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Hydrogel Nanostructures for Targeted Drug Delivery in Inflammatory Diseases: A Comprehensive Review

[1]Shadab Ali*, [2]Sayad Ahad Ali

[1] *IIMT College of Medical Sciences, IIMT University, O-Pocket, Ganga Nagar 250001, Meerut, Uttar Pradesh, India*
[2] *Kharvel Subharti College of Pharmacy, Swami Vivekanand Subharti University, NH 58, Subharti Puram, Meerut, Uttar Pradesh, India*

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Abstract

In the treatment of inflammatory illnesses, hydrogel nanostructures have shown themselves to be a flexible and promising substrate for targeted drug delivery. The biocompatibility, biodegradability, and controlled, localised drug release capabilities of these systems are highly regarded because they minimise systemic adverse effects and improve therapeutic efficacy. Systems based on hydrogel may be made to react to environmental cues like pH, temperature, or enzymatic activity that are frequently present in inflammatory tissues. Treatment results are improved by this responsiveness, which enables precise medication release at the location of inflammation. Targeting ligands, including peptides or antibodies, are added to improve the efficiency and specificity of medication delivery. By selectively binding to markers produced in inflammatory tissues, these ligands allow hydrogel nanostructures to improve medication accumulation at the intended region while minimising off-target effects. These developments might have a significant impact on diseases including psoriasis, inflammatory bowel illness, and rheumatoid arthritis. Clinical translation is nevertheless hampered by issues including stability, consistent biocompatibility, and manufacturing scalability, despite their potential. These restrictions should be solved by upcoming developments including combination medicines, stimuli-responsive hydrogels, and personalised medicine strategies. By providing more accurate control over medication distribution, these tactics may allow for patient-specific therapies and enhance overall results. A potential strategy for creating patient-centered, long-lasting, and efficient treatments for chronic inflammatory illnesses is the use of hydrogel nanostructures. These systems have the potential to revolutionise the treatment of a variety of inflammatory diseases by tackling present issues and utilising creative design techniques.

***Corresponding Author**
Shadab Ali (shadabali12341234@gmail.com)

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1. Introduction

Inflammatory diseases encompass a broad spectrum of conditions characterized by an overactive or dysregulated immune response [1]. Redness, swelling, heat, discomfort, and, in extreme situations, a loss of function in the afflicted tissues or organs are typical indications of immunological dysfunction. An essential defence mechanism, the body's natural inflammatory response works to fight off infections, heal damaged tissue, and bring the body back to equilibrium [2]. Immunological dysfunction is commonly characterised by redness, swelling, heat, pain, and, in severe cases, a loss of function in the affected tissues or organs. The body's natural inflammatory response is a vital defensive system that

helps the body recover from infections, repair damaged tissue, and regain homeostasis. Managing these conditions presents significant challenges due to their complex etiology, the diverse pathways involved in inflammation, and the potential for systemic complications [3]. Anti-inflammatory medications like corticosteroids, NSAIDs, or biologics like monoclonal antibodies are often administered systemically as part of traditional therapy approaches for inflammatory illnesses [4]. While these therapies can be effective in alleviating symptoms and controlling disease progression, they are often associated with several limitations. Systemic drug delivery exposes the entire body to pharmacologically active compounds, leading to off-target effects that can compromise other physiological systems. For instance, prolonged use of corticosteroids is linked to immunosuppression, osteoporosis, and metabolic disturbances. Similarly, NSAIDs can cause gastrointestinal irritation, renal toxicity, and cardiovascular complications. Moreover, the systemic route often results in suboptimal drug concentrations at the site of inflammation, reducing therapeutic efficacy and necessitating higher dosages, which further exacerbate adverse effects [5].

Biomimetic techniques are frequently used in the design of hydrogel-based drug delivery systems to improve their safety and effectiveness. By mimicking natural processes and structures, these systems can achieve higher levels of specificity and functionality [6]. For instance, ligands that preferentially bind to receptors that are overexpressed on inflammatory cells or tissues can be used to functionalise hydrogels [7]. In addition to increasing drug delivery effectiveness, this focused binding reduces unwanted interactions with healthy cells. Additionally, bioresponsive hydrogels that break down or release medications in response to certain biochemical cues guarantee that therapeutic substances are only active when and where they are required, lowering the possibility of widespread adverse effects. Along with its potential for treatment, hydrogels have a lot to offer in terms of ease and patient compliance [8]. Injectable hydrogels, for example, can be administered directly to the site of inflammation through minimally invasive procedures, reducing the need for surgical implantation [9]. These systems can also be designed to release drugs over days, weeks, or even months, eliminating the need for frequent dosing and improving adherence to treatment regimens. Moreover, their soft and flexible nature makes hydrogels well-suited for applications in delicate or irregularly shaped tissues, such as mucosal surfaces or joint spaces [10]. Despite their numerous advantages, the clinical translation of hydrogel-based drug delivery systems is not without challenges. Issues such as scalability, reproducibility, and regulatory approval must be addressed to bring these technologies from the laboratory to the bedside. Ensuring consistent performance across different batches and patients is critical for maintaining therapeutic efficacy and safety [11]. The long-term biocompatibility and potential immunogenicity of hydrogel components need to be thoroughly evaluated to mitigate the risk of adverse reactions. Ongoing research efforts are focused on overcoming these hurdles through innovations in material science, bioengineering, and manufacturing processes. A major advancement in the treatment of inflammatory illnesses has been made with the creation of hydrogel-based drug delivery devices [12]. These systems provide a viable foundation for patient-friendly, effective, and focused therapy alternatives by using the special qualities of hydrogels and resolving the drawbacks of traditional treatments. The combination of hydrogels with cutting-edge technologies like nanomedicines, bioelectronics, and regenerative medicine has the potential to completely transform the field of inflammatory therapy as research in this area progresses [13]. Hydrogels are well-positioned to play a crucial role in meeting the unmet requirements of patients with chronic inflammatory disorders because of their ability to distribute drugs precisely, multifunctionality, and flexibility to a variety of clinical settings [14].

2. Understanding Hydrogel Nanostructures

2.1 Definition and Properties

Three-dimensional networks of polymers called hydrogels are unique in their capacity to absorb and hold onto vast volumes of water or biological fluids while preserving their structural integrity [15]. Their cross-linked polymeric structure and hydrophilic nature, which resemble the extracellular matrix of biological tissues, give them this special quality [16]. When these hydrogels are scaled down to nanostructures, they exhibit enhanced and novel properties that significantly expand their potential in targeted drug delivery and biomedical applications [17]. Nanostructured hydrogels combine the intrinsic advantages of traditional hydrogels, such as biocompatibility and tunability, with Nano scale benefits like increased surface area, enhanced permeability, and precise control over drug release kinetics [18]. The Nano scale dimensions of hydrogel structures confer several unique advantages, making them ideal for applications in inflammation management and other medical fields [19]. Their

capacity to produce regulated and prolonged medication release is one of their main characteristics [20]. This property arises from the capacity of the hydrogel network to encapsulate therapeutic agents within its matrix and release them in a predictable manner [21]. It is possible to fine-tune the release profile to meet particular therapeutic requirements by modifying variables including the polymer composition, crosslinking density, and the material's reactivity to external stimuli. Nanostructured hydrogels, for example, may be designed to react to environmental cues like pH, temperature, or enzyme activity that are frequently linked to inflammatory tissues in inflammatory disorders, guaranteeing localised and on-demand drug delivery [22]. The capacity of hydrogel nanostructures to expand or contract in response to environmental stimuli, such as pH, temperature, ionic strength, or the presence of certain molecules, is one of its primary characteristics. They are very useful for drug delivery systems because of their responsiveness, which allows for the regulated and site-specific release of medicinal substances. Furthermore, when utilised in medical applications, their biocompatibility and biodegradability guarantee little negative consequences. Their ability to interact with biological components is further enhanced by their nanoscale size, which increases their effectiveness in tissue engineering and targeted medication delivery. Hydrogel nanostructures' network structure makes it possible to add different functional groups, which enables for the customisation of characteristics including mechanical strength, swelling behaviour, and degradation rates [23].

