of various origins. This trend emphasizes the need for affordable, safe, and highly effective hydrogel-based materials for local application. Such materials should not only protect the affected area but also modify the local microenvironment to promote faster healing [47].

The growing interest in natural bioactive compounds is fueled by a combination of scientific, technological, and practical factors. First, natural secondary metabolites exhibit

high chemical and biological diversity, offering a wide range of potential pharmacological activities. Additionally, their use as biochemical probes in fundamental research is expanding, enhancing the value of these molecules in modern experimental approaches.

Significant progress has been made through the development of highly sensitive analytical methods that allow for the efficient identification and quantitative measurement of biologically active compounds. Advances in extraction and purification techniques have further enhanced the availability, stability, and quality of natural compounds. Another important factor driving this interest is the increasing demand for natural formulations in the pharmaceutical, cosmetic, and biotechnological sectors, where they are considered safer and potentially more effective alternatives to synthetic counterparts [46, 48–49].

Plant extracts possess significant biological activity due to their rich content of secondary metabolites, such as flavonoids, terpenes, phenolic compounds, alkaloids, catechins, coumarins, and carbohydrates. The structural diversity of these compounds contributes to a range of activities, including antibacterial, antioxidant, anti-inflammatory, and regenerative effects. However, many bioactive compounds are prone to instability, degradation, and have a short duration of biological activity. To address these issues, one effective technological strategy is to incorporate extracts into hydrogel matrices. This approach helps to enhance the stability of the extracts and prolong their beneficial effects [48–49].

A particular focus in this field is on hydroxypropyl methylcellulose (HPMC) and synthetic copolymeric hydrogel networks such as poly(2-hydroxyethyl methacrylate)-co-poly(vinylpyrrolidone) (pHEMA-PVP). These matrices form stable, highly hydrated networks capable of providing controlled release of bioactive agents.

The therapeutic efficacy and translational potential of phytocompound-loaded hydrogels are supported by a growing body of preclinical and clinical evidence. In preclinical *in vivo* studies, including full-thickness burn and excision wound models in rodents, hydrogels enriched with polyphenol- and flavonoid-rich plant extracts (e.g., *Centella asiatica*, *Aloe vera*) significantly accelerated wound closure, promoted neovascularization, reduced oxidative stress, and downregulated the expression of key pro-inflammatory cytokines, including IL-6 and TNF-α. Clinically, herbal-derived hydrogel formulations have demonstrated promising outcomes in the management of chronic venous ulcers, burn wounds, and inflammatory skin conditions by maintaining an optimal moist wound environment while providing antimicrobial, anti-inflammatory, and analgesic effects [3, 50–51].

Our previous research has focused on HEMA-PVP hydrogel incorporating extracts from medicinal plants. Experimental studies demonstrated pronounced antioxidant and antibacterial activities *in vitro*, indicating their potential for future wound-healing applications [52–53].

Thus, incorporating natural extracts into hydrogel matrices enhances the stability of bioactive compounds and enables their controlled release. Supported by growing preclinical and emerging clinical evidence, these multifunctional systems represent promising platforms for advanced pharmaceutical and biomedical applications.

Industrial Scalability, Economic Feasibility, and Regulatory Challenges

Transitioning from laboratory synthesis to industrial-scale manufacturing requires strict compliance with Good Manufacturing Practice (GMP) and robust quality control strategies to ensure batch-to-batch reproducibility. This challenge is particularly pronounced for hydrogels incorporating natural plant extracts because the composition of botanical raw materials varies according to geographical origin, seasonal conditions, and extraction procedures. Consequently, standardization of bioactive compounds using validated analytical techniques (e.g., high-performance liquid chromatography, spectroscopic analysis, and rheological characterization) is essential for controlling extract composition, polymer crosslinking, and the physicochemical properties of the final hydrogel. Furthermore, scalable manufacturing requires continuous monitoring of critical process parameters to maintain product consistency and therapeutic performance [54].

Sterilization remains one of the major technological bottlenecks in hydrogel production. Conventional steam sterilization may degrade thermolabile bioactive compounds and alter the polymer network, whereas ionizing radiation can induce polymer chain scission or additional crosslinking, thereby affecting swelling behavior, mechanical properties, and drug release profiles. Ethylene oxide sterilization may also leave toxic

residues within highly hydrated matrices. Consequently, aseptic manufacturing, sterile filtration of precursor solutions, and other low-temperature sterilization approaches are increasingly considered as suitable alternatives, although they increase manufacturing complexity and production costs [55].

