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REVIEW

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Research Progress on Intelligent Drug Delivery Systems in Chronic Inflammatory Diseases

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Abstract

Chronic inflammatory diseases are a serious challenge in global public health, and traditional routes of administration have many limitations due to their lack of precision and controllability. As an innovative drug delivery strategy, intelligent drug delivery system (IDDS) has attracted widespread attention. This dosage form can respond to internal and external stimuli (such as changes in pH, temperature, enzyme activity, light sensitivity, and magnetic sensitivity), thereby achieving precise and selective release of drugs. This article systematically reviews electronic databases (PubMed, Web of Science, ScienceDirect, and CNKI) to find studies published between 2012 and 2025, focusing on the core characteristics of the chronic inflammatory microenvironment and its guiding significance in the design of IDDS. This article highlights the construction strategies and response mechanisms of various IDSS, including nanoparticles, liposomes, hydrogels, cell membrane-based biomimetic systems, and prodrug strategies, as well as their application progress in chronic inflammatory diseases such as inflammatory bowel disease, arthritis, skin diseases, respiratory diseases, liver and kidney diseases, ocular diseases, and cardiovascular diseases. The article also explores the mechanisms and advantages of IDDS in targeted delivery, controlled release, and various responsive systems (such as pH, enzyme, magnetic, thermal, light, and ultrasound), and investigates the benefits, challenges, and future application prospects of the latest research and application advances in the treatment of chronic inflammatory diseases. These IDDS has opened up new paths for enhancing therapeutic efficacy, reducing toxic side effects, and enabling personalized treatment in chronic inflammatory diseases, offering new hope for future medical treatment.

1 Introduction

Chronic inflammatory diseases, as a major challenge facing global public health, are often characterized by the involvement of multiple immune cells and factor types, periodic attacks, and complex course changes [1]. From rheumatoid arthritis and inflammatory bowel disease to atherosclerosis, chronic skin diseases and metabolic diseases, chronic inflammation can not only delay the course of disease and recur, but also induce tissue damage, fibrosis and even malignant transformation, seriously affecting patients' quality of life [2]. Although traditional drug therapy can control symptoms to a certain extent, it still faces many challenges such as poor targeting, high systemic toxicity, and low patient compliance, underscoring the urgent need for more precise, efficient, and safer therapeutic strategies [3].

With the in-depth exploration of the pathological mechanism of chronic inflammation, people gradually realize the core position of the inflammatory microenvironment in the occurrence and development of diseases. This microenvironment has a series of physiological and pathological characteristics that differ from normal tissues, including local acid-base imbalance, overexpression of specific enzymes, accumulation of reactive oxygen species (ROS), abnormal temperature, and changes in mechanical signals [4]. These features not only provide new insights into the persistence and complexity of inflammation, but also lay the biological foundation for developing intelligent drug delivery system (IDDS) that can respond to pathological signals and achieve precise drug delivery.

As a cutting-edge field of drug delivery technology, IDDS integrates multidisciplinary knowledge such as materials science, nanotechnology, molecular biology, and clinical medicine, aiming to achieve precise control of drugs in time, space, and dosage through response to external or internal stimuli (such as pH, enzymes, redox status, temperature, etc.). In recent years, various intelligent carriers, including nanoparticles, liposomes, hydrogels, biomimetic systems of cell membranes and prodrug strategies, have emerged continuously, and have demonstrated good targeting capability, controlled release performance and therapeutic potential in a variety of chronic inflammatory disease models [5].

This article systematically reviews the core characteristics of the chronic inflammatory microenvironment and its guiding significance in the design of IDDS, focusing on the construction strategies and response mechanisms of various IDSS, as well as their application progress in typical chronic inflammatory diseases. This article aims to provide theoretical references for subsequent research in this field and promotes its clinical translation, ultimately achieving precise, highly efficient, and personalized treatment of chronic inflammatory diseases. We hope to offer a new perspective for the development of IDDS for chronic inflammatory diseases through this review, and promote innovation in the research and development strategies of future novel drug delivery systems. We firmly believe that with the continuous advancement of science and technology, IDDS will play an increasingly essential role in the treatment of inflammatory diseases, bringing better therapeutic outcomes and improving the quality of life for patients.

2 Application of Chronic Inflammatory Microenvironment and IDDS

2.1 Core characteristics of the chronic inflammatory microenvironment

The chronic inflammatory microenvironment is a dynamic network formed by the interaction between inflammatory cells, immune factors, extracellular matrix, and diseased tissues. Its unique physiological and pathological characteristics provide specific targets for IDDS and are the core basis for designing "responsive" drug delivery systems.