Complex three-dimensional networks made of hydrophilic polymers, hydrogel nanostructures may absorb large amounts of biological fluids or water. These materials generate a gel-like matrix by cross-linking processes, which can be chemical or physical in origin. These hydrogels' distinctive qualities, such their large surface area and adjustable porosity, are made possible by their nanoscale dimensions and are crucial for a number of cutting-edge applications [24]. These nanostructures' soft and elastic characteristics make them perfect for simulating biological tissues' characteristics, which helps them become more well-known in the pharmaceutical and biomedical industries. The ability of hydrogel nanostructures to react to external stimuli is one of its outstanding qualities. In reaction to variations in temperature, ionic concentration, pH, or certain chemical cues, they may swell or contract. They are perfect candidates for controlled medication delivery systems, where accuracy and flexibility are essential, because of their stimulus-sensitive behaviour. Hydrogel nanostructures can release encapsulated medications in a targeted and sustained manner by altering their structural characteristics, reducing side effects and improving therapeutic effectiveness [24].

2.2 Advantages in Drug Delivery

2.2.1. Biocompatibility and Biodegradability

Because hydrogels are naturally biocompatible and biodegradable, they provide a number of benefits for drug delivery. The likelihood of negative responses is reduced by these materials' harmonic interactions with biological tissues and typically non-toxic nature. Their high water content, which replicates the natural extracellular matrix and guarantees smooth integration with living systems, is primarily responsible for their biocompatibility [25]. This property makes hydrogels ideal for applications in sensitive areas, such as inflamed tissues or delicate organs, where minimizing irritation and immune response is critical. Because hydrogels decompose into non-toxic metabolites that the body may readily remove, they are biodegradable [26]. Hydrogels are biodegradable because they break down into harmless metabolites that the body can easily eliminate [27]. This tunable biodegradability ensures that the hydrogel remains functional for the required duration while gradually disintegrating to avoid long-term accumulation. These characteristics work together to make hydrogels a safe and efficient platform for targeted and prolonged drug delivery, especially for treating illnesses and chronic conditions that call for localised therapeutic treatments. Fundamental characteristics that are essential to the design and use of materials, especially in the pharmaceutical and biomedical industries, are biocompatibility and biodegradability. The capacity of a substance to interact with biological systems without producing negative consequences like toxicity, immunological rejection, or inflammation is known as biocompatibility [28].

2.2.2. Controlled Drug Release

Because hydrogels may release therapeutic substances in a regulated and sustained manner, they are highly appreciated in the drug delivery industry. Their special porosity nature gives them the capacity to encapsulate medications inside the polymeric network and release them gradually over time [29]. Drug diffusion rate may be precisely controlled by varying the porosity of hydrogels by varying variables including polymer composition, crosslinking density, and hydration levels [30]. This lowers the frequency

of dose and improves patient compliance by guaranteeing a steady and long-lasting therapeutic impact. It is possible to design hydrogels to react to certain stimuli, including variations in temperature, pH, or enzyme activity. On-demand medication release is made possible by this stimuli-responsive behaviour, which reacts to the particular microenvironment of a disease location, such as the acidic pH and increased enzyme activity characteristic of inflammatory tissues. For example, hydrogels designed to degrade or swell in acidic conditions can selectively release drugs in inflamed regions while remaining stable elsewhere in the body [31]. Hydrogels are a flexible and effective platform for delivering medications with high accuracy and therapeutic efficacy because of their tailored release, which minimises systemic exposure and lowers the risk of adverse effects [32].

2.2.3. Targeting Capabilities

Through functionalisation with certain ligands, hydrogels can be modified for active targeting in drug delivery, improving their capacity to localise therapeutic molecules to sick cells or inflammatory regions [33]. These ligands, such as antibodies, peptides, or small molecules, are chosen for their affinity to receptors or markers that are overexpressed in pathological environments, such as inflamed regions [34]. By conjugating these ligands to the surface or within the matrix of hydrogels, the delivery system gains the ability to selectively bind to target cells or tissues, improving therapeutic precision [35]. This targeting capability is particularly advantageous in the management of inflammatory diseases, where affected tissues often exhibit unique biological markers. For instance, hydrogels functionalized with ligands that bind to adhesion molecules like integrins or selectins, which are up regulated in inflamed tissues, can enhance drug accumulation at the disease site while minimizing off-target interactions [36]. This selective delivery not only improves the efficacy of the therapeutic agent but also significantly reduces systemic toxicity and adverse effects. Ligand-functionalized hydrogels can be designed to release their payload only after binding to the target site, further refining their specificity. Such active targeting approaches transform hydrogels into smart drug delivery systems, capable of addressing complex disease mechanisms with heightened efficiency and safety [37]. By precisely directing therapeutic molecules to a desired location inside the body, targeting capabilities in drug delivery systems reduce off-target effects and improve treatment success. This accuracy is particularly crucial for treating complicated illnesses like cancer, where conventional systemic treatments frequently damage healthy cells and have serious adverse effects [38]. The goal of sophisticated drug delivery systems with targeting capabilities is to minimise systemic exposure to medications while optimising the therapeutic concentration at the site of action [39].

2.2.4. Minimized Systemic Side Effects

Since conventional techniques of delivering therapeutic drugs frequently result in the unintentional exposure of healthy tissues, minimising systemic adverse effects is a crucial objective in the development of improved drug delivery systems [40]. Systemic side effects occur when drugs circulate through the bloodstream and interact with non-targeted cells or organs, resulting in adverse reactions that can compromise patient safety and limit the effectiveness of treatment [41]. Innovative drug delivery technologies have emerged to address these challenges by enhancing drug localization and controlled release, thereby reducing systemic exposure and associated side effects. By directing therapeutic molecules precisely to the illness site, targeted drug delivery systems are a crucial strategy for reducing systemic adverse effects. Because tumours and inflammatory tissues have leaky vasculature, passive targeting—such as taking use of the increased permeability and retention (EPR) effect—allows nanoparticles to aggregate preferentially in these areas. By adding ligands like as antibodies, peptides, or tiny chemicals that bind specifically to receptors that are overexpressed on sick cells, active targeting further refines this process. This dual-layered targeting ensures that the therapeutic agent acts specifically where it is needed, sparing healthy tissues and reducing off-target toxicity [42].

3. Mechanisms of Targeting in Inflammatory Diseases

3.1 Passive Targeting

Passive targeting is a drug delivery approach that exploits the natural physiological and anatomical characteristics of specific tissues or pathological sites to direct therapeutic agents without the need for active intervention or molecular targeting [43]. This tactic is especially pertinent in diseases like cancer and inflammation, when the distinct characteristics of the impacted tissues—such as aberrant vasculature and compromised lymphatic drainage—allow drug carriers to accumulate preferentially. A fundamental idea in nanomedicines, passive targeting serves as the basis for several drug delivery methods based on nanoparticles. Commonly seen in tumours and inflammatory tissues, the Enhanced Permeability and

Retention (EPR) effect is one of the most important mechanisms allowing passive targeting [44]. Tumors often have rapidly growing vasculature that is leaky and disorganized, resulting in gaps between endothelial cells. These gaps allow macromolecules, nanoparticles, and liposomes to passively extravagate into the tumor interstitial space. Furthermore, the absence of effective lymphatic drainage in these regions prevents the clearance of accumulated drug carriers, resulting in prolonged retention. This dual phenomenon of enhanced permeability and retention enables passive targeting to deliver therapeutic agents more effectively to tumors than to healthy tissues [45].

3.2 Active Targeting

Active targeting is a cutting-edge method of medication delivery that uses certain molecular interactions to target therapeutic molecules to target organs, tissues, or cells [46]. Unlike passive targeting, which relies on physiological characteristics such as the enhanced permeability and retention (EPR) effect, active targeting uses ligands that bind selectively to receptors or biomarkers overexpressed on target cells [47]. Because of its specificity, drugs may be delivered precisely, increasing therapeutic efficacy while reducing systemic toxicity and off-target effects. In conditions like cancer, where the accurate localisation of therapeutic substances may greatly enhance treatment results, active targeting is especially advantageous [48].