The commercial viability of hydrogel-based biomaterials is largely determined by raw material costs, manufacturing efficiency, and storage stability. Although natural biopolymers such as cellulose derivatives, chitosan, collagen, and hyaluronic acid are widely available, purification to medical-grade quality substantially increases production costs. In contrast, synthetic polymers, including PHEMA, PVP, and PEG derivatives, generally provide superior reproducibility and more predictable material properties but require expensive high-purity monomers and controlled synthesis conditions. Additional economic challenges include specialized packaging, sterilization, and storage requirements, such as barrier packaging or lyophilization, to preserve hydrogel stability and prevent microbial contamination during transportation and long-term storage [56–57].

Commercialization of hydrogel-based medical products requires compliance with international regulatory standards, including GMP, ISO 13485, and ISO 10993, as well as the regulatory requirements established by the FDA and EMA. Depending on their intended application and composition, hydrogel systems containing pharmaceutical or biological components may be regulated as combination products, requiring comprehensive evaluation of safety, efficacy, manufacturing reproducibility, and long-term stability. Therefore, implementing sustainable manufacturing strategies and considering regulatory requirements in the early stages of product development are essential to successfully translate hydrogel technologies from laboratory research into clinically approved, commercially viable biomedical products [56–57].

Conclusions

An analysis of the literature indicates that hydrogels have become one of the most versatile platforms for biomedical and biotechnological applications. Their main advantages include high water retention capacity, biocompatibility, mechanical stability, the ability to achieve controlled release of active substances, and the potential for stimuli-responsive behavior. These properties are fundamental to their leading role in the development of innovative materials.

A rapidly growing area of research is the integration of natural bioactive compounds into hydrogel matrices. The incorporation of phytocomponents, secondary metabolites, and synergistic functional agents enhances the therapeutic potential of such systems by providing antibacterial, anti-inflammatory, and antioxidant properties, as well as promoting angiogenesis and tissue regeneration. Studies have shown that combining plant extracts with polymeric materials yields multicomponent platforms with tunable properties and enhanced functionality.

Overall, the synthesis of scientific data confirms that hydrogels are key materials in modern biotechnology, providing structural support, enabling controlled delivery of bioactive substances, and enabling the creation of personalized therapeutic systems. The integration of hydrogel materials with active compounds creates opportunities to develop multifunctional systems with high stability, biological activity, and adaptability for specific applications. This trend defines a strategic direction for future research in materials science and biomedical technologies.

Author Contributions

Ya. I. Holubovska and M. S. Kurka — conceptualization; Ya. I. Holubovska — literature search and data analysis, original draft preparation, M. S. Kurka — review and editing, supervision. All authors have read and agreed to the published version of the manuscript.

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ТЕНДЕНЦІЇ СТВОРЕННЯ ТА ВИКОРИСТАННЯ ГІДРОГЕЛІВ ЯК ІННОВАЦІЙНИХ БІОМАТЕРІАЛІВ

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Мета. Узагальнити та систематизувати сучасні наукові дани щодо гідрогелів як одного з провідних класів біоматеріалів, проаналізувати етапи їхнього історичного розвитку, структурної та функціональної модифікацій, а також оцінити перспективи використання гідрогелевих систем у біотехнології, фармації, медицині та косметології.

Методи. Проведено комплексний аналіз та узагальнення наукових публікацій, присвячених гідрогелям: їх класифікація, особливості структури, фізико-хімічні властивості та методи отримання. Проаналізовано сучасні підходи до модифікації гідрогелевих матриць та напрями їх практичного застосування у різних галузях науки й промисловості.

Результати. Систематизовано відомості щодо основних типів гідрогелів, їх структурних особливостей та функціональних характеристик. Висвітлено ключові етапи еволюції гідрогелевих матеріалів та сучасні тенденції їх використання як інноваційних платформ для клітинної терапії, тканинної інженерії, медицини, фармації та біотехнології. Особливу увагу приділено потенціалу насичення гідрогелевих матриць біологічно активними речовинами, що відкриває можливості для створення систем із керованими властивостями, спрямованих на відновлення та покращення функціонального стану організму.

Висновки. Підтверджено провідну роль гідрогелів серед сучасних біоматеріалів завдяки поєднанню високої гідрофільності, біосумісності та можливості регулювання фізико-хімічних характеристик. Окреслено перспективні напрями подальших досліджень, спрямованих на розроблення мультифункціональних гідрогелів для потреб фармацевтичної та медичної галузей.

Ключові слова: гідрогель, біоматеріали, біотехнологія, біоактивні речовини.

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