2.1.1 Acid-base disturbance

(1) Compared with normal tissues (pH 7.35-7.45), chronic inflammatory areas have significantly reduced pH values that usually maintained at 5.5-6.5 (such as rheumatoid arthritis joint effusion and tumor associated inflammatory tissues) due to enhanced anaerobic glycolysis and lactate accumulation. The existing evidence has pointed out that in the inflammatory microenvironment, lactate enters T cells through transport proteins (such as SLC5A12 and SLC16A1), inhibits their glycolysis, and induces the production of pro-inflammatory factors such as IL-17. However, digestive tract inflammation (such as inflammatory bowel disease) presents region-specific pH gradient: pH 1-3 in the stomach, pH 6.0-7.5 in the small intestine, and pH 7.0-7.5 in the colon. Local pH fluctuations in inflammatory lesions are greater due to mucosal damage. It has been documented that the pH gradient of the gastrointestinal microenvironment is a key factor in maintaining its homeostasis and achieving disease targeted therapy. In inflammatory bowel disease, the acid-base balance of the intestinal microenvironment is disrupted, and pH-responsive drug delivery systems developed based on this physiological feature have shown significant therapeutic potential [6].

2.1.2 High expressions of specific enzymes

Inflammation-activated immune cells, such as macrophages and neutrophils, secrete a large amount of hydrolytic enzymes, forming an "enzyme-catalyzed reaction enrichment zone". Typical overexpressed enzymes include matrix metalloproteinases (MMPs, which are overexpressed in rheumatoid arthritis synovium and atherosclerosis plaque), elastase (characteristic enzymes of airway inflammation such as asthma and chronic obstructive pulmonary disease (COPD)), and β-glucuronidase (biomarkers of liver inflammation and colitis). The activity of these enzymes is usually 10-100 times higher than in normal tissues, and they have substrate specificity, providing precise triggering signals for enzyme-responsive drug delivery systems [7].

2.1.3 Reactive oxygen species (ROS) and redox imbalance

Under chronic inflammatory conditions, the respiratory burst of neutrophils and abnormal mitochondrial function can lead to the generation of substantial ROS (such as superoxide anions and hydrogen peroxide), and the ROS concentration in the inflammatory area can be 5-20 times higher than in normal tissues. At the same time, the content of reducing substances such as glutathione (GSH) is increased, forming a unique redox microenvironment that provides triggering conditions for redox responsive drug delivery systems. Zorov et al. elaborate on the important role of mitochondrial ROS in the inflammatory process. They find that under inflammatory conditions, mitochondrial succinic acid levels in macrophages are markedly elevated upon stimulation by lipopolysaccharides and other factors. Succinic acid stabilizes HIF-1α and promotes the production of interleukin-1β, thereby linking mitochondrial metabolism with innate immune signals. Further, mitochondria-derived ROS can not only directly act as pro-inflammatory signaling molecules, but also further amplify inflammatory responses by activating inflammation-related pathways such as NF-κB. Mitochondrial ROS also participates in regulating the expression and activity of Nox4 (a mitochondria-associated NADPH oxidase), forming a feedforward loop that exacerbates oxidative stress and inflammatory damage. Therefore, mitochondrial ROS is not only an effector of inflammatory signals, but also a key node in the inflammatory amplification network, playing an important role in the initiation and maintenance of inflammation [8].

2.1.4 Abnormal temperature and mechanical signals

Local inflammatory reaction is accompanied by

vasodilation and increased metabolism, inducing an increase of 0.5-2.0 ℃ in the temperature of inflammatory region (such as skin inflammation and joint inflammation). Giles et al. systematically discuss the impact of environmental temperature on the development of inflammation and atherosclerosis. They reveal that housing wild-type C57BL/6 mice at thermoneutral temperature (~ 30 ℃) instead of conventional temperature (~ 22 ℃), combined with a high-fat "Western diet", can significantly promote obesity development, alter lipid composition (such as increasing high-density lipoprotein), and induce aortic plaque formation, which is difficult to achieve at conventional temperatures. In addition, a thermoneutral environment enhances systemic and local inflammatory responses (such as in the aorta and white adipose tissue), manifested by increased expressions of pro-inflammatory cytokines (such as IL-6, IFN-γ and TNF), polarization of macrophages towards M1 phenotype, and upregulation of gene pathways associated with poor cardiovascular outcomes in circulating immune cells. This study suggests that environmental temperature is a key factor in mediating the inflammatory state of the body and the occurrence of metabolic diseases. Moreover, changes in the mechanical properties of inflammatory tissues, such as increased joint cavity pressure and abnormal intestinal peristalsis, can also serve as design targets for mechanical force-responsive drug delivery systems [9].

3 IDDS and its drug-coated carriers

3.1 Definitions and concepts

IDDS represents a series of advanced technologies in the field of pharmacotherapy, designed to optimize targeted drug delivery, specifically involving precise control of time, dosage, and space. The core feature of these systems is the ability to respond to specific physiological or environmental stimuli, such as pH changes, temperature changes, or the presence of biomolecules, in order to control the release and activity of encapsulated drugs [10]. Through this intelligent response, IDDS can release appropriate amounts of drugs to specific pathological sites, when necessary, thereby enhancing treatment efficacy and reducing adverse reactions.

The main goal of IDDS is to improve the accuracy and personalization of pharmacotherapy. IDDS can reduce systemic exposure and related side effects by precisely controlling drug release, while ensuring effective drug concentration at the treatment site, thereby elevating treatment efficiency. Besides, these systems can tailor treatment regimens to individual patient needs or specific disease states. For example, in tumor treatment, IDDS can directly deliver chemotherapy drugs to tumor tissues, reducing the impact on healthy tissues [11].