3.3 Stimuli-Responsive Systems

A novel family of drug delivery technologies known as stimuli-responsive systems is made to release therapeutic compounds in reaction to particular internal or external triggers. Premature drug release, off-target effects, and systemic toxicity are some of the major issues that these systems address by providing a highly focused and regulated approach to drug delivery. By harnessing unique environmental cues or externally applied stimuli, stimuli-responsive systems ensure that drugs are delivered precisely when and where they are needed, enhancing therapeutic efficacy and patient safety. Internal stimuli-responsive systems rely on the distinct physiological conditions of diseased tissues, such as tumors, inflamed areas, or infected sites. One of the most widely utilized internal triggers is ph. Many pathological environments, including tumor microenvironments and inflamed tissues, exhibit an acidic pH compared to normal tissues. PH-sensitive drug delivery systems are engineered with materials that remain stable at neutral pH but undergo degradation, swelling, or solubilization in acidic conditions [49]. For example, nanoparticles or hydrogels made from pH-sensitive polymers can encapsulate drugs and release them only when they encounter the acidic microenvironment of a tumor. This targeted approach ensures that the drug is delivered directly to the diseased site, minimizing exposure to healthy tissues [50].

Enzymatic activity is another internal trigger leveraged by stimuli-responsive systems. Enzymes overexpressed in certain pathological conditions, such as matrix metalloproteinase in cancer or inflammation, can serve as specific activators for drug release. Enzyme-sensitive carriers are designed with linkers or coatings that degrade in the presence of these enzymes, triggering the release of their therapeutic payload [51]. This strategy not only ensures localized drug delivery but also takes advantage of the pathological overexpression of enzymes as a distinguishing feature of diseased tissues. External stimuli-responsive systems, on the other hand, are activated by externally applied triggers such as temperature, light, magnetic fields, or ultrasound. For instance, thermo responsive systems release drugs when exposed to elevated temperatures. These systems often use polymers that undergo a phase transition at a specific temperature, such as the mildly elevated temperatures found in inflamed or tumor tissues or induced externally through localized heating [52]. Similarly, light-responsive systems release drugs in response to specific wavelengths of light, enabling precise spatiotemporal control. By focusing the light source on the target site, clinicians can ensure that the drug is activated only at the desired location, reducing systemic side effects.

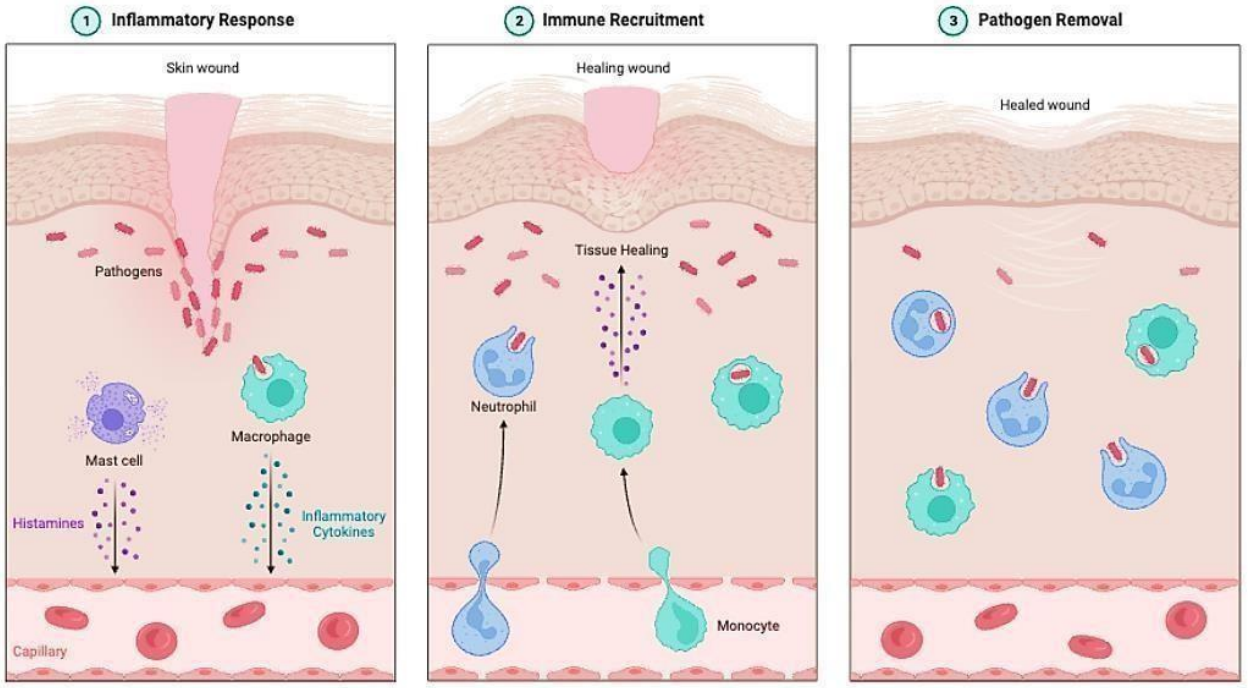

Figure 1: The Inflammatory Response

4. Fabrication Techniques

4.1 Physical Crosslinking

Through non-covalent interactions including hydrogen bonds, ionic contacts, van der Waals forces, hydrophobic interactions, or chain entanglements, three-dimensional polymer networks can be created via physical crosslinking. Physical crosslinking is particularly appealing for biomedical applications because it eliminates the need for potentially hazardous crosslinking chemicals, in contrast to chemical crosslinking, which depends on covalent connections created by chemical processes [53]. This method, which offers adaptability, biocompatibility, and reversibility, is frequently employed in the creation of hydrogels, drug delivery systems, and scaffolds for tissue engineering. One of the key mechanisms of physical crosslinking is hydrogen bonding, where hydrogen atoms interact with electronegative atoms such as oxygen or nitrogen to form reversible links between polymer chains [54]. Hydrogels cross-linked through hydrogen bonding exhibit significant elasticity and swelling behavior, making them suitable for applications where flexibility and adaptability are required. For instance, polyvinyl alcohol (PVA) hydrogels can be physically cross-linked through repeated freeze-thaw cycles, forming hydrogen bonds between hydroxyl groups. This method eliminates the need for chemical reagents, ensuring a biocompatible structure suitable for wound dressings or soft tissue replacements [55].

Ionic interactions are another prevalent mechanism in physical crosslinking, particularly in hydrogels composed of polyelectrolytes. These interactions occur between oppositely charged polymer chains or between polymers and multivalent ions. For example, alginate, a naturally derived polymer, forms physically cross-linked hydrogels in the presence of divalent cations like calcium ions (Ca^{2+}). The calcium ions act as crosslinking agents by bridging the negatively charged carboxylate groups on adjacent polymer chains [54]. Because alginate-based hydrogels provide gentle gelation conditions that maintain the bioactivity of encapsulated medicines or cells, they are widely employed in tissue engineering and drug delivery. The development of physically cross-linked networks also heavily relies on hydrophobic interactions. In these systems, amphiphilic polymers' hydrophobic regions group together in aquatic conditions to form physical connections inside the polymer matrix. Block copolymers, in which hydrophobic and hydrophilic segments self-assemble into micellar structures or networks, frequently exhibit this kind of crosslinking [56]. These hydrogels behave in a temperature-sensitive manner, changing between sol and gel states in response to external factors. One well-known example is poly(N-isopropyl

acrylamide) (PNIPAM), which forms temperature-responsive hydrogels that are appropriate for drug delivery applications needing regulated release based on body temperature or external heating.

4.2 Chemical Crosslinking

A stable, three-dimensional network is created via the process of chemical crosslinking, which joins polymer chains via covalent bonds [57]. This method of crosslinking is widely employed in the creation of hydrogels, coatings, adhesives, and other materials, particularly when higher structural integrity, strength, and resistance to dissolution are required [58]. Chemical crosslinking creates a more persistent and rigid network than physical crosslinking, which depends on non-covalent interactions like hydrogen bonds or ionic forces. This makes it perfect for applications requiring mechanical strength, controlled drug release, and long-term stability [59]. Chemical crosslinking usually entails the addition of chemicals or crosslinking agents that promote the creation of covalent connections between polymer strands. These crosslinking agents react with functional groups like hydroxyl, amine, carboxyl, or thiol groups that are present on the polymer backbone. They can be tiny molecules or bigger macromolecules. One common class of chemical crosslinking agents includes multifunctional compounds like glutaraldehyde or diisocyanates, which possess two or more reactive groups that can bond with the polymer chains, linking them together. In hydrogels, chemical crosslinking is often used to provide enhanced mechanical strength and resistance to swelling, which is critical for the stability of drug delivery systems and tissue engineering scaffolds [60].

