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Review

Hydrogel Encapsulation Techniques and Its Clinical Applications in Drug Delivery and Regenerative Medicine: A Systematic Review

Bahareh Farasati Far, Maryam Safaei, Reza Nahavandi, Amir Gholami, Mohammad Reza Naimi-Jamal, Sujina Tamang, Jung Eun Ahn, Marzieh Ramezani Farani,* and Yun Suk Huh*

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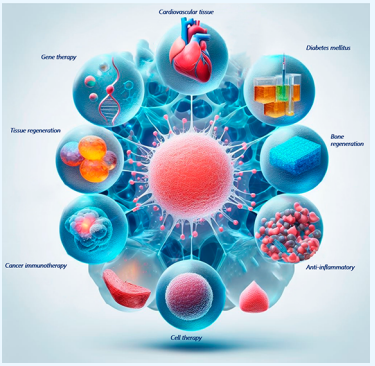
ABSTRACT: Hydrogel encapsulation is a promising carrier for cell and drug delivery due to its ability to protect the encapsulated entities from harsh physiological conditions and enhance their therapeutic efficacy and bioavailability. However, there is not yet consensus on the optimal hydrogel type, encapsulation method, and clinical application. Therefore, a systematic review of hydrogel encapsulation techniques and their potential for clinical application is needed to provide a comprehensive and up-to-date overview. In this systematic review, we searched electronic databases for articles published between 2008 and 2023 that described the encapsulation of cells or drug molecules within hydrogels. Herein, we identified 9 relevant studies that met the inclusion and exclusion criteria of our study. Our analysis revealed that the physicochemical properties of the hydrogel, such as its porosity, swelling behavior, and degradation rate, play a critical role in the encapsulation of cells or drug molecules. Furthermore, the encapsulation method, including physical, chemical, or biological methods, can affect the encapsulated entities' stability, bioavailability, and therapeutic efficacy. Challenges of hydrogel encapsulation include poor control over the release of encapsulated entities, limited shelf life, and potential immune responses. Future directions of hydrogel encapsulation include the development of novel hydrogel and encapsulation methods and the integration of hydrogel encapsulation with other technologies, such as 3D printing and gene editing. In conclusion, this review is useful for researchers, clinicians, and policymakers who are interested in this field of drug delivery and regenerative medicine that can serve as a guide for the future development of novel technologies that can be applied into clinical practice.



1. INTRODUCTION

Nanoscience is the study of materials and molecules on a scale of 1−100 nm.[1,2] Nanotechnology is an interdisciplinary science that uses nanostructures and special features and has made a great contribution to the progress and development of various sciences, such as nanomedicine and nanodrug delivery systems.[3] Nanomedicine refers to the application of nanotechnology in the field of medicine to treat diseases.[4] Advances in nanomedicine have led to the emergence of new aspects of medical science.[5] Nanobased drug delivery presents great advantages, including high charge efficiency, low clearance, combined treatment, and targeted delivery.[6,7] Many drug delivery systems (DDS) based on nanotechnology have been proposed in the past few years and applied to overcome drug-releasing challenges. Nanomedicine systems include a wide variety of nanostructures such as liposomes,[8] dendrimers,[9] nanocapsules,[10] solid lipid nanoparticles,[11] nanoemulsions,[12] hydrogels,[13,14] etc.

Hydrogels are a flexible and cross-linked polymer network based on hydrophilic macromonomers.[15,16] Since hydrogels have special properties such as biocompatibility, tunable mechanical and physicochemical properties, and high-water content, they have become a promising platform for drug delivery.[17−19] The unique mechanical and chemical properties of hydrogel have made it highly biocompatible. The softness and flexibility of hydrogel make it compatible with soft and biological tissues, which lowers the risk of inflammation and immune reaction.[20,21] Hydrogels act as a promising carrier for the delivery of drugs as they ensure various bioactive agents from antagonistic conditions of the body and thus have attained the great interest of researchers.[22−24] Encapsulation of cells or drug molecules within hydrogels can protect them from harsh physiological conditions, such as enzymatic degradation and immune responses, while enhancing their therapeutic efficacy and bioavailability.[25,26] Accordingly, hydrogel encapsulation has been assessed extensively in chronic conditions such as cancer and neurodegenerative disorders and other conditions like wound healing, tissue regeneration, and drug delivery. Despite the increasing interest in hydrogel encapsu-

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lation, there is no agreement on the optimal hydrogel type, encapsulation method, or clinical application. Moreover, the literature on hydrogel encapsulation for cell and drug delivery is scattered and fragmented, making it difficult to compare the different approaches and identify the most promising strategies for clinical translation. Therefore, a systematic review of hydrogel encapsulation techniques and their potential for clinical application is crucial to provide a comprehensive and up-to-date overview.

This systematic review's objective is to search the existing literatures on hydrogel encapsulation and evaluate the current advances in DDS. In particular, this review will focus on the following questions:

1- What are the different hydrogel types and their physicochemical properties, and how do they influence the encapsulation of cells or drug molecules?
2- What are the different methods used for encapsulating cells or drug molecules within hydrogels, and how do they affect the stability, bioavailability, and therapeutic efficacy of the encapsulated entities?
3- What are the clinical applications of hydrogel encapsulation, and what are the benefits and limitations of each application?
4- What are the challenges and future directions of hydrogel encapsulation for cell and drug delivery, and how can they be addressed?

In summary, this systematic review will provide an in-depth and critical analysis of hydrogel encapsulation techniques and their clinical application for cell and drug delivery. This review will be useful for researchers, clinicians, and policymakers who are interested in this field, as it will provide a comprehensive and up-to-date overview of the state-of-the-art at the moment and where hydrogel encapsulation is headed. Ultimately, the goal of this review is to accelerate the translation of hydrogel encapsulation techniques into clinical practice, leading to improved patient outcomes.

2. METHODOLOGY

The systematic literature review (SLR) was carried out in compliance with the 2020 update of the Preferred Reporting Items for Systematic Reviews (PRISMA) guidelines.[27] A systematic search of the PubMed databases to identify relevant studies published between 2008 and 2023 is conducted. The search terms will include "hydrogel encapsulation" and "hydrogel drug delivery". We include all the studies that investigate the use of hydrogel encapsulation in cell and drug delivery and exclude studies that focus on other biomaterials or applications. The titles and abstracts of the selected research will be screened by two independent and unbiased reviewers, and the full-text articles will be examined for eligibility. Data extraction from the qualifying studies will be done, and the Cochrane Risk of Bias tool will be used to evaluate the quality of research.

2.1. Database Selection. In this review, PubMed was searched for information on hydrogel encapsulation, and hydrogel-based drug delivery. The search yielded approximately 7,411 results.

2.2. Search Strategy and Strings' Recognition. As proposed,[28] the first stage of the SLR was the selection process of articles for this SLR, which was systematically performed. As Table 1 demonstrates, the identifying databases by screening the preagreed keywords which was employed for this SLR. The search resulted in 9 article studies. A total of 5 journals were identified featuring our aim of the study.

Table 1. Search Strings Applied to the SLR

Databases	Search Strings
PubMed, ScienceDirect, MDPI	Hydrogel; hydrogel encapsulation; hydrogel drug delivery

2.3. Screening Criteria and Data Analysis. The second step of this SLR involved screening the item for the application of the inclusion and exclusion criteria. Accordingly, the first features considered were the type of study, the language, and the timeline that was considered from 2008 to 2023. Hence, the SLR focused on the original English articles with empirical data from original research articles, randomized control trials (RCTs), and clinical trials. Some studies were filtered automatically from the databases, such as conference papers, case reports/series, non-English published papers, text books/chapters, and editorials. Also, no limitation was assumed for the intervention target. Additionally, all the possible potential for clinical application was taken into consideration (Figure 1).

Consequently, Table 2 criteria were used to filter the 7411 articles in the list. For a review analysis, the qualitative and quantitative aspects of the confirmed paper were performed, which allowed the researcher to define the answer concerning the question. Subsequently, by the assessment, the result was 43 screened articles. The very first steps in the data abstraction steps required gathering together all significant facts that addressed the study objectives and establishing links between the original data. Through concept or associated ideas, the basic data were transformed into usable data.

3. HYDROGEL AND ITS CHARACTERISTICS

Hydrogels are classified based on various factors, such as cross-linking, source, ionic charges, and stimuli response. Hydrogels are classified into three categories based on cross-linking: chemical, physical, and dual-network cross-linking. A chemical process, namely chemical covalent cross-linking (either simultaneously or postpolymerization), is employed to create a chemical hydrogel. Physical cross-linking is achieved through processes such as chain aggregation, hydrophobic association, hydrogen bonding, and crystallization. Physical hydrogels exhibit reversibility through conformational changes, while chemical hydrogels are permanent and irreversible due to configurational alterations. The third category is the dual-network hydrogel, created by combining chemical and physical cross-linked hydrogels through electrostatic interactions. Dual-network hydrogels exhibit a notable liquid uptake capacity across a broad pH range and demonstrate increased sensitivity to pH changes when compared to chemical hydrogels.[30,31] According to the source, hydrogels are divided into three categories: natural, synthetic, and hybrid.[32] Natural hydrogels are the result of natural polymerization of monomers, which are nontoxic and highly biocompatible.[33] Depending on the chemical structure, the natural hydrogel is divided into many subgroups, the main of which are polysaccharides (chitin, chitosan, alginate) and protein or polyamides (collagen, gelatin).[34,35] Synthetic hydrogels are obtained from polymerization of monomers by synthetic methods. These hydrogels have more flexibility, stability and higher water absorption capacity compared to natural hydrogels.[36] Poly(2-hydroxyethyl methacrylate) (pHEMA), or poly(2-hydroxyethyl methacrylate),[37] polycaprolactone,[38] Polyethylene glycol (PEG)[39] etc.