The development of IDDS is based on interdisciplinary achievements, including fields such as medicinal chemistry, materials science, biology, and engineering. The design and development of these systems involve the selection and optimization of biocompatible materials, such as nanoparticles, liposomes, microspheres and hydrogels [10]. These materials can respond to specific internal or external conditions, and can be designed to have specific shape, size and surface characteristics to achieve accurate control over drug loading and release patterns.

The concept and definition of IDDS have introduced a revolutionary field that pushes the precision of pharmacotherapy to the forefront. By finely controlling the release time, dosage, and spatial distribution of drugs, these systems offer a means to optimize drug delivery, enabling more precise targeting of specific disease sites. This intelligent delivery method is achieved through innovative design of drug carrier materials, where the carrier can sense specific changes in the body (such as pH, temperature, or changes in specific biomarkers) [2] and control drug

release accordingly.

The IDDS not only optimizes the targeted delivery of drugs and decreases their impact on normal tissues, but also improves the efficiency and safety of treatment. The development of this system is grounded in in-depth research and interdisciplinary collaboration in multiple disciplines such as medicinal chemistry, biocompatible materials science, nanotechnology, and biology. By utilizing a variety of biocompatible materials such as nanoparticles, liposomes, microspheres and hydrogels, IDDS can exist in a variety of forms, each of which has its own unique release mechanism and application scenarios.

3.2 Drug encapsulated carrier of IDDS

3.2.1 Nanoscale carriers

Nanoparticles have demonstrated significant advantages in the treatment of inflammatory diseases due to their unique physicochemical properties. These minute particles, typically ranging from 1 to 100 nanometers in size, function at the cellular and molecular levels. The small size and large surface area of nanoparticles are crucial for their targeted delivery ability, especially in diseases such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis. The core advantage of nanoparticles is their ability to efficiently carry and protect drug molecules. These particles are typically composed of biocompatible and biodegradable materials, such as poly lactic-co-glycolic acid (PLGA), natural liposomes, or synthetic polymers. These materials not only ensure the stability of drug molecules, but also increase the concentration of drugs in target tissues by controlling drug release, thereby enhancing therapeutic efficacy and reducing systemic side effects [12]. Nanoparticles can target specific lesion sites through unique design. For example, they can be adjusted to respond to specific pH values or enzyme activity at the site of inflammation, ensuring drug release only in the desired area. This precise positioning ability remarkably improves the accuracy and safety of treatment, especially in reducing the exposure of healthy tissues to drugs [13].

There are various methods for preparing nanoparticles, including co-precipitation, solvent evaporation, and self-assembly techniques, which allow scientists to precisely control the size, shape, and surface functionalization of nanoparticles, thereby fine-tuning the loading and release characteristics of drugs [14]. Additionally, these technologies enable surface modifications, such as the addition of specific targeting ligands or functional compounds, to enhance targeted delivery and biocompatibility [15].

Nanoparticles, as an important component of IDDS, have demonstrated great potential in the treatment of inflammatory diseases. Through precise targeting and controlled-release characteristics, they provide an efficient and safe therapeutic strategy for the intervention of chronic inflammatory diseases.

3.2.1.1 Nanocrystals

Nanocrystal technology is primarily aimed at addressing the solubility issues of poorly soluble drugs. By reducing drug particles to the nanometer scale, the specific surface area of drug is dramatically enlarged, which accelerates dissolution rate and improves oral bioavailability [16]. Preparation techniques for nanocrystals include high-pressure homogenization, wet milling, and ultrasound-assisted methods. The high-pressure homogenization method breaks down the drug particles into nanometer-sized particles in a liquid medium through high pressure, while the wet milling method grinds the drug particles using the mechanical force of the grinding medium [17]. The ultrasound-assisted method exploits utilizes cavitation effects generated by ultrasonic waves to reduce drug particle size. Beyond enhancing solubility and bioavailability of drugs, nanocrystals can optimize oral absorption by enhancing drug dispersibility and stability.

Nanocrystals, as a multifunctional nanomaterial, have shown significant potential in the diagnosis and treatment of inflammation-related diseases. For example, chitosan/bioactive glass coatings can effectively protect nanocrystalline titanium implants from hydrogen peroxide-mediated corrosion under simulated inflammatory conditions, extending the lifespan of the implants [18]. Hybrid drug nanocrystals have achieved real-time tracking of drug distribution and dissolution kinetics *in vivo* by integrating environmentally responsive fluorescent probes, providing a new strategy for targeted therapy of inflammatory diseases such as colitis [19]. Moreover, nanocrystalline cellulose has been proved to promote the expression of mucin MUC2 via activating the MAPK signaling pathway and regulate the gut microbiota (such as increasing Akkermansia and Odoribacter abundance), thereby repairing intestinal barrier function and attenuating inflammatory damage in ulcerative colitis [20]. These studies highlight the multi-mechanism role of nanocrystals in inflammation regulation, laying a theoretical foundation for their clinical translation.