Chemical crosslinking is frequently utilised in drug delivery applications to produce controlled-release systems that hold together and release medicinal ingredients gradually [61]. For instance, cross-linked hydrogels can be designed to encapsulate medications and release them at a regulated pace in response to physiological factors like pH, temperature, or the presence of certain enzymes. The covalent bonds formed during chemical crosslinking help retain the structure of the hydrogel in biological environments, ensuring that the drug is delivered consistently and that the hydrogel matrix does not degrade prematurely [62]. These systems are especially useful for applications like cancer treatment, wound healing, and tissue regeneration that call for localised or persistent drug administration. The creation of biomaterials for tissue engineering also heavily relies on chemical crosslinking. Cross-linked polymer scaffolds in this sector offer the structural support required for tissue development and cell proliferation. The scaffold's mechanical qualities are improved by the covalent network created during crosslinking, which increases its resistance to deformation under physiological stress [63]. Chemical crosslinking can also affect the material's rate of deterioration, enabling the creation of scaffolds that break down in time with the growth of new tissue. For instance, because their rates of breakdown may be precisely adjusted to meet the requirements of the regenerated tissue, cross-linked biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA) or polycaprolactone (PCL) are frequently utilised in tissue engineering applications [64].

5. Applications in Inflammatory Diseases

5.1 Arthritis

Arthritis, a group of inflammatory diseases that affect the joints, represents a major global health challenge, with millions of people suffering from conditions like rheumatoid arthritis (RA), osteoarthritis (OA), and psoriatic arthritis [65]. These conditions are characterized by chronic inflammation, pain, joint destruction, and impaired mobility. The inflammation in arthritis leads to cartilage degradation, synovial fluid changes, and bone erosion, severely affecting the quality of life. Over the years, therapeutic strategies have evolved from traditional NSAIDs and corticosteroids to more targeted biologic therapies, including disease-modifying antirheumatic drugs (DMARDs) [66]. However, because of the disease's complexity and the shortcomings of existing treatments—which may not effectively address the underlying causes of inflammation or may have serious side effects—treating arthritis remains difficult. Novel drug delivery techniques, such as hydrogels, nanoparticles, and stimuli-responsive materials, have surfaced in recent years as possible means of enhancing the results of arthritis treatment [67]. The capacity of these cutting-edge drug delivery devices to administer medications straight to inflammatory joints, minimising systemic exposure and minimising adverse effects, is one of its most intriguing uses. Specialised drug delivery systems can be used to target localised inflammation, which is a feature of inflammatory illnesses, including arthritis. For instance, injectable hydrogels containing biologic agents or anti-inflammatory medications can be made to release their payload just at the site of inflammation, providing a long-lasting therapeutic impact. These hydrogels can be engineered to react to certain joint stimuli, such as variations in

temperature, pH, or the presence of cytokines or other inflammatory mediators. Stimuli-responsive medication delivery systems increase the efficacy of medicinal medicines by releasing them only when required [68].

Because they can increase the solubility, bioavailability, and stability of medicinal drugs, nanoparticles have also demonstrated significant promise in the treatment of arthritis [69]. For example, nanoparticles can be engineered to encapsulate corticosteroids or anti-cytokine biologics, protecting them from degradation before reaching the target site. Upon reaching the inflamed joint, these nanoparticles can be designed to release their contents through mechanisms such as pH-sensitive release or by responding to enzymatic activity present in the inflamed tissue. Furthermore, ligands that selectively target inflammatory cells or receptors that are overexpressed in the arthritic joint, including macrophages or the tumour necrosis factor (TNF) receptor, can be used to functionalise nanoparticles [70]. This targeted approach ensures that drugs are delivered directly to the inflamed area, maximizing their therapeutic potential while minimizing off-target effects and systemic toxicity. Another important advancement in arthritis treatment is the use of biologic therapies, such as monoclonal antibodies, which target specific components of the immune system involved in the inflammatory response. These biologics are often delivered systemically via injections or infusions, but their effectiveness is limited by their poor bioavailability, short half-life, and the potential for immune system activation against the biologic itself. Advanced drug delivery systems can overcome these challenges by encapsulating biologics in nanoparticles or liposomes, which help protect the drugs from immune system clearance and extend their circulation time [71]. Additionally, nanoparticles can be designed to release biologic agents in a controlled manner, ensuring that they are available at the site of inflammation over an extended period, thereby improving their therapeutic efficacy.

5.2 Inflammatory Bowel Disease (IBD)

IBD, or inflammatory bowel disease, is a chronic, recurrent gastrointestinal inflammatory illness that includes ulcerative colitis and Crohn's disease [72]. Persistent intestinal inflammation is a hallmark of many illnesses, resulting in a variety of symptoms such as weariness, weight loss, diarrhoea, stomach discomfort, and occasionally bloody stools. Although the precise origin of IBD is still unknown, it is thought to result from a confluence of environmental variables such infections and nutrition, immune system failure, and genetic predisposition [73]. With its rising incidence in both developed and developing countries, IBD is a worldwide health problem that places a heavy cost on healthcare systems. Anywhere along the gastrointestinal system, from the mouth to the anus, inflammation can be a hallmark of Crohn's disease. It frequently impacts the intestinal wall's inner layers and can lead to the development of strictures, fistulas, and abscesses [73].

Drug delivery methods based on nanoparticles have drawn a lot of interest because of their capacity to encapsulate medications and shield them from the upper gastrointestinal tract's acids and digestive enzymes. Drugs can be delivered precisely where inflammation occurs by using nanoparticles that react to particular factors like pH or enzyme activity [74]. For example, pH-sensitive nanoparticles can be designed to release their contents in the acidic environment of the colon, where inflammation is typically most severe in ulcerative colitis. By limiting the amount of time that medications are exposed to healthy tissues, this tailored delivery lowers adverse effects and increases the treatment's therapeutic efficacy. Using localised drug delivery devices to distribute biologics is another potential strategy. Many IBD patients have found that biologic therapy, such as anti-TNF medicines, are quite successful in decreasing inflammation and attaining remission [75]. However, due to their systemic nature, these therapies are associated with significant side effects. By developing biologic drug delivery systems, such as those encapsulated in nanoparticles or liposomes, these therapies can be targeted directly to the inflamed areas of the gastrointestinal tract, allowing for more localized effects and reducing systemic exposure. This approach not only enhances the therapeutic efficacy of biologics but also minimizes the risk of adverse effects associated with their systemic use [76]. In addition to pharmacological treatments, lifestyle modifications, such as dietary changes, smoking cessation, and stress management, play an essential role in managing IBD. Certain dietary components, like fiber, fat and specific food additives, can exacerbate inflammation, while a well-balanced diet can help support the immune system and intestinal health. Smoking is a known risk factor for Crohn’s disease and can exacerbate disease activity, so cessation is often recommended. Stress, while not a direct cause of IBD, can influence disease flare-ups, and managing stress through techniques

like mindfulness and relaxation exercises can be beneficial [77].

5.3 Psoriasis

Psoriasis is a long-term autoimmune condition that mostly affects the skin, causing thick, scaly areas and fast skin cell development [78]. About 2-3% of people worldwide suffer with this chronic inflammatory skin condition, which is among the most prevalent. Even while psoriasis can strike at any age, it usually first appears in early adulthood or between the ages of 15 and 35. The condition is often characterized by periods of flare-ups and remissions, and its severity can range from mild, localized patches to widespread involvement that affects large areas of the body. Psoriasis is also associated with other comorbidities, such as psoriatic arthritis, cardiovascular disease, and mental health conditions like depression and anxiety [79]. The pathophysiology of psoriasis is complex and involves the interplay of genetic, immune, and environmental factors. Fundamentally, an overreactive immune response that causes skin inflammation is the cause of psoriasis. When the immune system unintentionally targets healthy skin cells, the skin cells in the afflicted areas rapidly change. Skin cells normally take 28 to 30 days to migrate from the epidermis's bottom layer to the surface, but in psoriatic skin, this process takes only a few days, which leads to an accumulation of immature skin cells [80]. These cells accumulate, form scales, and create the characteristic plaques that are a hallmark of the disease. Because they release cytokines that further encourage the proliferation of skin cells and the generation of inflammation, T cells, a kind of white blood cell, are essential in psoriasis' inflammatory process [81].