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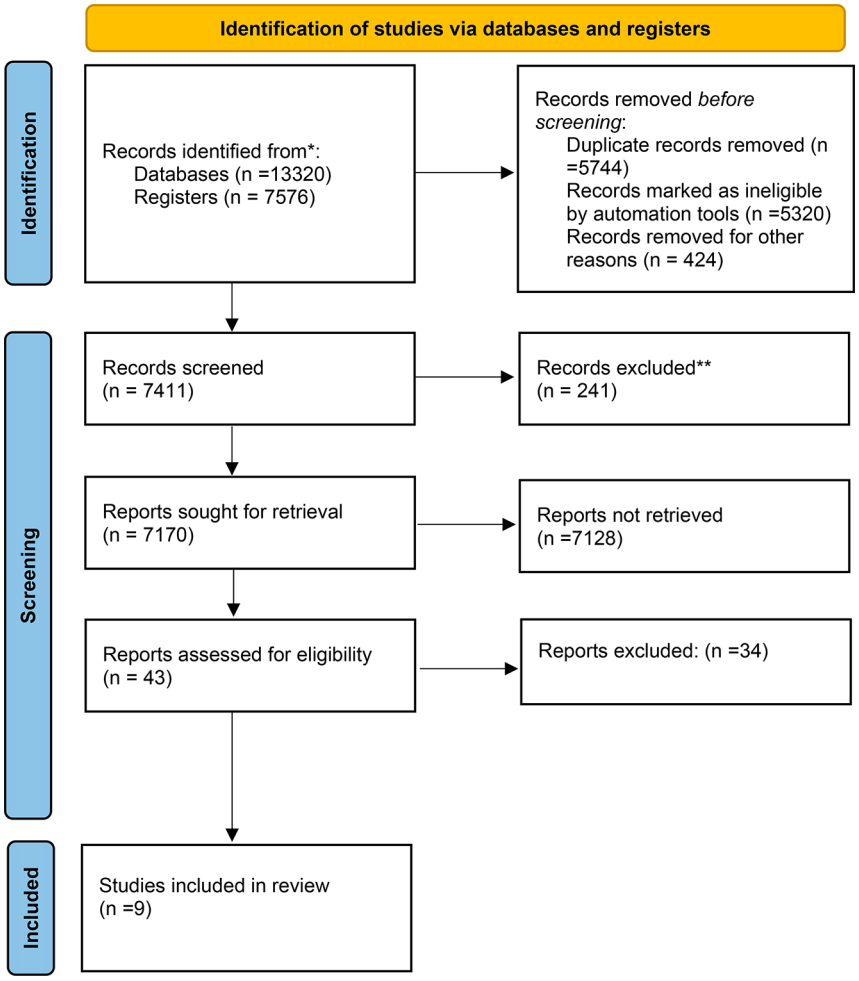

Figure 1. PRISMA SLR 2020 flow diagram for inclusion or exclusion criteria (based on ref 29).

Table 2. Inclusion and exclusion Criteria for the SR in Hydrogel Encapsulation Technique and Its Clinical Applications in Cell and Drug Delivery

Criteria	Inclusion	Exclusion
Languages	English	Non-English
Type of Study	Articles with empirical data, including RCTs, clinical research, original in vivo article	Review, case series and reports, conference papers, book chapters, editorials, mechanism studies, *in vitro* studies
Timeline	2008−2023	<2008
Intervention Targets	Cancer, tumor, tissue regeneration, anti-inflammatory, neuroprotection, cardiovascular, diabetes mellitus	All possible potential for clinical application
Clinical Outcome	Efficacy, safety and comparable effects	Quality of life (QOL)

Are synthetic polymers that is frequently employed. Hybrid hydrogels are the result of combining natural and synthetic hydrogels that can have combined properties of both synthesis and hybrid hydrogels. These hydrogels offer better mechanical properties due to the presence of synthetic hydrogel and higher biocompatibility due to the presence of natural hydrogel compared to net hydrogels.[40−42] Furthermore, hydrogels can be classified according to their electrical charge, such as ionic (cationic or anionic), neutral, or zwitterionic (containing both cationic and anionic groups). Stimuli-responsive hydrogels react to environmental stimuli, undergoing unforeseen alterations in their growth actions, network structure, mechanical strength, and permeability. Consequently, they are referred to as environmentally sensitive smart hydrogels. Physical stimuli encompass pressure, light, temperature, magnetic fields, electric fields, and mechanical stress, all of which induce molecular interactions to change at critical onset points. Chemical stimuli involve factors such as pH, chemical agents, and ionic conditions. These factors bring about changes in interactions between polymer chains and solvents, as well as between polymer chains at the molecular level. A biochemical stimulus includes responses to enzymes, ligands, antigens, and other biochemical agents. Therefore, stimuli-responsive (smart) hydrogels are appealing biomaterials for applications in biomedicine, pharmaceuticals, and biotechnology (Figure 2).

3.1. Hydrogel Encapsulation Methods. When creating an appropriate hydrogel for encapsulating cells, various factors need to be taken into account. Before encapsulation, cells are held in a liquid precursor solution. It is crucial that the gelation

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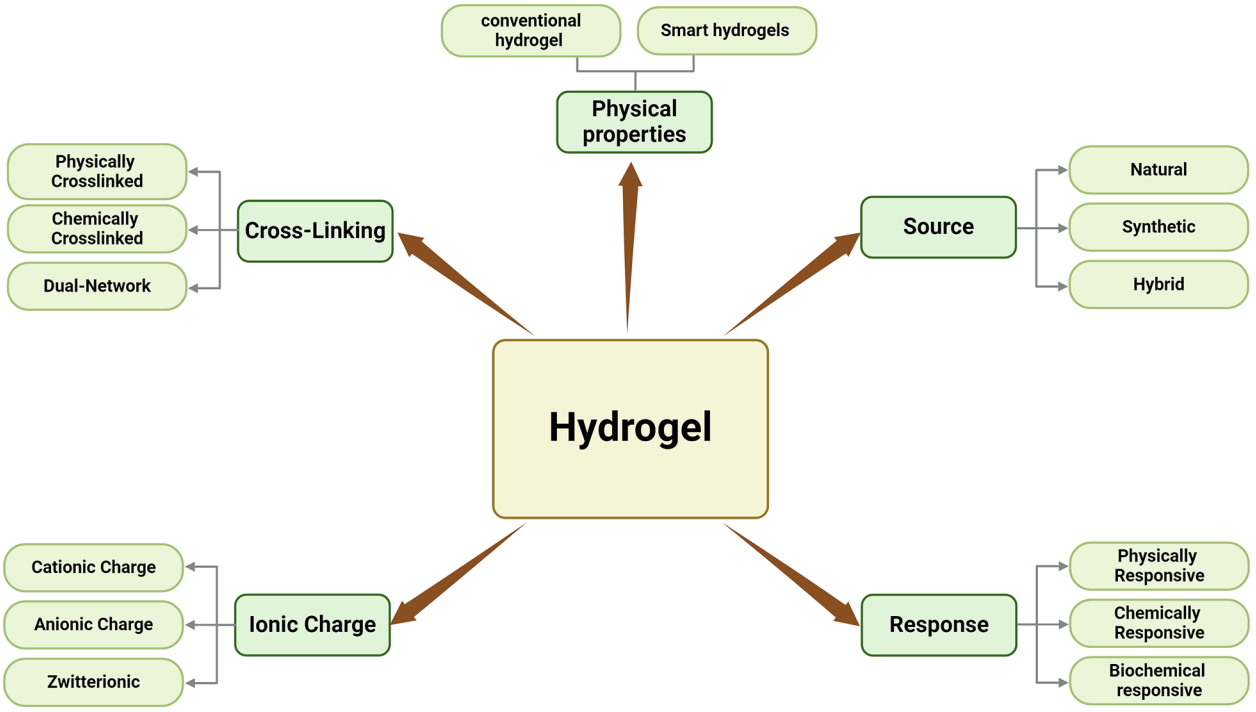

Figure 2. Schematic illustration of the classification of hydrogels.

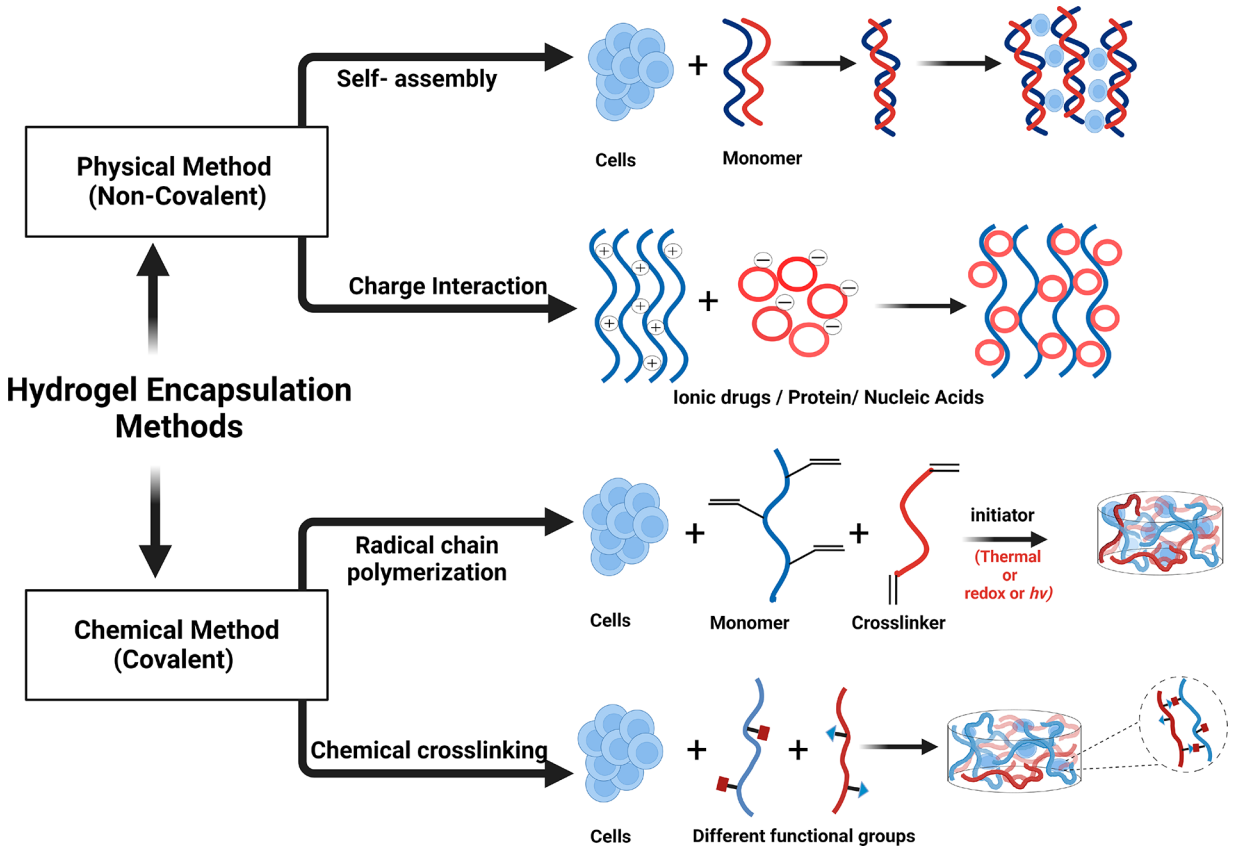

Figure 3. Schematic illustration of the hydrogel encapsulation methods.

process is gentle and favorable for the cells. The hydrogel's structure and chemistry should support cell survival and tissue formation, and its degradation should align closely with tissue growth. Importantly, the products resulting from degradation should not negatively impact the cells encapsulated within.[43,44]

Hydrogel formation involves the conversion of liquid precursor solutions into solid materials, accomplished through either physical (noncovalent) or chemical (covalent) cross-linking[45] (Figure 3).