3.2.1.2 Drug co-crystals

Nano co-crystals represent an emerging solid-state morphology optimization technology for drugs, which forms nanoscale crystals through intermolecular non-covalent interactions between two or more drug molecules or between drug and excipient molecules [21]. Compared with traditional drug co-crystals, nano co-crystals have higher dissolution rates and bioavailability due to their nanoscale size [22]. The preparation methods of nano co-crystals include anti-solvent precipitation, spray drying, and supercritical fluid technology. These methods achieve nanonization of drug co-crystals by controlling precipitation conditions, drying processes, or the supercritical state of solvents. Nano co-crystals can not only improve the solubility and bioavailability of drugs, but also enhance their stability and storage performance by selecting appropriate co-crystal ligands. In recent years, natural deep eutectic solvents (NADES) and drug-drug co-crystal systems have shown broad prospects in the local treatment of inflammatory diseases owing to their excellent drug solubility, biocompatibility, and controllable release characteristics. For example, etodolac-acetaminophen (EP) co-crystals evidently downregulates key inflammatory factors such as TNF-α, COX-2, and IL-6 in a macrophage model, exhibiting a synergistic anti-inflammatory effect. In addition, NADES can be used as a drug carrier to construct transdermal or mucosal delivery systems, apparently enhancing the local permeability and retention of anti-inflammatory drugs, and providing a new strategy for targeted therapy of diseases such as rheumatoid arthritis and skin inflammation [23].

3.2.1.3 Self-assembly

In recent years, the self-assembly nanotechnology has garnered significant attention in the field of novel drug delivery systems. The synthesis of traditional nanoparticles relies heavily on exogenous polymer carrier materials such as polyvinyl alcohol (PVA) and polyvinylpyrrolidone (PVP), which not only have potential biological toxicity risks, but also limit clinical translation due to their complex preparation process and insufficient quality control. Further, traditional nanoparticles load drugs in a passive encapsulation form, which can easily lead to drug leakage and failure owing to structural damage. In contrast, self-assembly nanoparticles are formed through intermolecular forces (e.g., van der Waals forces, electrostatic forces, and hydrogen bonds), which have the following advantages: firstly, van der Waals forces promote spontaneous binding of nanoparticles at close range; secondly, charged particles form ordered assemblies through electrostatic attraction; thirdly, particles containing functional groups such as hydroxyl

and amino groups can align directionally via hydrogen bonds. This molecular recognition-based self-assembly mechanism not only significantly reduces the risk of toxic side effects, but also achieves precise control of quality properties without the need for exogenous carrier materials [24].

Self-assembling microcapsules are a nanoscale drug carrier system prepared based on the principle of molecular self-assembly. These microcapsules are spontaneously assembled through interactions between drug molecules and polymers or other excipient molecules, and can effectively encapsulate various drug molecules [25]. Especially for pH-responsive self-assembling microcapsules for treating gastric ulcers, their design utilizes the pH sensitivity of the gastric acid environment. In the gastric acid environment, microcapsules remain stable without drug release; when entering a relatively alkaline intestinal environment, microcapsule materials undergo structural changes in response to pH changes, triggering drug release [26]. This pH-responsive self-assembly microcapsule can not only achieve targeted drug delivery and reduce gastric irritation, but also control the release rate and time of drugs based on the pH environment differences at the disease site, thereby achieving more precise therapeutic effects. The preparation techniques of self-assembly microcapsules cover various methods, including solvent evaporation, layer-by-layer self-assembly, and microfluidic technology. The solvent evaporation method guides the self-assembly of drugs and carrier materials into microcapsules through the evaporation of solvents. The layer-by-layer self-assembly method utilizes the electrostatic interactions or hydrogen bonding between drugs and carrier materials to prepare multi-layer microcapsule structures by stacking them layer by layer. Microfluidic technology utilizes microfluidic chips to precisely control reaction conditions, achieving self-assembly of drugs and carrier materials in a microscale environment [27]. These techniques not only allow precise control over the size and morphology of the microcapsules but also enable precise control of drug release behavior by selecting different carrier materials and adjusting assembly conditions. Self-assembling microcapsules provide new ideas and methods for solving various problems in traditional drug delivery methods due to their unique design and functionality. Particularly for drugs that need to be released in specific pH environments or require prolonged controlled release, self-assembly microcapsules provide an effective solution. In addition, by introducing targeted ligands or responsive functional groups, self-assembly microcapsules can also achieve targeted delivery to specific cells or tissues, thus further improving the efficacy and safety of drugs [28].

Self-assembling micelles are thermodynamically stable nano-aggregates formed by the spontaneous assembly of amphiphilic molecules in selective solvents, which possess self-assembly driving force due to hydrophobic interactions, hydrogen bonding and electrostatic interactions. Also, their molecules have the ability to spontaneously form micelles internally [29]. Self-assembling micelles can significantly improve the apparent solubility and bioavailability of poorly soluble drugs, avoid premature degradation or inactivation of drugs in circulation, and reduce toxic side effects on normal tissues. They can also be loaded through physical embedding, chemical bonding (prodrug strategy), and electrostatic interactions, the main types of which include traditional micelles, mixed micelles, prodrug self-assembling micelles, stimulus-responsive micelles, targeted micelles, etc [30].