Although the precise aetiology of psoriasis is still unknown, environmental factors and genetic predisposition are thought to have a role. Psoriasis has been linked to certain genes, including those found in the major histocompatibility complex (MHC). In those who are genetically predisposed, environmental factors such as infections, stress, skin damage (Koebner phenomenon), and some drugs can cause or worsen psoriasis. Furthermore, it has been demonstrated that certain lifestyle choices, including smoking, being overweight, and drinking too much alcohol, can either raise the chance of getting psoriasis or exacerbate its symptoms. The goals of psoriasis treatment are to manage symptoms, lessen inflammation, and avoid flare-ups. Topical therapies that decrease inflammation, such as topical retinoid, coal tar, corticosteroids, and vitamin D analogues, can frequently be used to treat mild instances [82]. Systemic therapy can be required for more moderate to severe instances. These include oral drugs that inhibit the immune system or alter skin cell turnover, such as methotrexate, cyclosporine, and acitretin. Psoriasis therapy has been transformed by biologic medicines, which are targeted medications that inhibit particular immune system molecules implicated in the inflammatory process. Many patients' skin appearance and quality of life have significantly improved as a result of the high effectiveness of biologics such as anti-TNF, anti-IL-17, and anti-IL-23 medications in treating moderate to severe psoriasis. Light therapy, often known as phototherapy, is another successful psoriasis treatment [83]. It entails exposing the skin to ultraviolet (UV) radiation, which lowers inflammation and decreases the skin's fast cell turnover. Commonly utilised is narrow-band UVB therapy; occasionally, psoralen coupled with UVA (PUVA) treatment may be used. Phototherapy is usually used for brief periods of time or in conjunction with other therapies since prolonged usage might raise the risk of skin cancer [84].

6. Challenges and Future Perspectives

6.1 Current Limitations

Hydrogel nanostructures have shown significant promise in the targeted delivery of therapeutic agents for inflammatory diseases, offering unique advantages such as biocompatibility, biodegradability, and controlled release properties [85]. However, despite their potential, several challenges and limitations continue to hinder their widespread application in clinical settings. The difficulty of creating hydrogel nanostructures that can efficiently carry medications to certain inflammatory areas is one of the main obstacles [86]. Overcoming physiological obstacles such inadequate tissue penetration, clearance by the mononuclear phagocyte system, and quick drug carrier breakdown prior to reaching the targeted spot are necessary for precision targeting [87]. Additionally, the stability of hydrogel nanostructures is often a concern, as they may undergo physical or chemical changes under certain physiological conditions, leading to a loss of their drug-delivery capacity. Another significant challenge is the optimization of drug release profiles. While hydrogel nanostructures are capable of controlled release, ensuring that the drug is released at the right time and in the right amount remains difficult. The release rate must be fine-tuned to match the dynamics of the inflammatory response, which varies from patient to patient and over time within the same patient [88].

Moreover, achieving a balance between controlled release and efficient targeting requires further refinement in the design of hydrogel nanostructures, particularly in the incorporation of stimuli-responsive materials that can react to the local inflammatory environment, such as pH, temperature, or specific enzymes [89].

Another challenge in the creation of drug delivery systems based on hydrogel is biocompatibility. Although many hydrogels are composed of biocompatible and biodegradable natural or synthetic polymers, toxicity may result from the buildup of breakdown products or from the nanostructures' prolonged stay in the body. For chronic inflammatory disorders, when frequent or prolonged treatment is necessary, this is especially troubling. Furthermore, it is still difficult to fabricate hydrogel nanostructures with exact control over their dimensions, form, and surface properties. The particle size must be small enough to penetrate the inflamed tissues, but large enough to avoid rapid renal clearance or unwanted side effects [90]. Surface modification techniques are frequently employed to enhance biocompatibility and targeting, but these modifications need to be optimized to ensure that they do not affect the hydrogel's stability or its ability to deliver drugs effectively. On the regulatory front, the path to regulatory approval for hydrogel-based drug delivery systems is complex and time-consuming. Hydrogel nanostructures, being relatively novel, face stringent regulatory scrutiny, and the lack of standardized protocols for their testing, especially for long-term toxicity and clinical efficacy, complicates their translation from the laboratory to clinical practice. The complexity of the manufacturing process, including the scaling up of production for commercial use, adds further challenges in making hydrogel nanostructures a viable option for widespread clinical application [91].

6.2 Future Directions

By utilising cutting-edge technology and transdisciplinary advancements, the creation of hydrogel nanostructures for targeted drug delivery, especially for inflammatory illnesses, is set to revolutionise treatment techniques [92]. Enhancing stimuli-responsive systems, in which hydrogel nanostructures are designed to release medications in response to certain environmental triggers at the site of inflammation, is one of the most promising approaches [93]. This can involve elements such as temperature, pH, and the existence of certain chemicals or enzymes linked to the inflammatory process [94]. Drug distribution can be more precisely regulated by creating hydrogels that react dynamically to the disease microenvironment, reducing off-target effects and enhancing therapy effectiveness [95]. The creation of multifunctional nanostructures that can integrate therapeutic and diagnostic properties onto a single platform, allowing for real-time tracking of medication distribution and disease progression, is another important avenue [96]. This might be accomplished by integrating imaging techniques like magnetic resonance imaging (MRI) or fluorescence, which would enable physicians to monitor the drug's release and the hydrogel's behaviour in vivo. Personalized medicine is another frontier, where hydrogel nanostructures can be tailored to individual patient needs based on genetic, immunological, and disease-specific factors. This could lead to more effective and targeted therapies, as the hydrogel can be designed to adapt its drug release profile according to the patient's unique condition [97]. Additionally, advances in biomaterials will allow for the creation of more biocompatible, sustainable, and environmentally friendly hydrogels, using natural polymers and biodegradable materials to minimize toxicity and long-term side effects [98]. The integration of combination therapies, where multiple drugs targeting different aspects of the inflammatory process are delivered simultaneously, holds great potential for improving outcomes in complex inflammatory diseases [99]. Finally, regulatory advancements are expected to address the complexities of developing and commercializing these advanced hydrogel systems, with clearer guidelines for testing, approval, and long-term safety, ultimately leading to their widespread clinical adoption [100]. The accuracy, effectiveness, and sustainability of hydrogel-based drug delivery systems will be greatly improved by these future directions taken together, which will also improve the treatment options for chronic inflammatory illnesses.

Conclusion

In summary, the use of hydrogel nanostructures for targeted drug delivery in inflammatory disorders is a quickly developing and extremely promising field of study that has the potential to completely transform the way chronic illnesses are treated. These systems have a number of benefits, including as regulated, localised drug release, biocompatibility, and biodegradability, all of which are essential for reducing systemic adverse effects and improving therapeutic efficacy. As research progresses, innovations in stimuli-responsive design, nanoparticle

engineering, and multifunctional hydrogels will enable more precise drug delivery, better targeting of inflamed tissues, and improved patient outcomes. The integration of personalized medicine, real-time monitoring through advanced imaging technologies, and combination therapies is expected to further refine and optimize treatment strategies, offering more tailored and effective solutions for patients. Despite the challenges related to the stability, biocompatibility, and scalability of these systems, ongoing advancements in materials science, biomedical engineering, and regulatory frameworks are steadily overcoming these barriers. In the future, hydrogel nanostructures might have a big influence on how inflammatory illnesses are treated by improving the efficacy, sustainability, and accessibility of medicines while offering a platform for creative drug delivery methods. As these technologies evolve and mature, they are set to become an integral part of personalized, targeted, and minimally invasive treatment approaches for a wide variety of chronic inflammatory conditions.

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Author Contributions

S.A. conceptualized the review and drafted the manuscript. **S.A.A.** contributed to the literature review and provided critical revisions to enhance the content.

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The authors declare that there is no conflict of interest.