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Table 3. Clinical Applications of Encapsulated Hydrogel

Application	Clinical target	Study type	Encapsulated hydrogel	Result	ref
Cancer and immunotherapy	breast cancer	*in vivo* and *in vitro*	injectable thermosensitive photothermal-network hydrogel	well-controlled drug delivery, photothermal anti-cancer effect	83
	CT-26 carcinoma and 4T1 breast tumor in mice	*in vivo*	alginate-collagen thermosensitive hydrogel/indocyanine green/polycytidylic acid	anticancer and metastatic properties	84
	glioblastoma multiforme	*in vivo* (mouse)	zinc 2-methylimidazole/mitoxantrone/hydrogel	inducing immune tumor cell death, indoleamine 2,3-dioxygenase-1 suppression	85
Tissue engineering	women with knee osteoarthritis	double-blind RCT	pequi oil/carbopol/hydrogel	no cytotoxicity biocompatibility not irritating knee extensor and flexor muscle strength ↑	87
	rat models	*in vivo*	rat bone marrow mesenchymal stem cell (rBMSCs) /HA/chitosan/collagen thermosensitive hydrogel	biocompatibility well biomimic behavior good mechanical properties	88
	rat models with femoral defects	*in vivo*	alginate/sericin/graphene oxide/hydrogel	inflammation inhibition ↑ distal femur defects repair speed ↑ osteogenic differentiation ↑	89
	cancellous bone defect	*in vivo*	BMSCs/Gelatin methacrylamide photocross-linked hydrogel	nontoxic nonimmunogenic biodegradable high BMSC loading capacity proliferation	90
	rat models with calvarium defect	*in vitro* and *in vivo*	MSC/nanohydroxyapatite/nano silicate/gelatin-methacryloyl hydrogel	cellular viability ↑, spreading behavior ↑, cell proliferation ↑	91
	endometrial ECM (proliferation)	*in vitro* and *in vivo* (mice)	collagen, elastin, and glycosaminoglycans hydrogels/endoECM	endoECM proliferation ↑ cytocompatibility ↑	92
	diabetic wound treatment	*in vitro* and *in vivo*	HA methacrylate/phenylboronic acid/catechin hydrogel	glucose-responsive catechin release, biocompatibility, skin tissue structure biomimicry angiogenesis ↑, inflammatory response ↓	93
	focal full-thickness cartilage defected patients	CT	hydrogel-based autologous articular chondrocytes	knee osteoarthritis outcome score (KOOS) ↑ biocompatibility ↑	94
	spinal cord injury repair	*in vivo* and *in vitro*	umbilical cord mesenchymal stem cells/fibroblast growth factor/extracellular matrix/heparin-poloxamer	cell apoptosis ↓ mitochondrial function ↑	95
	diabetic wound	*in vivo* and *in vitro*	human umbilical vein endothelial cells/Protamine, calcium alginate, hyaluronan	bacterial chronic inflammation accelerating wound healing angiogenesis ↑	96
Cardiovascular tissue	chronic ischemic heart disease	RCT	injectable collagen/human umbilical cord-derived mesenchymal stromal cell	ejection fraction ↑ infarct size ↑ safety	26
	cardiac repair	*in vivo*	induced pluripotent stem cell-derived cardiac progenitors (iPS-CPCs) /ECM, Methacrylic anhydride, HA hydrogel	iPS-CPCs cardiac differentiation ↑ cardiac repair exosome delivery ↑ cardiac functions↑	97
	vascularization inducing	*in vivo* and *in vitro*	polysaccharide chitosan/sodium β-glycerophosphate/gelatin/loaded with VEGF and stromal cell-derived factor-1	inducing MSCs and endothelial cells to differentiate into vessels biocompatibility ↑ selective drug release	98
	myocardial infarction	*in vivo*	dendritic cell-derived exosomes/alginate hydrogel	regulatory T cells activity ↑ macrophage polarization ↑	99

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Table 3. continued

Application	Clinical target	Study type	Encapsulated hydrogel	Result	ref
				cardial function ↑	
	myocardial infarction	*in vivo*	Tβ4-exosomes/GelMA/PEGDA hydrogel	coronary collateralization ↑ angiogenic capacity ↑	100
	myocardial infarction-ischemia	*in vivo*	UCMSCs/epoxy macromer/thiolated hyaluronic	tissue repair ↑ angiogenesis ↑ biocompatibility ↑	101
Gene and cell therapy	osteoarthritis	*in vivo*	phenylalanine-modified generation 5 polyamidoamine/microRNA-140	gene transfection efficacy ↑ long-term bioactivity ↑ endocytosis ↑	102
	breast cancer	*in vivo* and *in vitro*	RNA-triple-helix hydrogel (miRNA-221/miRNA-205(	selectivity uptake ↑ miRNA expression control ↑	103
	allergic rhinitis	*ex vivo* and *in vitro*	sodium glycerophosphate/chitosan/PEG−PLA/miRNA-146a	nasal mucosal adhesion ↑ RNA delivery stability ↑ release time ↑	104
	subcutaneous human medulloblastoma	*in vivo*	hydroxypropyl methylcellulose/PEG−PLA NPs/CAR-T cells/	inflammatory niche generating CAR-T cell treatment efficacy ↑ long-term viability and activation of T cells ↑	105
Neural tissue	spinal cord injury	*in vivo*	peptide-modified HA hydrogel/mesenchymal stem cell derived exosomes	nerve recovery ↑ inflammation ↓ sustainable release	106

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3.1.1. Physically (Noncovalent) Encapsulation Methods. The majority of protein or peptide-based systems rely on self-assembly through physical cross-linking processes. In other instances, natural materials may assemble through charge interactions. Synthetic polymers have also been modified with various functional groups to facilitate physical cross-linking.[46,47]

3.1.2. Chemically (Covalent) Encapsulation Methods. Strategies for cell encapsulation using covalently cross-linked hydrogels usually employ macromolecular monomers (i.e., macromers) derived from biocompatible polymers, as opposed to low-molecular-weight monomers, which tend to be cytotoxic.[48] The most common mechanisms to create covalently cross-linked hydrogels for cell encapsulation are through radical chain polymerizations and chemical cross-linking. Recently, the combination of radical and step growth polymerization, referred to as mixed-mode polymerization, has been investigated for cell encapsulation. Both mechanisms rely on specific liquid precursors containing multifunctional macromers to facilitate cross-linking. It is essential to assess the cytocompatibility of these components, and each system has its limitations in terms of suitability for cell encapsulation.[49,50]

3.1.2.1. Radical Chain Polymerization. Biocompatible polymers, whether synthetic or natural, have undergone modifications to incorporate two or more vinyl groups to produce multifunctional macromers. In the presence of an initiator, an initiating signal change (such as temperature or exposure to light), radicals are generated. These radicals then propagate through multiple carbon−carbon double bonds, forming high-molecular-weight chains that are covalently cross-linked within the network. It is worth noting that the presence of initiators and the generation of radicals may have potential toxicity to cells. The concentration of radicals depends on various factors, including initiator chemistry and concentration, the intensity of the initiating signal (e.g., light), and polymerization kinetics. Various initiating conditions, including thermal, redox, and photo initiating processes, have been effectively employed to encapsulate a diverse range of cells.[43,51,52]

3.1.2.2. Chemical Cross-Linking. Alternative approaches have been utilized for encapsulating cells in hydrogels created through chemical cross-linking or step-growth polymerization. An advantageous aspect of this cross-linking mechanism is its independence from additional components, such as initiators. Chemical cross-linking does not generate extra components during polymerization, and as a result, no additional components are produced during degradation. However, it is important to note that the gelation rates are generally slower compared to radical chain polymerizations.[53−56]

3.1.2.3. Mixed-Mode Polymerizations. Utilizing mixed-mode polymerization reactions for cell encapsulation offers several benefits, such as quicker polymerization times when contrasted with step-growth polymerization or chemical cross-linking. The presence of shorter kinetic chains, crucial for fine-tuning degradation, and the ease of incorporating peptides into the network are additional advantages.[57,58]

3.2. Potential for Clinical Application. Hydrogel is a three-dimensional hydrophilic structure consisting of polymer cross-links with an extraordinary ability to absorb water and biological fluids.[59,86] The various characteristics of hydrogel, including the ability to absorb high amounts of water while maintaining the three-dimensional physical structure, stability, softness, biocompatibility, and matrix characteristics for drug delivery, have attracted the attention of researchers as a special material in the field of biomedicine.[60−62] The applications of this structure in the field of medicine include drug delivery,[63,64] cell delivery and wound healing,[65] tissue engineering and regenerative medicine.[66,67] The similarity of behavior and characteristics of hydrogel to living tissue has made it a special choice in various fields of biomedicine.[68,69] The ability to swell and absorb water and biological fluids of hydrogel, along with the mentioned structural features, creates an environment for cellular interaction,[70,71] connection, growth, and division of body tissue cells, which makes it a suitable choice for tissue engineering[72−74] and regenerative medicine[75,76] (Table 3). When hydrogels filled with medicine, they can keep drug inside their spongy structure and release it slowly in a controlled manner.[77,78] Based on the therapeutic need, by changing the structure and composition of the hydrogel, the drug release rate can be adjusted to achieve the appropriate therapeutic requirement.[79] Drug release in this manner offers many advantages, such as reducing the frequency of dosage,[80] the long-term therapeutic effect,[81] and drug protection.[82]

3.2.1. Cancer Immunotherapy. As of today, cancer is one of the deadliest diseases, causing almost one in six deaths worldwide. Among the essential approaches aiming to cure it, drug discovery and development of potential anticancer drugs remain on the frontline. Due to the known benefits of 3D culture, one of the widely focused techniques is hydrogel-based culture. It holds a remarkable promise for targeted cancer therapy. To fully bring it to clinical use, further investigations concerning its safety and efficacy need to be done.[107]

Meanwhile, one of the promising anticancer methods is immunotherapy. In research of 2022, hydrogel-based codelivery of cytokine-induced killer (CIK) cells and oncolytic adenovirus armed were researched for cancer immunotherapy. Adenoviruses that are oncolytic and release antitumor cytokines are paired with an intertumoral injection of different effector cells to suppress tumor progression effectively. Meanwhile, there are some limitations in add-on therapy. Effector cells and oncolytic viruses have the ability to quickly spread to surrounding nontargeted tissues when utilized in high concentrations.