As an innovative drug delivery strategy, self-assembly technology demonstrates great potential in the treatment of inflammatory diseases. Through non-covalent interactions (such as π - π stacking,

hydrogen bonding and electrostatic interaction), natural small molecules or peptides can spontaneously form hydrogels or nanoparticles, achieving controlled drug release and precise regulation of inflammatory microenvironment. For example, Zhao et al. develop Fmoc-phe3 self-assembling hydrogel loaded with CNPs and DMP1, which evidently inhibits inflammation of dental pulp stem cells and promotes dentin regeneration [31]. Zheng et al. report that rhein self-assembling hydrogel can effectively alleviate neuroinflammation through TLR4/N-κB pathway [32]. Gao et al. construct the berberine-hesperetin self-assembling nanoparticles that can markedly improve ulcerative colitis by regulating the immune microenvironment and repairing the intestinal barrier [33]. These studies not only reveal the multiple functions of self-assembling materials in inflammation treatment, but also provide theoretical and experimental basis for the development of new anti-inflammatory agents. There are authors who has designed and synthesized hydrogels composed of ibuprofen (IPF) and GFFY peptide, which are linked by cleavable ester bonds, and the synthesized hydrogel agent has been confirmed to self-assemble into hydrogel during heating-cooling process. When the hydrogel was acted upon by esterases, IPF is released in a continuous manner, which demonstrates therapeutic effects in suppressing ocular inflammation resulting from lipopolysaccharide (LPS)-induced uveitis comparable to current treatments with diclofenac sodium (DIC) eye drops [34].

3.2.2 Micrometer-scale carriers

3.2.2.1 Microspheres

Microspheres, as micron-sized particles made of biodegradable polymers, have become a key drug delivery system in the treatment of chronic inflammatory diseases. These microspheres can encapsulate drugs and control the time and rate of drug release through precise design. In the treatment of chronic inflammatory diseases such as rheumatoid arthritis, microspheres reduce fluctuations in drug concentration via providing sustained and stable drug release during the treatment process, thereby enhancing the effectiveness and reliability of treatment [35].

A key advantage of microspheres lies in their ability to maintain a constant concentration of drugs within the treatment area, which is crucial for long-term and continuous disease management. This sustained-release characteristic not only optimizes drug efficacy, but also evidently diminishes the frequency of patients taking medicine and improves patient compliance with treatment plans. Microsphere-based formulations are particularly suitable for chronic diseases that require long-term treatment and control.

The preparation of microspheres involves various techniques, including solvent evaporation and solvent extraction, which enable scientists to precisely control the size, shape, and surface properties of microspheres, thereby finely regulating the encapsulation efficiency and release kinetics of drugs. Moreover, the design of microspheres can be tailored to the specific needs of diseases, such as by changing the composition of polymers or adding specific targeting ligands to enhance their targeting and therapeutic effects. The flexibility of microsphere technology is also reflected in its ability to encapsulate multiple types of drugs, including those that are challenging to deliver effectively via conventional methods. This multifunctionality makes microspheres a versatile drug delivery platform that can provide personalized and optimized treatment options for various inflammatory diseases. Lon č arevi ć Vrabec et al. (2026) develop intelligent chitosan/calcium phosphate (CHT Cu/CaP) microspheres as a multifunctional drug delivery platform [36]. These microspheres exhibit significant pH-sensitive

doxorubicin release, with remarkably enhanced drug elution in acidic buffer (pH 6.0) compared to physiological conditions (pH 7.4). This feature is essential for targeting pathological sites with acidic microenvironments, such as tumors or inflammatory tissues. Research has shown that the addition of calcium phosphate bioceramics further enhances drug loading capacity and release curve. Although evaluated in osteosarcoma models, the potential pH-responsive mechanism of these microspheres provides a promising and adaptable strategy for developing targeted delivery systems against inflammation, with local acidosis being a hallmark [37].

In conclusion, microspheres, as a part of IDDS, have demonstrated outstanding potential and application value in the treatment of chronic inflammatory diseases.

3.2.2.2 Micron-sized liposomes

Micron-sized liposomes are lipid bilayer vesicles with a size in the micrometer range (usually 1-5 μm), exhibiting higher drug encapsulation capacity and efficiency than nanoliposomes due to their larger internal aqueous core. Micron-sized liposomes can efficiently load hydrophilic or hydrophobic drugs and have excellent long-term stability. The passive drug leakage rate is extremely low, making them suitable as long-term drug delivery carriers.