References

1. M. Jelinek and K. Duris, ―Inflammatory response in sepsis and hemorrhagic stroke,‖ Brain Hemorrhages. 2023. doi: 10.1016/j.hest.2022.10.005.
2. L. Rojas-Velázquez et al., ―The regulatory function of Blastocystis spp. on the immune inflammatory response in the gut microbiome,‖ Frontiers in Cellular and Infection Microbiology. 2022. doi: 10.3389/fcimb.2022.967724.
3. L. Lafuente-Gracia, E. Borgiani, G. Nasello, and L. Geris, ―Towards in silico Models of the Inflammatory Response in Bone Fracture Healing,‖ Frontiers in Bioengineering and Biotechnology. 2021. doi: 10.3389/fbioe.2021.703725.
4. D. Maseda and E. Ricciotti, ―NSAID–Gut Microbiota Interactions,‖ Frontiers in Pharmacology. 2020. doi: 10.3389/fphar.2020.01153.
5. C. Zhang, Y. Wang, D. Wang, J. Zhang, and F. Zhang, ―NSAID exposure and risk of Alzheimer's disease: An updated meta-analysis from cohort studies,‖ Frontiers in Aging Neuroscience. 2018. doi: 10.3389/fnagi.2018.00083.
6. S. F. Mohseni-Motlagh, R. Dolatabadi, M. Baniassadi, and M. Baghani, ―Application of the Quality by Design Concept (QbD) in the Development of Hydrogel-Based Drug Delivery Systems,‖ Polymers. 2023. doi: 10.3390/polym15224407.
7. S. Trombino, C. Servidio, F. Curcio, and R. Cassano, ―Strategies for hyaluronic acid-based hydrogel design in drug delivery,‖ Pharmaceutics. 2019. doi: 10.3390/pharmaceutics11080407.
8. S. S. Han, S. M. Ji, M. J. Park, M. Suneetha, and U. T. Uthappa, ―Pectin Based Hydrogels for Drug Delivery Applications: A Mini Review,‖ Gels. 2022. doi: 10.3390/gels8120834.
9. P. He et al., ―Nanocellulose-based hydrogels as versatile drug delivery vehicles: A review,‖ International Journal of Biological Macromolecules. 2022. doi: 10.1016/j.ijbiomac.2022.09.214.
10. S. Sun et al., ―Drug delivery systems based on polyethylene glycol hydrogels for enhanced bone regeneration,‖ Frontiers in Bioengineering and Biotechnology. 2023. doi: 10.3389/fbioe.2023.1117647.
11. N. H. Thang, D. Q. Minh, N. Van Phuc, T. T. T. Nhi, and D. X. Cuong, ―Novel polymer-based hydrogels of recent research in drug delivery for disease treatment related to SARS-CoV-2 virus,‖ Express Polymer Letters. 2024. doi: 10.3144/expresspolymlett.2024.13.
12. D. Filho, M. Guerrero, M. Pariguana, A. Marican, and E. F. Durán-Lara, ―Hydrogel-Based Microneedle as a Drug Delivery System,‖ Pharmaceutics. 2023. doi: 10.3390/pharmaceutics15102444.
13. S. A. Ali, D. Pathak, and S. Mandal, ―INTERNATIONAL JOURNAL OF COVID-19 AND THEIR RELATIONSHIP WITH ENVIRONMENT,‖ vol. 14, no. 1, pp. 1–5, 2023.

14. S. Ali et al., ―Quality Standards and Pharmacological Interventions of Natural Oils : Current Scenario and Future Perspectives,‖ 2023, doi: 10.1021/acsomega.3c05241.
15. T. C. Ho et al., ―Hydrogels: Properties and Applications in Biomedicine,‖ Molecules. 2022. doi: 10.3390/molecules27092902.
16. N. H. Thang, T. B. Chien, and D. X. Cuong, ―Polymer-Based Hydrogels Applied in Drug Delivery: An Overview,‖ Gels. 2023. doi: 10.3390/gels9070523.
17. R. Ekbbal et al., ―Indian Medicinal Plants for the Management of Endometriosis: A Comprehensive Review on their phytopharmacology,‖ Natural Resources for Human Health. 2024. doi: 10.53365/nrfhh/174668.
18. S. N. A. S. Azhar, S. E. Ashari, N. Zainuddin, and M. Hassan, ―Nanostructured Lipid Carriers-Hydrogels System for Drug Delivery: Nanohybrid Technology Perspective,‖ Molecules. 2022. doi: 10.3390/molecules27010289.
19. L. Daelemans, I. Steyaert, E. Schoolaert, C. Goudenhooft, H. Rahier, and K. De Clerck, ―Nanostructured hydrogels by blend electrospinning of polycaprolactone/gelatin nanofibers,‖ Nanomaterials, 2018, doi: 10.3390/nano8070551.
20. S. R. Montoro, S. de F. Medeiros, and G. M. Alves, ―Nanostructured Hydrogels,‖ in Nanostructured Polymer Blends, 2013. doi: 10.1016/B978-1-4557-3159-6.00010-9.
21. V. V. A. Fernandez, N. Tepale, J. C. Sánchez-Díaz, E. Mendizábal, J. E. Puig, and J. F. A. Soltero, ―Thermoresponsive nanostructured poly (N-isopropylacrylamide) hydrogels made via inverse microemulsion polymerization,‖ Colloid Polym. Sci., 2006, doi: 10.1007/s00396-005-1395-1.
22. C. S. A. de Lima et al., ―An updated review of macro, micro, and nanostructured hydrogels for biomedical and pharmaceutical applications,‖ Pharmaceutics. 2020. doi: 10.3390/pharmaceutics12100970.
23. D. Kratzer, A. Ludwig-Husemann, K. Junges, U. Geckle, and C. Lee-Thedieck, ―Nanostructured bifunctional hydrogels as potential instructing platform for hematopoietic stem cell differentiation,‖ Front. Mater., 2019, doi: 10.3389/fmats.2018.00081.
24. R. Campos-Cuerva et al., ―Nanostructured fibrin agarose hydrogel as a novel haemostatic agent,‖ J. Tissue Eng. Regen. Med., 2019, doi: 10.1002/term.2831.
25. N. Singh, S. Qutub, and N. M. Khashab, ―Biocompatibility and biodegradability of metal organic frameworks for biomedical applications,‖ Journal of Materials Chemistry B. 2021. doi: 10.1039/d1tb01044a.
26. K. Zhu et al., ―Mechanically Strong Chitin Fibers with Nanofibril Structure, Biocompatibility, and Biodegradability,‖ Chem. Mater., 2019, doi: 10.1021/acs.chemmater.8b05183.
27. S. Chowdhury, A. Rakshit, A. Acharjee, and B. Saha, ―Biodegradability and biocompatibility: Advancements in synthetic surfactants,‖ Journal of Molecular Liquids. 2021. doi: 10.1016/j.molliq.2020.115105.
28. E. Nazarzadeh Zare et al., ―Biomedical applications of engineered heparin-based materials,‖ Bioactive Materials. 2024. doi: 10.1016/j.bioactmat.2023.08.002.
29. H. Cheng, X. Yang, X. Che, M. Yang, and G. Zhai, ―Biomedical application and controlled drug release of electrospun fibrous materials,‖ Materials Science and Engineering C. 2018. doi: 10.1016/j.msec.2018.05.007.
30. F. Priese, D. Wiegel, C. Funaro, G. Mondelli, and B. Wolf, ―Comparison of Mini-Tablets and Pellets as Multiparticulate Drug Delivery Systems for Controlled Drug Release,‖ Coatings, 2023, doi: 10.3390/coatings13111891.
31. T. T. D. Tran and P. H. L. Tran, ―Controlled release film forming systems in drug delivery: The potential for efficient drug delivery,‖ Pharmaceutics. 2019. doi: 10.3390/pharmaceutics11060290.
32. B. Rashidzadeh, E. Shokri, G. R. Mahdavinia, R. Moradi, S. Mohamadi-Aghdam, and S. Abdi, ―Preparation and characterization of antibacterial magnetic-/pH-sensitive alginate/Ag/Fe3O4 hydrogel beads for controlled drug release,‖ Int. J. Biol. Macromol., 2020, doi: 10.1016/j.ijbiomac.2020.03.028.
33. X. Peng, Z. Sun, P. Kuang, and J. Chen, ―Recent progress on HDAC inhibitors with dual targeting capabilities for cancer treatment,‖ European Journal of Medicinal Chemistry. 2020. doi: 10.1016/j.ejmech.2020.112831.
34. S. Bruno et al., ―A photosensitizing fusion protein with targeting capabilities,‖ Biomol. Concepts, 2022, doi: 10.1515/bmc-2022-0014.
35. M. J. Fonseca, H. J. Haisma, S. Klaassen, M. H. Vingerhoeds, and G. Storm, ―Design of immuno-enzymosomes with maximum enzyme targeting capability: Effect of the enzyme density on the enzyme targeting capability and cell binding properties,‖ Biochim. Biophys. Acta - Biomembr., 1999, doi: 10.1016/S0005-2736(99)00073-5.
36. D. Francis and J. Bessant, ―Targeting innovation and implications for capability development,‖ Technovation, 2005, doi: 10.1016/j.technovation.2004.03.004.
37. X. Cai, J. Zhang, Y. Ouyang, D. Ma, S. Tan, and Y. Peng, ―Bacteria-adsorbed palygorskite stabilizes the quaternary phosphonium salt with specific-targeting capability, long-term antibacterial activity, and lower cytotoxicity,‖ Langmuir, 2013, doi: 10.1021/la400824f.
38. D. A. Bedoya, C. Vasti, R. Rojas, and C. E. Giacomelli, ―Risedronate functionalized layered double hydroxides nanoparticles with bone targeting capabilities,‖ Appl. Clay Sci., 2017, doi: 10.1016/j.clay.2017.03.001.