Additionally, the combination of both treatments had brief biological action and was immunogenic, meaning that several injections were needed to achieve a respectable therapeutic index. To overcome these disadvantages, we developed a gelatin-based hydrogel that can simultaneously deliver CIK cells and an oncogenic adenovirus (CRAd-IL12-IL15) loaded with IL12 and IL15, thereby enhancing and prolonging the antitumor effect of both treatments after a single one injection. A biodegradable injectable hydrogel reduced the distribution of high-dose oncogenic adenoviruses and CIK cells from the injection site to the liver and other nontargeted tissues. The results suggest that coadministration of RAd-IL12-IL15 and CIK cells in hydrogel could be an approach to overcome these limitations.[108] A study on the topic of individualized cancer immunotherapy was conducted in 2022, focusing on the use of flexible drug delivery technologies to enhance antitumor T cell immunity.

Because immunotherapies have the potential to stimulate significant antitumor immune responses, they are of great interest in the field of tumor therapy. Its widespread clinical adoption has been limited by a number of issues, including low immunogenicity, off-target consequences, and suppressive

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microenvironment. Effective cancer vaccine delivery technologies have been created to address and overcome these challenges. Generally speaking, there are three types of ATV vaccines: whole tumor antigen, whole tumor cell, and whole tumor lysate. Different drug delivery strategies, such as hydrogels and nanoparticles, have been designed to administer ATV locally or systemically for protection in order to ease the delivery of these antigens and improve the efficiency of immunization of autologous tumor sources. Tumor-specific immunity is produced, immunological resistance is eliminated, and immunity is sustained.[109] Another successful approach to cancer treatment is photothermal immunotherapy, which combines topical photothermal therapy and immunostimulants. Nevertheless, photothermal immunotherapy demands a strategy that strengthens strong antitumor immune responses and causes heat stress in cancer cells. Therefore, Yata et al. created a hybrid gold nanoparticle-DNA hydrogel for photothermal tumor immunotherapy, consisting of CpG sequences and hexapod-like DNA (hexapoDNA) loaded with gold nanoparticles. By combining oligodeoxynucleotide-modified gold nanoparticles with aligning hexapoDNA, composite gold nanoparticle-DNA hydrogels were created. HexapoDNA was released when hydrogels were exposed to laser light, and this effectively promoted the release of pro-inflammatory cytokines by immune cells in mice.[110]

A hydrogel-based on glycol chitosan (GCS) has been easily produced through a mild mixing process of GCS and DF-PEG4000 solutions. The hydrogel fragments resulting from its injection through a 21-gauge needle could self-heal into a homogeneous hydrogel. The DF-PEG's low cytotoxicity was confirmed through evaluation. Moreover, the 3D hydrogel encapsulation and self-healing processes were tolerated by cells, thus indicating the potential of this GCS-PEG hydrogel for 3D cell culture and injection cell therapy. Due to the low cost and biocompatibility of the gelators, as well as the simplicity of the method used to produce the hydrogel, it is expected that this self-healing hydrogel could reduce the cost and enhance the feasibility of cell therapy.[111]

For three-dimensional (3D) cell culture in cell therapy and tissue regeneration, Liu et al. have developed a novel injectable, biodegradable, thermoresponsive hydrogel-based on carboxymethyl chitin (CMCH). At lower temperatures, the CMCH solution flowed easily and was transparent; however, at 37 °C, it gelled quickly. The degree of carboxymethylation and temperature can be changed to modify the gelation time of the CMCH hydrogel, enabling in situ hydrogel production at body temperature and cell encapsulation at room temperature. Furthermore, the CMCH-14 hydrogels were stable and porous in PBS buffer and could be degraded in the presence of lysozyme or hyaluronidase. HeLa cells self-organized and formed 3D multicellular spheroids with high activity on the surface of the CMCH-14 hydrogel, while encapsulation of COS-7 cells within the CMCH hydrogel-forming in situ enhanced cell survival and proliferation promoted. Furthermore, in vivo studies in mice demonstrated good in situ gel formation and tissue biocompatibility. The novel CMCH hydrogel represents a promising candidate for use in minimally invasive surgical procedures due to its injectability, easy handling and complete filling of defect areas.[112]

In order to better understand the possibility of using a hydrogel Pluronic F-127 (PF-127), vitamin C (Vc), and a mixture of bone marrow stromal cells (BMSC) to promote endometrial regeneration in a mechanical injury model of intrauterine adhesion (IUA) in rats, Yang et al. undertook a study. The combination promoted cell survival and proliferation, resulting in endometrial restoration with increased gland number, thickness, and decreased fibrosis regions, according to the results. According to the study, BMSCs, VC, and a biomaterial scaffold combined with cell treatment may be an efficient way to aid in the healing of injured IUA endometrium.[113]

Successful cell-based therapy depends on the efficient movement of stem/progenitor cells without impairing their viability and functionality. However, there are several technical difficulties, expensive expenses, and short time windows associated with the existing liquid nitrogen-based method of stem cell transportation. In lieu of traditional cryopreservation, this study looked into the potential applications of semipermeable alginate hydrogels cross-linked by strontium for encapsulating, storage, and releasing stem cells throughout a global distribution period. In a sealed cryo-vial, the study effectively preserved mouse embryonic stem cells (mESC) and human mesenchymal stem cells (hMSC) for 5 days at room temperature using alginate hydrogels. Retrieval of the cells from the alginate gel revealed survival rates of 80% (hMSC) and 74% (mESC) which were similar to cryopreservation. Furthermore, after the retrieved hMSC and mESC were cryopreserved, the proliferation rates and the identification of common stem cell markers (at both the mRNA and protein levels) were on par with, if not better than, the results. These results imply that the application of alginate hydrogels may offer a practical means of transferring stem cells while maintaining their viability and potential for therapeutic effects.[114]

In 2008, Yuki et al. introduced a method for injectable hydrogel matrixes to deliver dendritic cells, demonstrating the potential of hydrogels as carriers for cancer immunotherapy.[115] Since then, researchers have explored the use of hydrogels to deliver immune cells and anticancer vaccines to tumors, offering new possibilities for cancer immunotherapy.[116]

Hydrogels have been found to mimic the extracellular matrix (ECM) and provide a suitable environment for 3D cell culture.[117] Encapsulated cells' adhesion, growth, migration, secretion, infiltration, differentiation, and vascularization are all directly impacted by the hydrogels' porosity and interconnectivity.[118] Hydrogels have been used as polymer scaffolds to localize T cells and enable their release when the polymer network at the tumor site is degraded.[119] For instance, Lerouge et al. created a chitosan hydrogel to encapsulate and stimulate T lymphocytes. When these cells were cocultured with melanoma cells, the T lymphocytes displayed cytotoxic biomarkers, released interferon-γ (IFN-γ), and stimulated the production of annexin V.[120]

Furthermore, Smith et al. created an implanted polymer scaffold that enabled the direct delivery of CAR-T cells to solid tumors, enabling the long-term coculture of immune cells and cancers. Moreover, they increased the effectiveness of therapy by codelivering CAR-T cells with stimulators of IFN genes (STING) agonists to eliminate tumor cells that escaped lymphocyte detection agonists to eradicate tumor cells that eluded lymphocyte recognition, and they improved the efficacy of therapy.[121] These studies combined the ability of hydrogels to support cell culture with their use as drug carriers, allowing immune cells to proliferate and be delivered to the tumor site at the same time.

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Hydrogels are great vehicles for delivering vaccines in addition to acting as carriers for certain cells. Dendritic cells (DCs) can be recruited and given a localized environment in hydrogels that mimic the ECM and are loaded with adjuvants and highly related antigens. In order to draw in and stimulate the body's DC cells, Ali et al. studied a microporous polylactide-co-glycoside (PLG) polymer that was cytokine-loaded (GM-CSF), or granulocyte-macrophage colony-stimulating factor) and warning signals.[122] Ye et al. created a customized photothermal vaccination in addition to an antibody that blocks PD-1 checkpoints GM-CSF, lipopolysaccharide (LPS), and black phosphorus quantum dot nanovesicles (BPQD-CCNVs) were incorporated into a thermoresponsive hydrogel into tumor cell membranes to generate gel-BPQD-CCNVs. Subcutaneous injection of the hydrogel activated and attracted DCs, enabling antigen presentation to $CD8^+$ T cells In addition, following resection, the PD-1 antibody assisted in the removal of lung metastases and remaining tumor cells.[123] In the future, hydrogels will be loaded with more individualized cancer-specific neoepitopes to create personalized local anticancer vaccines. Hydrogels are essential for both the activation or proliferation of immune cells and the preservation of a stable microenvironment for antigens associated with tumors. To further this potential therapy approach, future studies should concentrate on comprehending the hydrogel degradation and cell recruitment process in greater depth, necessitating interdisciplinary collaboration.