Micro-scale drug delivery systems are rapidly developing towards functional integration, intelligent control and precise targeting, displaying enormous clinical translational potential. Yuan et al. develop photoactivatable micron-sized liposomes that achieve multiple and quantitative drug releases triggered by near-infrared laser irradiation combined with gold nanorods. Their structural reversibility and long-term stability provide a new paradigm for long-term, on-demand treatment of chronic diseases [38]. Polak et al. take a different approach by integrating nanoliposomes as "cargo units" into a "backpack" that can attach to cell surfaces, cleverly utilizing cell-mediated targeting mechanisms to greatly enhance drug enrichment at the lesion site, while achieving drug sustained release through liposomes themselves [39]. Furthermore, the "liposome-in-glucan particle" composite system constructed by Garello et al. combines the high drug-loading capacity of nanoliposomes with the natural targeting of micron-sized dextran particles toward immune cells, and a heat-triggered release mechanism is introduced to provid an efficient delivery solution for small-molecule water-soluble drugs that are difficult to load [40]. This strategy of combining "cell-mediated targeting" with "externally triggered release" can accurately deliver therapeutic drugs to chronic inflammatory lesions, while improving efficacy and minimizing systemic toxicity to healthy tissues, thus providing a new route for the treatment of chronic inflammatory diseases such as rheumatoid arthritis and inflammatory bowel disease.

In summary, these studies mark a shift in the field of drug delivery from single-carrier design to the construction of multi-level, multi-responsive, cell-involving IDDS. The next step is to design "intelligent" carriers that can respond to multiple endogenous (such as pH, enzymes) and exogenous stimuli, and fully utilize the body's own biology (such as immune cell chemotaxis) to achieve precise drug navigation. These micron-scale carriers, especially the hybrids of nanotechnology, biomaterials science, and cell engineering, are poised to deliver revolutionary breakthroughs to the treatment of major diseases including cancers and chronic inflammatory diseases, ultimately achieving true precision medicine.

3.2.2.3 Micron-sized vesicles

Micron-sized vesicles typically refer to membrane-bound vesicular structures with diameters ranging from 1 to 10 micrometers, often with

spherical or Ω-shaped contours and a bilayer lipid membrane structure. For example, in synthetic polymer systems, micron-sized vesicles can form monodisperse and uniform vesicles via active self-assembly methods (such as PDA-10 polymer vesicles, with a diameter of about 1 micron and a thickness of about 3 nanometers), and the formation involves a process from nanodisks to circular nanosheets and finally to spherical caps through gradual bending and closure [41]. In biological systems, exocrine vesicles (such as large secretory vesicles in fly salivary glands) exhibit dynamic membrane deformation during fusion, including membrane wrinkling and total collapse-like patterns, and their structures are regulated by actin and BAR domain proteins . In addition, microvesicles in extracellular vesicles can also reach the micrometer level, formed by budding from the plasma membrane, which can carry proteins, lipids, nucleic acids, and other cargoes, and play a key role in inflammatory environments [42].

In inflammation, micron-sized vesicles serve as important mediators of intercellular communication, participating in mediating the initiation and maintenance of inflammatory responses. Studies have shown that in metabolic diseases such as obesity and type 2 diabetes, the level of micron-sized vesicles (especially those from fat cells, macrophages and endothelial cells) is significantly increased in the circulation, and promote endothelial dysfunction, insulin resistance and atherosclerosis by transferring proinflammatory factors (e.g. TNF-α and IL-1β), microRNAs (e.g. miR-155, miR-126) and lipids (e.g. ceramide). For example, micron-sized vesicles derived from macrophages can activate the NF-κB pathway through membranous TNF-α, inducing vascular inflammation and plaque instability. Vesicles derived from adipose tissue can polarize macrophages towards M1 phenotype, exacerbating chronic low-grade inflammation. Further, micron-sized vesicles also participate in inflammation regulation in gut microbiota-host interactions, such as vesicles derived from obesity-related microbiota that can induce insulin resistance and systemic inflammation.

Research on micron-sized vesicles is expanding from structural characterization to functional regulation and clinical applications. The active self-assembly technology provides a new template-free strategy for synthesizing monodisperse micron-sized vesicles, which is expected to be used for precision drug delivery and microreactor construction [43]. The analysis of the release mechanism of biological micron-sized vesicles (e.g. actomyosin-mediated membrane dynamics) provides new targets for targeted secretion disorders [44]. In the future, micron-sized vesicles are expected to act as early diagnostic biomarkers for inflammation-related metabolic diseases (such as detecting vesicle miRNA through liquid biopsy), and as carriers for personalized treatment, such as engineering modified vesicle membranes to modulate inflammatory signaling transmission. Meanwhile, integrating new technologies such as acoustic microfluidics can achieve high-purity separation of vesicles, promoting their widespread application in clinical practice. Overall, as a double-edged sword in inflammation regulation, the in-depth study of micron-sized vesicles will deepen our understanding of the immune metabolic network and open up new avenues for intervention in chronic inflammatory diseases.

3.2.3 Hydrogels

Hydrogels, defined by their three-dimensional, hydrophilic polymer network structure, have become a crucial drug delivery system for the treatment of inflammatory diseases. The uniqueness of this material lies in its excellent water absorption and retention capabilities, which endow them with remarkable advantages in achieving localized and sustained drug release [45]. The application of

hydrogels is particularly important in managing diseases that require precise treatment, such as skin diseases and arthritis.