39. H. Gao et al., ―Improved in vivo targeting capability and pharmacokinetics of 99mTc-labeled isoDGR by dimerization and albumin-binding for glioma imaging,‖ Bioconjug. Chem., 2019, doi: 10.1021/acs.bioconjchem.9b00323.
40. S. Onoue, S. Yamada, and H. K. Chan, ―Nanodrugs: Pharmacokinetics and safety,‖ International Journal of Nanomedicine. 2014. doi: 10.2147/IJN.S38378.
41. W. Liao et al., ―Oligonucleotide therapy for obstructive and restrictive respiratory diseases,‖ Molecules. 2017. doi: 10.3390/molecules22010139.
42. S. Sethi, S. L. Harikumar, and Nirmala, ―Review on advances in colon targeted drug delivery system,‖ Int. J. Pharm. Sci. Res., 2012.
43. M. Alavi and M. Hamidi, ―Passive and active targeting in cancer therapy by liposomes and lipid nanoparticles,‖ Drug Metabolism and Personalized Therapy. 2019. doi: 10.1515/dmpt-2018-0032.
44. M. K. N. Mazlan et al., ―Antituberculosis targeted drug delivery as a potential future treatment approach,‖ Antibiotics, 2021, doi: 10.3390/antibiotics10080908.
45. Y. Takakura, K. Maruyama, and M. Yokoyama, ―Passive targeting of drug,‖ Drug Deliv. Syst., 1999, doi: 10.2745/dds.14.425.
46. J. Yoo, C. Park, G. Yi, D. Lee, and H. Koo, ―Active targeting strategies using biological ligands for nanoparticle drug delivery systems,‖ Cancers (Basel)., 2019, doi: 10.3390/cancers11050640.
47. C. S. Kue, A. Kamkaew, K. Burgess, L. V. Kiew, L. Y. Chung, and H. B. Lee, ―Small Molecules for Active Targeting in Cancer,‖ Med. Res. Rev., 2016, doi: 10.1002/med.21387.
48. D. Pollalis, D. Kim, G. K. G. Nair, C. Kang, A. V. Nanda, and S. Y. Lee, ―Intraocular RGD-Engineered Exosomes and Active Targeting of Choroidal Neovascularization (CNV),‖ Cells, 2022, doi: 10.3390/cells11162573.
49. M. Zhang, W. Hu, C. Cai, Y. Wu, J. Li, and S. Dong, ―Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment,‖ Materials Today Bio. 2022. doi: 10.1016/j.mtbio.2022.100223.
50. M. Pourmadadi, M. J. Ahmadi, H. S. Dinani, N. Ajalli, and F. Dorkoosh, ― Theranostic Applications of Stimulus-Responsive Systems based on Fe 2 O 3 ,‖ Pharm. Nanotechnol., 2022, doi: 10.2174/2211738510666220210105113.
51. R. Jia et al., ―Advances in multiple stimuli-responsive drug-delivery systems for cancer therapy,‖ International Journal of Nanomedicine. 2021. doi: 10.2147/IJN.S293427.
52. M. Alsehli, ―Polymeric nanocarriers as stimuli-responsive systems for targeted tumor (cancer) therapy: Recent advances in drug delivery,‖ Saudi Pharmaceutical Journal. 2020. doi: 10.1016/j.jsps.2020.01.004.
53. V. Perez-Puyana, P. Cuartero, M. Jiménez-Rosado, I. Martínez, and A. Romero, ―Physical crosslinking of pea protein-based bioplastics: Effect of heat and UV treatments,‖ Food Packag. Shelf Life, 2022, doi: 10.1016/j.fpsl.2022.100836.
54. M. Farokhi, M. Aleemardani, A. Solouk, H. Mirzadeh, A. H. Teuschl, and H. Redl, ―Crosslinking strategies for silk fibroin hydrogels: Promising biomedical materials,‖ Biomedical Materials (Bristol). 2021. doi: 10.1088/1748-605X/abb615.
55. C. Guo et al., ―Synthesis of bovine serum albumin-gelatin composite adhesive hydrogels by physical crosslinking,‖ J. Polym. Res., 2022, doi: 10.1007/s10965-022-03130-2.
56. K. S. Weadock, E. J. Miller, L. D. Bellincampi, J. P. Zawadsky, and M. G. Dunn, ―Physical crosslinking of collagen fibers: Comparison of ultraviolet irradiation and dehydrothermal treatment,‖ J. Biomed. Mater. Res., 1995, doi: 10.1002/jbm.820291108.
57. S. Li, N. Wang, B. Yu, W. Sun, and L. Wang, ―Genetically encoded chemical crosslinking of carbohydrate,‖ Nat. Chem., 2023, doi: 10.1038/s41557-022-01059-z.
58. M. Z. Ahmad, H. Pelletier, V. Martin-Gil, R. Castro-Muñoz, and V. Fila, ―Chemical crosslinking of 6FDA-ODA and 6FDA-ODA:DABA for improved CO2/CH4 separation,‖ Membranes (Basel)., 2018, doi: 10.3390/membranes8030067.
59. A.Korpela, A. Tanaka, and J. Asikainen, ―Effect of Chemical Crosslinking on the Biodegradation Rate of Kraft Paper,‖ BioResources, 2023, doi: 10.15376/biores.18.3.6336-6347.
60. T. Young, O. C. White, and M. A. Daniele, ―Rheological Properties of Coordinated Physical Gelation and Chemical Crosslinking in Gelatin Methacryloyl (GelMA) Hydrogels,‖ Macromol. Biosci., 2020, doi: 10.1002/mabi.202000183.
61. Oryan, A. Kamali, A. Moshiri, H. Baharvand, and H. Daemi, ―Chemical crosslinking of biopolymeric scaffolds: Current knowledge and future directions of crosslinked engineered bone scaffolds,‖ International Journal of Biological Macromolecules. 2018. doi: 10.1016/j.ijbiomac.2017.08.184.
62. J. Liu, B. Yang, and L. Wang, ―Residue selective crosslinking of proteins through photoactivatable or proximity-enabled reactivity,‖ Current Opinion in Chemical Biology. 2023. doi: 10.1016/j.cbpa.2023.102285.
63. M. Ma et al., ―Effective removal of cation dyes from aqueous solution using robust cellulose sponge,‖ J. Saudi Chem. Soc., 2020, doi: 10.1016/j.jscs.2020.09.008.
64. M. Götze et al., ―StavroX-A software for analyzing crosslinked products in protein interaction studies,‖ J. Am. Soc. Mass Spectrom., 2012, doi: 10.1007/s13361-011-0261-2.