Immune checkpoint inhibitors have emerged as effective strategies for preventing tumors from evading immune surveillance. Combining immune checkpoint inhibitors with other tumor therapies has gained significant attention recently.[124] Researchers are also exploring innovative approaches to deliver these drugs.[116] Wang et al. created a hydrogel scaffold that responds to reactive oxygen species (ROS) in situ for the simultaneous administration of gemcitabine (GEM) and an antibody that blocks PD-L1 (aPDL1).[125] A ROS-sensitive linker in the hydrogel would break down when high ROS levels were present in tumor tissues, releasing GEM and aPDL1 and ultimately causing tumor cell death. The hydrogel's outstanding biodegradability was demonstrated by its gradual deterioration over a period of about 7 days and its destruction after 3 weeks.[126]

Due to its high expression in tumor cells, CD47 molecules have become frequently targeted in cancer treatments. However, because red blood cells express CD47 at a high level, systemic treatment of anti-CD47 antibodies may result in anemia and other negative effects.[126] A fibrin gel was created in situ by Chen et al. using calcium carbonate nanoparticles, thrombin, fibrinogen, and anti-CD47 antibodies. Conveniently applied, this gel regulated tumor tissue pH, promoted macrophage destruction of tumor cells by anti-CD47 antibodies and aided in the healing of surgical wounds.[127] The accomplishments of these studies demonstrate how crucial novel drug delivery strategies are to the field of immune checkpoint investigations. Advancements in drug delivery techniques are highly valued by the scientific community, even though researchers are always looking for new targets. Immunotherapy treating cancers has enormous potential if the fundamental processes of immunity are better understood.

3.2.2. Anti-inflammatory. It is critical to find novel therapeutic strategies for IMID treatment due to the immune-mediated inflammatory diseases' (IMIDs) and difficult pharmacological management. Though mesenchymal stromal cells (MSCs) have been extensively studied for their immunomodulatory and anti-inflammatory properties as possible therapeutic modalities, direct transplantation of MSCs has several drawbacks and is not recommended for clinical use. Hydrogel encapsulation may be among the most effective delivery strategies because of its ease of use and effectiveness. However, there have been no published studies on MSCs secretion delivery systems for IMID treatment. Recently, EV encapsulation in hydrogels has been studied for tissue regeneration purposes. So, it is important to look into this tactic as soon as possible. For the purpose of treating IMID, all these facts present fresh, promising directions for the creation of secretion-based medicines. Also, among the latest high-quality engineering materials, chitosan hydrogel possesses excellent properties such as biodegradability, biocompatibility, nontoxicity, reversibility of swelling, flexible adaptation to external triggers, and drug loading ability. Recently, the application of chitosan hydrogels to promote human biological processes such as inflammation has become an interesting topic. Chitosan hydrogels have great potential for use in biological applications. Experiments conducted by Lac et al. showed that hydrogels could be molded into different drug delivery systems, depending on the route of administration or drug molecule. Due to their extraordinary properties, hydrogels have provided an effective new anti-inflammatory approach. High porosity, biocompatibility, biodegradability, and flexibility make hydrogels ideal for drug delivery applications. Additionally, in many special situations, people with diabetes may benefit greatly from hydrogels acting as a drug delivery system.[128]

Consisting of ulcerative colitis and Crohn's disease, inflammatory bowel disease (IBD) produces inflammatory processes in the gastrointestinal tract that result in ulcers, diarrhea, and abdominal pain. IBD is multifactorial in its etiology. The inflammatory conditions mentioned above are brought on by immune dysregulation, which is a result of several genetic and environmental factors.[129] Presently available treatment regimens, mainly based on anti-inflammatory drugs, immunosuppressive agents, and biologics, are responsible for the ability of Mesenchymal stem cells (MSCs) to release excess immunomodulators in inflammatory bowel disease (it has become a valuable candidate for overcoming IBD). Nevertheless, this cell therapy method has drawbacks due to the use of naked MSCs, such as a quick loss of an immunomodulatory phenotype that hinders factor secretion, low persistence, and the inability to recover cells in the event of adverse effects. There are still significant issues limiting it. We have created a hydrogel licensing system here, in order to do away with these restrictions and guarantee a steady flow of bioactive factors. A three-dimensional (3D) microenvironment that guarantees ongoing inflammatory control, cell persistence, and implant removability is created by encasing IFNγ-loaded heparin-coated beads in situ injectable cross-linked alginate hydrogels. Human MSCs (hMSCs) that have been approved and encapsulated in hydrogel were injected subcutaneously into an acute ulcerative colitis mouse model. The findings demonstrate that encapsulated hMSCs provide delocalized systemic protection and that their scores on the colon weight-to-length ratio, disease activity index, and histology do not differ significantly from those of healthy mice. Ex vivo testing revealed fully viable hMSCs that maintained an immunomodulatory phenotype and continued to secrete factors like PGE2

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and Gal-9 on day seven when the cells were easily harvested. The results showed that it was possible to license hMSCs encapsulated in hydrogel to slow the in vivo progression of their IBD.[130]

The available delivery methods for IBD drug regimens incudes oral, injectable, and rectal administration. Traditional mesalamine suppositories and enema formulations are frequently prescribed for mild to moderate cases of colitis. The use of hydrogels for targeted medication delivery in IBD has, nevertheless, been examined and researched in recent studies by Zhang and associates. A hydrogel that targets inflammation was created for IBD patients' local medication delivery.[131] An admixture of ascorbic palmitate and dexamethasone was used to create the hydrogel. *In vivo*, colitis models were able to show preferential adhesion to inflammatory areas because dexamethasone was only released when matrix metalloproteinase broke down the hydrogel. With a colitis score of 1 point 4 in the hydrogel-treated group compared to 3 points 3 in the free drug-treated group, the hydrogel enemas significantly decreased disease activity index (DAI) scores when compared to free drug enemas. A hydrogel vehicle for rectal biologic delivery in IBD was created in another study. Rectal administration is preferred because the hydrogel showed a consistent rate of drug release at 37 °C.[132] Furthermore, the hydrogel improved the biologics' transintestinal permeability in Caco-2 cells, indicating that it may be used to administer biologics to treat IBD.

Mehrban et al. evaluated rat partial-thickness abdominal wall defects and murine macrophages, respectively. The immunological response to hydrogels made from decellularized extracellular matrix (ECM) and synthetic α-helical peptides was assessed *in vitro* and *in vivo*. Over the course of 28 days, the study discovered no evidence of hydrogel encapsulation or the formation of multinucleate giant cells. However, it did find an increase in mononuclear cell infiltration at the hydrogel-tissue interface without inciting a foreign body reaction. All hydrogels promoted an anti-inflammatory environment after an initial spike in the pro-inflammatory phenotype. The hydrogels also upregulated myogenic differentiation markers and the expression of anti-inflammatory markers Arginase1, IL-10, and CD206, indicating pro-remodeling. After 28 days, there was no discernible change between the injected site and the healthy tissue, suggesting complete integration. According to the results, there is a lot of promise for these hydrogels' use in regenerative medicine and meeting clinical needs in the future.[133]

Soranno et al. outlined the use of injectable Dock-and-Lock hydrogels that self-assemble to deliver interleukin-10 (IL-10) locally to slow the development of fibrosis and inflammation that cause chronic kidney disease. Hydrogels remained in the kidney for up to 30 days in vivo, but they broke down and matched IL-10 release profiles in a matter of days when observed *in vitro* using a fluorescent tag. In vivo results following hydrogel injection and delivery of IL-10 were examined using a unilateral ureteral obstruction (UUO) mouse model. In 7, 21, 35 days, n = 54, eight groups were examined: hydrogel/IL-10 was injected under the renal capsule 3 days after the UUO, UUO, UUO 1 IL-10, UUO 1 hydrogel, sham, healthy, and healthy injected with mouse serum albumin (MSA). Trichrome staining was utilized to assess fibrosis, and immunohistochemistry (IHC) was applied to paraffin sections to detect macrophages and apoptotic cells. Between any of the control groups, there were no appreciable variations in inflammatory markers. When hydrogel delivery was used, compared to untreated animals, macrophage infiltration and apoptosis were significantly lower on days 21 and 35. When compared to IL-10 injection alone, IL-10 delivery via hydrogel decreased macrophage infiltration and apoptosis by day 35. By day 35, all treatment groups showed a reduction in fibrosis. This work supports the use of hydrogel delivery of IL-10 to treat chronic kidney disease.[134]

3.2.3. Tissue Engineering. The development of controlled-release systems for the bone, cartilage regeneration and osteochondral interfaces is one of the trend topics in the field of tissue engineering. However, most developed systems consider the release of only one growth factor, which is the limiting step for therapeutic success. Recent research has focused on designing and tailoring appropriate combinations of bioactive factors to achieve desired tissue regeneration goals.[135]

Multiple controlled-release systems that facilitate the delivery of growth factors (GFs) have been strategically combined with cells to act synergistically and help promote new tissue formation. Co-encapsulation of GFs and cells in hydrogels and seeding of stem cells in microparticles or scaffolds loaded with bioactive agents are among the most popular TE strategies. GF-loaded microspheres can be incorporated into scaffolds or hydrogels, increasing their functionality and complexity and providing biochemical cues to stimulate tissue regeneration.[136]

Functional biomaterials that combine the processes of angiogenesis and osteogenesis are crucial for bone tissue engineering and bone remodeling.[87,90] Here, Jayakumar R et al. developed an injectable nanocomposite hydrogel of carrageenan combined with whitlocks nanoparticles and the angiogenic drug dimethyloxalylglycine. The synthesized whitlockite nanoparticles and nanocomposite hydrogels were characterized by SEM, TEM, EDS and FTIR. The developed hydrogels were injectable, mechanically stable, cytocompatible and with better protein adsorption. The addition of dimethyloxalylglycine resulted in an initial burst release followed by a sustained release for 7 days. Human umbilical vein endothelial cells exposed to a nanocomposite hydrogel containing dimethyloxalylglycine showed increased cell migration and capillary tube-like structure formation. Osteogenic differentiation in rat adipose-derived MSC after 7 and 1 days showed increased alkaline phosphatase activity *in vitro*. In addition, cells exposed to the nanocomposite hydrogel showed increased protein expression of RUNX2, COL and OPN. Taken together, these results indicate that the incorporation of whitlocks and dimethyloxalylglycine into a carrageenan hydrogel promoted osteogenesis and angiogenesis.[137]