Another core feature of hydrogels is the intelligent responsiveness. These materials can be designed to be sensitive to specific environmental stimuli, such as changes in pH, temperature increases, or the presence of specific biomolecules, so as to trigger drug release under specific conditions at lesion sites. For example, when treating inflammatory skin diseases, hydrogels can release drugs according to the pH change or temperature rise of the inflammatory region to achieve accurate treatment. This self-regulating drug release mechanism not only improves the accuracy of treatment, but also enhances the efficacy of the drug. In addition, hydrogels have a high degree of customizability, enabling them to adapt to different treatment demands. They can be customized for specific diseases or treatment targets to include various drugs or bioactive molecules. This versatility makes hydrogels an ideal treatment option, especially when dealing with complex inflammatory diseases. The design and preparation methods of hydrogels, such as the construction and functionalization of cross-linked polymer networks, enable them to be precisely adjusted to meet specific drug release curves and treatment needs. Anti-inflammatory hydrogels, as a multifunctional biomaterial, has shown broad prospects in the treatment of inflammatory skin diseases. Hydrogels not only have good biocompatibility and controllable physical and chemical properties, but also can effectively regulate the inflammatory microenvironment through eliminating excessive ROS, isolating proinflammatory chemokines and mediating macrophage polarization. For example, Huang et al. systematically review the role of anti-inflammatory hydrogel in wound healing, emphasizing its multiple functions in ROS scavenging, chemokine capture and immune regulation [46]. Furthermore, Wu et al. develop a hydrogel loaded with hollow manganese dioxide nanoparticles, which significantly improves skin inflammation and tissue repair by efficiently clearing ROS and inhibiting Th2 type immune response in the atopic dermatitis model [47]. These studies provide important theoretical and experimental basis for the precise treatment of hydrogel in inflammatory diseases.

In conclusion, hydrogel, as a part of IDDS, presents a wide range of possibilities and remarkable potential in the treatment of inflammatory diseases, especially in providing customized and precise treatment schemes.

3.2.4 Bio-derived carriers

3.2.4.1 Liposomes

Liposomes, as a drug delivery system based on a lipid bilayer vesicular structure, have demonstrated prominent advantages in the treatment of inflammatory diseases. Such advantages stem from the excellent biocompatibility of liposomes and their ability to fuse with cell membranes, making liposomes an ideal carrier for directly delivering therapeutic agents to inflammatory tissues. Liposomes, as an efficient drug delivery system, have exhibit remarkable potential in anti-inflammatory therapy [48]. For example, in a rheumatoid arthritis model, Zhang et al. develop a hyaluronic acid modified liposome drug library (HA-Lipo@G/D) for local intra-articular injection to sustain release of dexamethasone, effectively inhibiting macrophage-derived inflammatory factors and promoting cartilage repair [49]. In the liver insulin resistance and inflammation related to type II diabetes, Rocha et al. verified that quercetin encapsulated in liposomes can enhance the regulation of Akt and NF-κB pathways, apparently reduce the levels of PGE_2 and ROS, and finally improve the inflammatory microenvironment . In addition, Ryu et al. construct a hybrid system by fusing liposomes with plant extracellular vesicles, which significantly suppresses the expressions of inflammatory

mediators such as PAR-2, TSLP, and IL-6 in a skin model, underscoring the potential of liposomes in synergistic anti-inflammatory therapy [50]. These studies collectively indicate that liposomes have important application value in the treatment of various inflammatory diseases via improving drug targeting and stability.

The structure and composition of liposomes endow them with exceptional flexibility in drug delivery. They are composed of natural or synthetic lipids such as phospholipids and cholesterol, and can encapsulate various types of drugs, including hydrophilic and hydrophobic drugs. This diversity enables liposomes to be applied in a wide range of disease treatments, especially those that require specific drug delivery methods. The preparation techniques of liposomes, such as thin film hydration and microemulsion methods, allow scientists to precisely control their size, surface properties, and drug loading. The application of these technologies ensures the stability of drugs during delivery and allows for precise regulation of the rate and timing of drug release. The ability to finely control is crucial as it ensures the effective concentration of drugs at the inflammation sites while diminishing their distribution in non-targeted areas, thereby reducing systemic side effects. In practical applications, the use of liposomes significantly improves the bioavailability and therapeutic efficacy of drugs [51]. For example, when targeting articular or intestinal inflammation, liposomes can provide concentrated and effective drug release, which, compared with traditional administration methods, can more effectively alleviate inflammatory symptoms and improve patients' quality of life.

In summary, liposomes have shown great potential as drug delivery systems in the treatment of inflammatory diseases, and their unique characteristics make them an indispensable tool for treating such diseases.