65. S. Dahl-Popolizio, ―Arthritis,‖ in Primary Care Occupational Therapy: a Quick Reference Guide, 2023. doi: 10.1007/978-3-031-20882-9_12.
66. S. Hayer et al., ―SMASH recommendations for standardised microscopic arthritis scoring of histological sections from inflammatory arthritis animal models,‖ Ann. Rheum. Dis., 2021, doi: 10.1136/annrheumdis-2020-219247.
67. A.B. Gottlieb and J. F. Merola, ―Axial psoriatic arthritis: An update for dermatologists,‖ Journal of the American Academy of Dermatology. 2021. doi: 10.1016/j.jaad.2020.05.089.
68. E. A. Littlejohn and S. U. Monrad, ―Early Diagnosis and Treatment of Rheumatoid Arthritis,‖ Primary Care - Clinics in Office Practice. 2018. doi: 10.1016/j.pop.2018.02.010.
69. J. Yi et al., ―Hydrogels for the treatment of rheumatoid arthritis,‖ Frontiers in Bioengineering and Biotechnology. 2022. doi: 10.3389/fbioe.2022.1014543.
70. M. Slouma et al., ―Reactive arthritis occurring after COVID-19 infection: a narrative review,‖ Infection. 2023. doi: 10.1007/s15010-022-01858-z.
71. L. Zeng et al., ―Efficacy and Safety of Curcumin and Curcuma longa Extract in the Treatment of Arthritis: A Systematic Review and Meta-Analysis of Randomized Controlled Trial,‖ Front. Immunol., 2022, doi: 10.3389/fimmu.2022.891822.
72. M. Lee and E. B. Chang, ―Inflammatory Bowel Diseases (IBD) and the Microbiome—Searching the Crime Scene for Clues,‖ Gastroenterology, 2021, doi: 10.1053/j.gastro.2020.09.056.
73. S. S. Seyedian, F. Nokhostin, and M. D. Malamir, ―A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease,‖ J. Med. Life, 2019, doi: 10.25122/jml-2018-0075.
74. A. Gampierakis et al., ―Hippocampal neural stem cells and microglia response to experimental inflammatory bowel disease (IBD),‖ Mol. Psychiatry, 2021, doi: 10.1038/s41380-020-0651-6.
75. M. Hagan, B. H. Hayee, and A. Rodriguez-Mateos, ―(Poly)phenols in inflammatory bowel disease and irritable bowel syndrome: A review,‖ Molecules. 2021. doi: 10.3390/molecules26071843.
76. S. Zhang, Y. Liang, J. Yao, D. F. Li, and L. S. Wang, ―Role of Pyroptosis in Inflammatory Bowel Disease (IBD): From Gasdermins to DAMPs,‖ Frontiers in Pharmacology. 2022. doi: 10.3389/fphar.2022.833588.
77. D. Patel, C. Trivedi, and N. Khan, ―Management of Anemia in Patients with Inflammatory Bowel Disease (IBD),‖ Curr. Treat. Options Gastroenterol., 2018, doi: 10.1007/s11938-018-0174-2.
78. A.V. E. de Carvalho and L. L. Leite, ―Psoriasis,‖ in Dermatology in Public Health Environments: A Comprehensive Textbook, Second Edition, 2023. doi: 10.1007/978-3-031-13505-7_20.
79. Z. Young, M. K. Sarkar, and J. E. Gudjonsson, ―Pathophysiology of generalized pustular psoriasis,‖ Experimental Dermatology. 2023. doi: 10.1111/exd.14768.
80. A.E. M. Griffiths, A. W. Armstrong, J. E. Gudjonsson, and J. N. W. N. Barker, ―Psoriasis,‖ The Lancet. 2021. doi: 10.1016/S0140-6736(20)32549-6.
81. M. C. Buhaş et al., ―Gut Microbiota in Psoriasis,‖ Nutrients. 2022. doi: 10.3390/nu14142970.
82. M. Kamata and Y. Tada, ―Dendritic Cells and Macrophages in the Pathogenesis of Psoriasis,‖ Frontiers in Immunology. 2022. doi: 10.3389/fimmu.2022.941071.
83. Guidelines for the Diagnosis and Treatment of Psoriasis in China: 2019 Concise Edition#,‖ Int. J. Dermatology Venereol., 2022, doi: 10.1097/JD9.0000000000000074.
84. T. Kampe et al., ―PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH PSORIASIS,‖ Cent. Eur. J. Public Health, 2022, doi: 10.21101/cejph.a6806.
85. Mitrovic, G. Richey, S. Kim, and M. O. Guler, ―Peptide Hydrogels and Nanostructures Controlling Biological Machinery,‖ Langmuir. 2023. doi: 10.1021/acs.langmuir.3c01269.
86. Z. S. Nishat et al., ―Hydrogel Nanoarchitectonics: An Evolving Paradigm for Ultrasensitive Biosensing,‖ Small. 2022. doi: 10.1002/smll.202107571.
87. Lachance-Brais et al., ―Small Molecule-Templated DNA Hydrogel with Record Stiffness Integrates and Releases DNA Nanostructures and Gene Silencing Nucleic Acids,‖ Adv. Sci., 2023, doi: 10.1002/advs.202205713.
88. O. Ko, S. Han, and J. B. Lee, ―Selective release of DNA nanostructures from DNA hydrogel,‖ J. Ind. Eng. Chem., 2020, doi: 10.1016/j.jiec.2020.01.005.
89. Mao et al., ―Photo-Inspired Antibacterial Activity and Wound Healing Acceleration by Hydrogel Embedded with Ag/Ag@AgCl/ZnO Nanostructures,‖ ACS Nano, 2017, doi: 10.1021/acsnano.7b03513.
90. F. Y. Pong, M. Lee, J. R. Bell, and N. T. Flynn, ―Thermoresponsive behavior of poly(N-isopropylacrylamide) hydrogels containing gold nanostructures,‖ Langmuir, 2006, doi: 10.1021/la0534165.
91. A.Sidorenko, T. Krupenkin, and J. Aizenberg, ―Controlled switching of the wetting behavior of biomimetic surfaces with hydrogel-supported nanostructures,‖ J. Mater. Chem., 2008, doi: 10.1039/b805433a.
92. S. S. Athukorala et al., ―3D printable electrically conductive hydrogel scaffolds for biomedical applications: A review,‖ Polymers. 2021. doi: 10.3390/polym13030474.
93. Yang, M. J. Campolongo, T. N. Nhi Tran, R. C. H. Ruiz, J. S. Kahn, and D. Luo, ―Novel DNA

materials and their applications,‖ Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology. 2010. doi: 10.1002/wnan.111.

94. Z. Yao, J. Xu, J. Shen, L. Qin, and W. Yuan, ―Biomimetic Hierarchical Nanocomposite Hydrogels: From Design to Biomedical Applications,‖ Journal of Composites Science. 2022. doi: 10.3390/jcs6110340.
95. H. Hamedi, S. Moradi, S. M. Hudson, and A. E. Tonelli, ―Chitosan based hydrogels and their applications for drug delivery in wound dressings: A review,‖ Carbohydrate Polymers. 2018. doi: 10.1016/j.carbpol.2018.06.114.
96. Y. Yang, M. J. Campolongo, T. N. N. Tran, R. C. H. Ruiz, J. S. Kahn, and D. Luo, ―WILEY INTERDISCIPLINARY REVIEWS-NANOMEDICINE AND NANOBIOTECHNOLOGY,‖ Novel DNA materials and their applications. 2010.
97. J. E. Sosa-Hernández et al., ―Poly-3-hydroxybutyrate-based constructs with novel characteristics for drug delivery and tissue engineering applications—A review,‖ Polymer Engineering and Science. 2020. doi: 10.1002/pen.25470.
98. A.Oltean et al., ―Cereal Straw Production,‖ Cereal Straw as a Resour. Sustain. Biomater. Biofuels, 2016.
99. R. Ajdary, B. L. Tardy, B. D. Mattos, L. Bai, and O. J. Rojas, ―Plant Nanomaterials and Inspiration from Nature: Water Interactions and Hierarchically Structured Hydrogels,‖ Advanced Materials. 2021. doi: 10.1002/adma.202001085.
100. Y. Guo, J. Bae, F. Zhao, and G. Yu, ―Functional Hydrogels for Next-Generation Batteries and Supercapacitors,‖ Trends in Chemistry. 2019. doi: 10.1016/j.trechm.2019.03.005.