To improve MSC function, increase retention at the injury site, and achieve targeted delivery, Huang et al. encapsulated them in hydrogels. Both synthetic hydrophilic polymers like PEG and acrylic acid, as well as a variety of natural polymer hydrogels like alginic acid, hyaluronic acid, chitosan, and collagen, were used. MSCs were also directed to perform more specialized tasks by incorporating bioactive factors and hydrogel mixtures. Bone, cartilage, the heart, kidney, skin, and the spinal cord are just a few of the tissues and organs in which encapsulated MSCs have been studied.[138]

Furthermore, to increase the survival of adherent cells in suspension culture, Karoubi et al. created a single-cell hydrogel capsule with immobilized matrix molecules inside. The capsules exhibited improved cell-cytoskeletal patterning, increased metabolic activity, and increased viability of human

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marrow stromal cells (hMSCs). Utilizing the encapsulation system in a rat hindlimb model, research revealed a notable increase in the number of engrafted cells in vivo. The system may increase therapeutic cell survival in targeted tissues by attenuating the initial anoikis stimuli, compensating for their absence, and shielding the cells from subsequent apoptosis.[139]

Ji et al. also created a scaffold for bone regeneration using chitin hydrogels in 2020. In this study, hydroxypropyl chitin (HPCH) hydrogel was injected into a poly ε-caprolactone (PCL)/nanohydroxyapatite (nHA) scaffold to encapsulate MSC. The PCL/nHA/HPCH scaffold exhibited enhanced mechanical properties, biocompatibility, and osteo-differentiation. The hybrid scaffold was found to improve bone induction, growth factor secretion, and vascularization. MSCs also lessen inflammatory and immunological responses, as demonstrated by the Trans well culture.[140]

Particularly for cartilage and bone tissue engineering, injectable hydrogels have shown promise as scaffolds for tissue engineering applications. Huang et al. highlighted the benefits of injectable hydrogels, including their high-water content, similarity to the extracellular matrix (ECM) in nature, porous structure for growing and transplanting cells, low invasiveness, and capacity to conform to irregular defects. Because of these properties, injectable hydrogels are excellent materials for using in tissue engineering to construct three-dimensional cell culture scaffolds.[141] The approach of Tang et al. approach involved encasing adipose-derived stromal cells (ASC) in an injectable gelatin microribbon (μRB) hydrogel cell delivery system for bone regeneration. Through wet-spinning, μRB-based hydrogel was created. A study using in vivo models of mice with cranial bone defects was used to assess the findings. The usefulness of the synthesized hydrogel for cell delivery and bone regeneration was demonstrated using bioluminescence and micro-CT. Moreover, histological testing was used to assess biocompatibility. ASC proliferation, vascularization, and bone regeneration were all found to be aided by μRB. Furthermore, the addition of 100 ng BMP2 per scaffold was reported to accelerate bone mineralization in the defected areas. Immunostaining additionally demonstrated the excellent biocompatibility and lack of immune system stimulation of BMP and μRB.[142]

Due to hydrogel extensive physicochemical characteristics and significant modification flexibility have led to extensive research and application in the field of regenerative medicine. Several effective uses exist, including encapsulation matrixes or scaffolds for cell support, as well as as multiple therapeutic agents or carriers for release-regulated bioactive agents. Numerous intricate studies on tissue regeneration and clinical trials have thoroughly examined a variety of approaches. Tissue regenerative medicine's ultimate goal still needs to be accomplished, though, and certain obstacles can only be overcome by fusing multidisciplinary research from the engineering and biology domains. One of the main challenges is to replicate a dynamic and all-encompassing microenvironment that can mimic the biochemical processes involved in the healing of native tissue or organs. Another is to develop efficient and effective production techniques that can meet the macro and micro requirements of cultivating native tissue. Upon surmounting the obstacles, these hydrogel methods have the potential to become primary medications for the efficient management of critical organ dysfunction.[143]

Degenerative changes in cartilage and lubricant in synovial fluid cause the degeneration of joints in osteoarthritis. For this illness, there is not presently a reliable long-term cure. A research project undertaken by Musumeci et al. explored the expression of lubricin in chondrocytes encapsulated in hydrogels based on polyethylene glycol and cartilage explants from patients with osteoarthritis and normal cartilage. Encapsulated chondrocytes from osteoarthritic cartilage were able to restore lubricin biosynthesis when grown in the hydrogel scaffold, despite the fact that lubricin expression was found to be lower in osteoarthritic cartilage than in normal cartilage. According to these findings, patients with osteoarthritis may be able to repair cartilage lesions and slow the progression of their disease by combining scaffold materials with autologous cell transplantation.[144]

Wang et al. created a hydrogel scaffold and functionalized nano aggregates to create an injectable nanomaterial-based platform for the delivery of therapeutic cells. The encapsulation of the nano aggregates in the hydrogel mitigates potential toxicity, and the composite structure promotes the survival and proliferation of human mesenchymal stem cells in 3D matrixes. For experts in the fields of toxicology, tissue engineering, cell biology, and nanomaterials science, in particular, this technology has profound consequences for biology, chemistry, and physics. The manipulated tissue's mechanical strength is enhanced by the nano aggregates, which also carry different biomolecules and support cell viability and proliferation. The possible cytotoxicity of nanoparticles can be successfully avoided by encasing the nano aggregates in hydrogel encapsulation.[145]

Ren et al. investigated how BMSCs in a three-dimensional (3D) culture were affected by the mechanical strength of hyaluronic acid (HA) hydrogel scaffolds in terms of their stemness and differentiation properties. By stimulating the Wnt/β-catenin pathway, the low-strength hydrogel was found to preserve the stemness properties of BMSCs. In contrast, the high molecular weight hydrogel with a higher mechanical strength encouraged the direction of BMSCs' differentiation into cartilage by opening transient receptor potential vanilloid 4 (TRPV4)/Ca^{2+} molecular channels and boosting the expression of type II collagen and SOX9 in BMSCs. Based on molecular mechanisms, the findings have significant implications for the development of drug delivery programs for cartilage repair as well as the design of biomaterials for the in vivo delivery of BMSCs.[146]

A recently published study describes a novel kind of cell-filled hydrogel microfiber with enhanced mechanical characteristics that can enclose pancreatic β cells and preserve their viability and functionality. Because it is composed of a double-network (DN) hydrogel made of polyacrylamide and alginate, the microfiber has greater strain and tensile strength than other forms of alginate. By successfully lowering the blood glucose levels of diabetic mice after transplantation, the DN hydrogel microfiber showed promise for a range of biomedical uses.[147]

To help diabetic patients heal their wounds and regenerate new tissue, Shi et al. created a chitosan/silk hydrogel system. Exosomes produced from gingival mesenchymal stem cells (GMSC) were intended to be applied to diabetic ulcers in rat models using the hydrogel that was synthesized. Immunohistochemical, immunofluorescence and histological analysis supported the efficacy findings. In the diabetic wound area, it has been shown that combining hydrogel with GMSC-derived exomes enhances tissue regeneration and repair. In comparison with other groups that displayed themselves, the hydrogel-

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exome-treated group displayed greater vascular, neural, collagen, and nonepithelial repair.[148]

Due to the poor engraftment, retention, and survival of the transplanted cells, stem cell therapy's therapeutic efficacy for wound regeneration is limited. In order to increase the efficiency of Wharton Jelly mesenchymal stem cells (WJMSCs) in skin wound healing in mice, this study looked into the use of Pluronic F-127 hydrogel and the antioxidant sodium ascorbyl phosphate (SAP). The biological effects of PF-127 and SAP on WJMSCs were assessed using *in vitro* experiments. On the eighth day postsurgery, topical transplantation of WJMSCs, PF-127, and SAP to a full-thickness wound bed led to enhanced wound healing and dermal regeneration, as demonstrated by higher skin thickness, newly formed hair follicles, and deposits of collagen fibers with a narrower scar. In the WJMSCs/PF-127/SAP group, there was an increase in WJMSC engraftment, as evidenced by in vivo tracking. These cells are concentrated in the dermis. When comparing the WJMSCs/PF-127/SAP group to other groups, immunohistochemical analysis showed a greater quantity of proliferating cells, newly formed blood vessels, and anti-inflammatory M2 macrophages. SAP increased WJMSCs' survival when embedded in PF-127, despite PF-127 being cytotoxic to them.[149]

3.2.4. Cardiovascular Tissue Regeneration. The supply of human heart tissue is far short of the demand. For the purpose of expanding applications ranging from drug testing and clinical cardiac regeneration to the investigation of cardiac development and disease mechanisms, the production of functional cardiac tissue *in vitro* is essential. Positive interactions between cells and the ECM around them are facilitated by simulating the physiological conditions of the natural heart. Encapsulating cells in a suitable microenvironment can sustain and encourage the formation of tissues by preserving the viability of the cells at the beginning, encouraging their proliferation later on, triggering differentiation, and enhancing their function.[150] To achieve scalable tissue production, hydrogel matrixes can offer the necessary biomimetic microenvironment. A 2016 study found the right materials and advantageous material properties to support hiPSC encapsulation and subsequent cardiac differentiation, thereby shedding light on the significance of cell−cell and cell−cell interactions produced by 3D culture technology. For the first time, hiPSCs were successfully encapsulated and differentiated for the creation of gelatin methacryloyl (GelMA) artificial heart tissue (GEhECT) using a printable gelatin-methacryloyl (GelMA) hydrogel biomaterial in this study. Time-saving, tissue growth, and highly efficient cardiac differentiation are achieved by using low-density GelMA hydrogels with an elastic modulus of less than 1 kPa, which support high hiPSC viability following encapsulation and temporary hydrogel remodeling. The frequency and rate of spontaneous contractions increased gradually over the course of the event.[151]

After a myocardial infarction (MI), stem cell therapy is a potentially effective treatment option. Its therapeutic efficacy is compromised, nevertheless, by the low retention rate of induced pluripotent stem cells (iPS) in MI hearts. Li and colleagues conducted a study. To better retain and sustain iPS cells in MI hearts, a supramolecular hydrogel was created to encapsulate them. By encouraging cardiac cell differentiation and neovascularization, which leads to improved cardiac function and less harmful cardiac remodeling, the folic acid-modified peptide-based hydrogel increased the therapeutic efficacy of iPS cells. This study demonstrates the FA peptide hydrogel's potential for treating MI.[152]

An investigation was conducted by Wang et al. showed that a bioactive hydrogel containing HA, chitosan, and immobilized IGF-1C domain peptide (IGF-1C) enhanced the pro-angiogenic activity and viability of ASC *in vitro*. The hydrogel, when cotransplanted into mice with ischemic hindlimbs, improved blood perfusion and muscle regeneration, resulting in superior limb salvage. A viable option for cell-based therapy of critical limb ischemia, the hydrogel also improved the antifibrotic activity of ADSCs.[153]

A rat model of myocardial infarction (MI) induced by left anterior descending artery (LAD) ligation was used to develop and inject a self-assembling peptide hydrogel (SAPE) modified with the SDKP motif into the infarct border zone. The BMSC (BM-MSCs) or this hydrogel alone were utilized as a cardioprotective scaffold. According to the findings, the hydrogel, either by itself or in combination with BM-MSCs, increased the infarct area's microvasculature, decreased the production of fibrotic tissue, and enhanced left ventricular ejection fraction (LVEF). The SAPE hydrogel with SDKP modification demonstrated promise as a cell-free construct for functional recovery in acute myocardial infarction (AMI) and may reduce the risks associated with cardiac cell therapy.[154]

In vitro tests of a novel hydrogel construct based on chitosan showed minimal cytotoxicity and high cell survival rates when loaded with VEGF-releasing microtubes and encapsulating both ESC-derived endothelial cells and CD31-expressing BM mononuclear cells. By implanting it into a mouse model of hindlimb ischemia, it effectively restored blood flow to the ischemic hindlimbs and strongly retained cells while promoting neovascularization via vasculogenesis, acetogenesis, and angiogenesis. The hydrogel-based on chitosan presents a promising therapeutic option for a range of cardiovascular conditions.[155]

An additional crucial factor to consider is the biocompatibility of hydrogels as allografts. The immunological characteristics of various scaffolds were compared, and it was discovered that MSC-hydrogel structures inhibited the proliferation of allogeneic lymphocytes, especially when the hydrogel was made with higher collagen concentrations.[156] Furthermore, innate immune responses can be reduced by altering hydrogels. Ghanta et al. after an acute myocardial infarction, improved cardiac function by using immune-evasive and small-molecule-modified alginate encapsulation to increase MSC persistence and localization.[157] On the same note, Alvarado-Velez and co. In order to improve MSC survival in allogeneic transplantation close to the injury site, scientists engineered an agarose hydrogel that released Fast ligand and caused cytotoxic CD^{8+} T cells to undergo apoptosis.[158] Moreover, He and colleagues conducted a clinical study proved the viability and safety of injecting collagen hydrogel loaded with UC-MSCs intramyocardially, with no significant adverse effects seen.[159]

Overall, the discussed studies highlight the importance of evaluating the compatibility of hydrogel-encapsulated MSCs and the biocompatibility of hydrogels as allografts. These results advance our knowledge of and ability to use hydrogel based MSC therapies for a range of purposes.

3.2.5. Diabetes Mellitus (DM). Globally, diabetes prevalence is rising, necessitating the development of efficient clinical treatments. Encapsulation techniques have been suggested to support β-cell replacement therapy, which has emerged as a safe choice for the treatment of diabetes in recent years. Here,

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we created high cell viability (>90%) in less than 30 min by using a coaxial microfluidic electrospray technique to create microcapsules with porous alginate shells and β-cell-containing cores. The alteration in size of the microcapsules that benefited from microfluidic electrospray is possible. The β-cells were protected against immune rejection due to the presence of a biocompatible porous hydrogel shell. This shell also facilitated the exchange of small-molecule nutrients during the process of transplantation. The liquid core effectively maintained the viability of the encapsulated cells. Following epididymal transplantation in diabetic mice, this cell-engineered biosystem, which is alive, demonstrated its potential as an artificial island for the purpose of regulating blood sugar levels and treating diabetes. With its numerous highly viable encapsulated β-cells to increase treatment efficiency and its intricate structure, we think this system can be used in a wide range of clinical scenarios.[160,161]

The treatment of diabetes with islet transplantation shows promise. In an islet transplant, the liver is the intended recipient. However, the biggest drawback of islet transplantation at this location is the high rate of portal vein graft loss or damage during the initial phases of the procedure.[93,162] A number of procedural complications and the challenge of monitoring the islets are additional drawbacks.

A study from 2020 looked into the use of thermosensitive methoxy poly (ethylene glycol)-poly(Ala) and mPEG-poly-(Ala) hydrogels as materials for encapsulating cells when transplanting MIN6 cells subcutaneously. Additionally, it verified that materials and cells had favorable biocompatibility *in vitro*, including insulin secretion and cell viability. Histopathological tissue analysis revealed that 1 day after implantation, transplanted MIN6 cells continued to live in nude mice and secrete insulin. Furthermore, at 7- and 1-days following implantation, the MIN6 cell-free graft showed positive CD31 staining, indicating the development of new blood vessels. These findings suggest that MIN6 cell subcutaneous transplantation may be accomplished using mPEG-poly (Ala) hydrogels. Insulin release in diabetic patients can be encapsulated and controlled using hydrogel-based drug delivery systems. The oral administration of this medication has not been able to provide the patient's body with enough bioavailability due to the high molecular weight of insulin and its low stability in gastrointestinal tubes.[163] Thus, in order to reduce the need for insulin administration and minimize side effects, researchers have concentrated on injectable hydrogel-based drug delivery systems for people with diabetes. As a result, injectable insulin is typically prescribed as the preferred treatment option for type 1 diabetes.[164]

Xue worked on an injectable shear-thinning hydrogel to encapsulate insulin and control its release rate. It was based on supramolecular cyclodextrin-adamantane cross-linked with HA. Changes in molecular weight and concentration have been shown to modulate insulin release both *in vitro* and in vivo. For 30 days, both in vivo and *in vitro* subcutaneous spaces showed the encapsulated insulin's biocompatibility.[165]

Zhau et al. created an insulin-encapsulated hydrogel that is injectable and glucose-responsive. With unique qualities like shear-thinning for injectability, long-lasting adhesion through strong tissue adhesion, and quick glucose responsiveness at physiological pH, the synthesized hydrogel was based on phenylboronic acid-poly (lactic-co-glycolic acid) (PBA–PLGA). To prove biocompatibility and efficacy, both *in vitro* and in vivo experiments were performed. It was reported that stable blood sugar was achieved in diabetic mice for about 14 days after a subcutaneous injection of insulin-encapsulated hydrogel.[166]

3.2.6. Cell and Gene Therapy. The study of Doerfer et al. explains the creation of a platform for externally sterilizable cell encapsulation that will allow genetically modified bacteria to be delivered to the gastrointestinal tract. The platform satisfies design requirements for in vivo delivery and enhances postencapsulation biocontainment through the use of a UV-absorbent, reinforced hydrogel formulation. The objective is to ensure the safety and effectiveness of genetically modified bacteria for the treatment of digestive disorders by bridging the gap between biocontainment techniques and delivery platforms.[167]

Due to low cell viability and retention rates brought on by high shear forces and mechanical washout, maintaining the survival and localization of therapeutic cells following direct injection is a frequent challenge in cell therapy. To overcome this, a specially designed microfluidic device that quickly and uniformly encapsulates high cell concentrations was used to encapsulate endothelial colony-forming cells (ECFCs) in polyethylene glycol (PEG-Fb) fibrinogen hydrogel microspheres. With respect to cell markers, tubule formation capacity, and low-density lipoprotein uptake, the encapsulated ECFCs remained viable at a rate exceeding 95% and continued to multiply. Delivered in vivo in a large animal model, encapsulated ECFCs were retained and survived in the surrounding host tissue following injection. They also remained viable after shearing through needles. Retaining cell viability and retention following local injection in large animal cell therapy can be accomplished practically and clinically with encapsulation in PEG-Fb microspheres.[168]

An et al. suggested a method for creating macroscopic-sized nanofiber-based hydrogel encapsulation devices, or Nanofiber-Enabled hydrogel Encapsulation Devices (NEEDs). In order to cross-link hydrogel precursor solutions into different devices without altering the hydrogels' inherent chemistry or water content, they employed capillary action to impregnate electrospun nanofiber membranes with the hydrogel precursor solutions. These devices showed easy mass transfer for encapsulating and culturing different types of cells while maintaining the characteristics of the hydrogel and nanofibers. Furthermore, additional compartmentalization allowed for the coculture of paracrine cells. By giving pancreatic islets from rats to diabetic mice, a proof-of-concept study demonstrated that the devices could be used for therapeutic purposes. This would result in diabetes correction for 8 weeks with little fibrosis and functional islets in the devices that were harvested. According to the study, the NEEDs design concept may help future cell therapies develop by overcoming problems with cell encapsulation.[169]

The study by Lee et al. provides a tissue-specific microenvironment to enhance cell culture and cell therapy, and it does so by a novel platform known as tissue beads. Using an ECM from decellularized tissues and a microfluidic device, these tissue beads are created. In comparison to conventional microbeads, the tissue beads significantly improved the viability, maturation, and functionality of the various types of reprogrammed cells that were tested for encapsulation. Tissue beads stimulated functional tissue regeneration in animal models with tissue defects, according to in vivo experiments. The findings of this study indicate that tissue-specific extracellular matrix microbeads (ECM microbeads) can be

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enhanced by reprogrammed cell-based therapy through the use of microfluidic techniques and reduced tissue matrix.[170]

For MSCs to be used in clinical settings, their viability and safety must be established. Numerous investigations have looked into MSC compatibility with hydrogels and their capacity to continue serving therapeutic purposes. Wu et al. showed that the hydrogels' biocompatibility and lack of cytotoxicity were demonstrated by the fact that MSCs encapsulated in self-assembled supramolecular hydrogels retained their morphology and viability.[171] According to this, Boido et al. revealed that MSC viability and paracrine activity were unaffected by chitosan-based hydrogels, permitting the release of MSC vesicles and the maintenance of their antioxidant capacities.[172]

3.2.7. Neurodegenerative Disease. Evans et al. developed a novel Parkinson's disease treatment that focuses on synapsing cells in a hydrogel to prevent detrimental host reactions, thereby resolving the issue of cell survival following implantation. Encapsulated in an alginate hydrogel, human-induced pluripotent stem cells underwent differentiation into dopaminergic neurons. HA and poly-L-ornithine were added to the hydrogel to lessen the host response, and the hydrogel was further characterized and optimized for use as a transplantable CNS biomaterial. Investigations were also conducted into the local administration of immunosuppressants. This strategy suggests that cell survival in Parkinson's disease transplants could be enhanced.[173]

Hotta et al. explored the possibility of using postnatal enteric neuronal stem/progenitor cells (ENSCs) as a source of neuronal growth from serotonin receptor agonism, increasing the potential of these cells as a therapeutic target for neurointestinal disorders. A notable increase in neuronal density and proliferation was observed by the researchers when they cultivated ENSCs that were isolated from the colon of mice using liposomal nanoparticles loaded with 5-HT4 receptor agonists. In the presence of the agonist-loaded nanoparticles, colon explants and ENSCs cocultured showed the same outcome. A notable increase in neuronal density and proliferation was also observed in vivo upon delivery of the ENSCs with the nanoparticles. The study found that using postnatal ENSCs for cell-based therapies for neurointestinal diseases could be optimized with this approach.[174]

Papa et al. revealed that MSCs retained their cellular structure when encapsulated in hydrogel scaffolds containing ECM and arginine-glycine-aspartate (RGD). These scaffolds also allowed the MSCs to gradually release the chemokine CCL2, which aided in the functional recovery of spinal cord injuries.[175] According to Bussche et al., the microencapsulation of MSCs did not impede the release of bioactive factors either.[176] Li et al. examined the promise of hydrogels in the context of spinal cord injuries. To this end, they utilized a peptide-modified adhesive hydrogel (Exo-pGel) to encapsulate exosomes derived from human mesenchymal stem cells (MSCs). The Exo-pGel was then implanted in a rat long-span spinal cord transection model. The results were encouraging, with restored motor function and improved urinary function observed in the treatment group compared to the control group. These findings suggest that the nerve repair potential of the trial was effective.[106]

In order to shield the host tissue from harm and minimize inflammation, it is necessary to match the hydrogel's degree of stiffness to that of the spinal cord injury therapy. Notwithstanding, their application in clinical settings has been impeded by the absence of in vivo clinical measures of spinal cord injury stiffness. Prager et al. determined that an injured spinal cord has less stiffness than an uninjured spinal cord using noninvasive ultrasound elastography on dogs with spontaneous spinal cord injury. It was also demonstrated that hydrogels encasing olfactory cells can have their stiffness measured via ultrasound elastography, which makes it possible to synthesize hydrogels that are as stiff as those found in spinal cord injuries. This shows how hydrogel cell implants can be made more flexible to match actual spinal cord injuries. This technique can also be used to modify the stiffness of other biomaterial implants for regenerative medicine.[177]

4. CONCLUSION

Hydrogels can shield drugs and cells, increasing their therapeutic efficacy as well as the ability to deliver a variety of cell types and medications to different tissues and organs is another benefit of hydrogel encapsulation techniques' versatility. Aside from this, the reviewed studies also focused on how crucial it is to choose the right hydrogel properties for cell and drug delivery, such as mechanical strength, biodegradability, and biocompatibility. Most importantly, Hydrogel-based delivery systems offer a few advantages over other delivery platforms. These systems give spatiotemporal control over the release of drugs, development components, or immunizations, which can progress their efficacy and decrease potential side effects. Hence, the development of innovative treatments for a range of disease is greatly promising when it comes to hydrogel encapsulation. The development of hydrogel encapsulation methods for use in clinical settings requires more investigation. Hydrogel property optimization to meet the needs of various cell and drug types is one of the issues that need to be resolved. To ensure their safety and effectiveness, more research must be considered on the long-term stability and biocompatibility of hydrogel-encapsulated cells and medications. To confirm the efficacy of hydrogel encapsulation in diverse animal models and to furnish information on the pharmacokinetics and pharmacodynamics of hydrogel-encapsulated medications, in vivo investigations are also imperative. Lastly, a thorough analysis of ethical and regulatory concerns is necessary before bringing hydrogel encapsulation to the clinic. Hydrogel encapsulation yet has the potential despite these obstacles.

■ ASSOCIATED CONTENT

Data Availability Statement

Data will be made available in a repository on acceptance.

■ AUTHOR INFORMATION

Corresponding Authors

Marzieh Ramezani Farani − *NanoBio High-Tech Materials Research Center, Department of Biological Sciences and Bioengineering, Inha University, Incheon 402-751, Republic of Korea;* orcid.org/0000-0002-4184-5670; Phone: +82-10-9609-1367; Email: farani.marzi@inha.ac.kr

Yun Suk Huh − *NanoBio High-Tech Materials Research Center, Department of Biological Sciences and Bioengineering, Inha University, Incheon 402-751, Republic of Korea;* orcid.org/0000-0003-1612-4473; Phone: +82-10-9633-6377; Email: yunsuk.huh@inha.ac.kr

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Authors

Bahareh Farasati Far − *Department of Chemistry, Iran University of Science and Technology, Tehran 13114-16846, Iran;* orcid.org/0000-0002-1598-2487

Maryam Safaei − *Department of Pharmacology, Faculty of Pharmacy, Eastern Mediterranean University, Famagusta, TR. North Cyprus 99628, Turkey*

Reza Nahavandi − *School of Chemical Engineering, College of Engineering, University of Tehran, Tehran 1417935840, Iran*

Amir Gholami − *Faculty of Medicine, Kurdistan University of Medical Science, Sanandaj 6618634683, Iran*

Mohammad Reza Naimi-Jamal − *Department of Chemistry, Iran University of Science and Technology, Tehran 13114-16846, Iran;* orcid.org/0000-0002-8305-7234

Sujina Tamang − *NanoBio High-Tech Materials Research Center, Department of Biological Sciences and Bioengineering, Inha University, Incheon 402-751, Republic of Korea*

Jung Eun Ahn − *NanoBio High-Tech Materials Research Center, Department of Biological Sciences and Bioengineering, Inha University, Incheon 402-751, Republic of Korea*

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.3c10102

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article for important intellectual content; and agreed to be accountable for all aspects of the work.

Notes

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■ ABBREVIATIONS

(NM)Nanomedicine; (SLR)Systematic literature review; (PRISMA)Preferred Reporting Items for Systematic Reviews; (RCTs)Randomized control trials; (PEG)Polyethylene glycol; (pHEMA)Poly(2-hydroxyethyl methacrylate); (GCS)Glycol chitosan; (CMCH)Carboxymethyl Chitin; (BMSC)Bone marrow stromal cells; (Vc)vitamin C; (IUA)Intrauterine adhesion; (mESC)mouse embryonic stem cells; (hMSC) human mesenchymal stem cells; (IFN-γ)Extracellular matrix (ECM);interferon-γ; (DCs)Dendritic cells; (PLG)polylactide-co-glycoside; (LPS)lipopolysaccharide; (BPQD-CCNVs)Black phosphorus quantum dot nanovesicles; (ROS)Reactive oxygen species; (IMIDs)immune-mediated inflammatory diseases'; (IBD)Inflammatory bowel disease; (MSCs)Mesenchymal stem cells; (hMSCs)Human MSCs; (DAI)disease activity index; (ECM)extracellular matrix; (UUO)Unilateral ureteral obstruction; (MSA)Mouse serum albumin; (IHC)Immunohistochemistry; (GFs)Growth factors; (SEM)Scanning electron microscope; (TEM)Transmission electron microscopy; (EDS)Energy Dispersive Spectrometry; (FTIR)Fourier transform infrared spectroscopy; (HPCH)Hydroxypropyl chitin; (PCL)poly ϵ-caprolactone; (nHA)nanohydroxyapatite; (ECM)Extracellular matrix; (ASC)Adipose-derived stromal cells; (μRB)microribbon; (3D)Three-dimensional; (TRPV4) transient receptor potential vanilloid 4; (DN)Double-network; (GMSC)Gingival mesenchymal stem cells; (WJMSCs)Wharton Jelly mesenchymal stem cells; (SAP)Sodium ascorbyl phosphate; (GelMA)gelatin methacryloyl; (GEhECT)gelatin methacryloyl artificial heart tissue; (MI)myocardial infarction; (iPS)induced pluripotent stem cells; (FA)folic acid; (IGF-1) Insulin-like growth factor 1; (ADSCs)Adipose-derived stem cells; (LAD)left anterior descending artery; (SAPE)Self-assembling peptide hydrogel; (LVEF)Left ventricular ejection fraction; (AMI)Acute myocardial infarction; (PBA−PLGA) phenylboronic acid-poly(lactic-co-glycolic acid); (ECFCs) endothelial colony-forming cells; (PEG-Fb)polyethylene glycol-fibrinogen; (NEEDs)Nanofiber-Enabled hydrogel Encapsulation Devices; (ENSCs)Enteric neuronal stem/progenitor cells; (5-HT4)5-Hydroxytryptamine receptor 4; (RGD) arginine-glycine-aspartate; (CCL2)chemokine (C−C motif) ligand 2; (CAR-T)Chimeric antigen receptor T; (STING) Stimulator of interferon genes; (RUNX2)Runt-related transcription factor 2; (OPN)Osteopontin; (BMP-2)Bone morphogenetic protein 2; (Wnt)Wingless-related integration site; (hiPSC)Human Induced Pluripotent Stem Cell; (ASC) Adipose-Derived Stem Cells; (ADSCs)Adipose-Derived Stem Cells; (SDKP)Serine-Aspartate-Lysine-Proline; (UC-MSCs) Umbilical Cord-Derived Mesenchymal Stem Cells

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