3.2.4.2 Cells or cell membranes

In the research field of chronic inflammatory diseases treatment, the application of cells or cell membranes, as IDDS, has shown unprecedented potential and progress. Most strikingly, by exploiting the inherent biological properties and excellent biocompatibility of the cells, these delivery systems achieve both high loading capacity and pinpoint drug release, markedly boosting therapeutic efficacy while minimizing adverse reactions. For example, natural product delivery systems based on yeast microcapsules have yielded significant results in the treatment of ulcerative colitis. Yeast microcapsules not only effectively encapsulate and protect natural products, but also utilize their targeting properties towards specific parts of the colon to ensure precise drug release at the inflammation sites, thereby greatly improving therapeutic efficacy and attenuating systemic side effects [52].

Neutrophils are typically known for their pro-inflammatory and pathogen-scavenging abilities, and can help alleviate inflammation by actively producing anti-inflammatory extracellular vesicles. Neutrophils have several advantages, including short lifespan that makes them as "disposable carriers", fast migration speed that ensures deep penetration into tissue targets, and highly efficient pathological response with a natural tendency towards inflammation. As drug responsive carriers, neutrophils have unique surface adsorption and intracellular loading modes that make them suitable for live cell delivery. For example, neutrophils loaded with vancomycin liposomes can cross the blood-brain barrier, achieving higher drug concentrations in meningitis sites compared to free drugs. Neutrophils with surface adsorbed nanoparticles can target ischemic hearts, leading to an increase in ROS clearance rate. Neutrophils have a natural tendency towards inflammation and the ability to cross physiological barriers, making them a natural carrier

for IDDS [53].

Stem cells are a type of undifferentiated or poorly differentiated cell with self-renewal and multi-directional differentiation potential, which can maintain their population stability and exhibit differentiation abilities beyond their traditional lineage under specific microenvironments. Stem cells are mainly divided into embryonic stem cells, adult stem cells, tissue-specific stem cells, induced pluripotent stem cells, hematopoietic stem cells, etc. Among them, mesenchymal stem cells, endowed with inherent inflammatory tropism and homing capacity, potent immunomodulatory properties, the ability to cross biological barriers, synergistic therapeutic effects, and large carrier capacity, have emerged as ideal "natural living carrier" for the construction of inflammation-targeted IDDS [54]. Utilizing stem cells as intelligent drug delivery media can enhance drug homing, diversify drug loading methods, and achieve intelligent responsive release (enzyme response, pH response, ROS response, multiple response), opening new avenues for the development of IDDS for chronic inflammatory diseases. The stem cell IDDS is expected to become an effective tool for treating various refractory inflammatory diseases in the future, achieving more precise, efficient, and safe treatment goals.

Besides, research on red blood cell-based drug delivery systems for lung-targeted therapy has shown great potential. Red blood cells, as a part of the natural circulatory system, provide new avenues for the treatment of lung diseases due to their biocompatibility and long-term circulation ability. Through engineered modifications of red blood cells, efficient localization and release of drugs targeting pulmonary inflammation can be achieved, which not only enhances therapeutic efficacy but also reduces potential side effects on other organs. Similarly, white blood cell-based drug delivery systems have demonstrated excellent application prospects. The natural migration and recognition ability of white blood cells make them an ideal drug delivery carrier, especially for liver diseases. By loading drugs into or on the surface of white blood cells, precise attacks on liver-specific disease targets can be achieved, thereby enhancing therapeutic efficacy while minimizing the impact on other parts of the body [55].

In summary, the application of cells or cell membranes as IDDS not only provides new ideas and methods for treating chronic inflammatory diseases, but also achieves dual optimization of drug delivery accuracy and therapeutic effects by utilizing the characteristics and functions of cells themselves. With the continuous deepening of research in this field and the continuous improvement of technology, there will be more possibilities for the treatment of chronic inflammatory diseases in the future.

3.2.4.3 Exosomes and biomimetic exosomes

In recent years, biomimetic exosomes have shown significant application prospects as an emerging drug delivery system in the treatment of chronic inflammatory diseases. By mimicking the biological characteristics and functions of natural exosomes, these engineered nanocarriers can effectively package and protect drugs, while achieving precise localization of disease targets and controlled release, thereby improving therapeutic efficacy and reducing adverse reactions [56]. The preparation of biomimetic exosomes mainly adopts three strategies: top-down, bottom-up, and biological methods. The top-down method uses cell membrane or extracellular vesicles as starting materials and prepares them through techniques such as extrusion or ultrasonic disruption. The bottom-up method constructs exosomes from synthetic or semi-synthetic components via precisely controlled assembly processes. Biological methods leverage the natural assembly mechanisms of viruses to create exosome-like vesicles with specific delivery

capabilities. In terms of drug packaging, biomimetic exosomes can effectively transport various therapeutic agents such as small molecule drugs, proteins, RNA, and DNA. These carriers demonstrate excellent biocompatibility and low immunogenicity, and overcome biological barriers to achieve targeted delivery and controlled release of drugs. At the application level, the potential of biomimetic exosomes in the treatment of chronic inflammatory diseases is particularly prominent. By precisely controlling drug release, these nanocarriers can exert effects at specific disease sites, thereby improving treatment efficiency and reducing side effects. In addition, they can also be used for the delivery of RNA and DNA, providing a new pathway for gene therapy.

Exosomes, as natural sources of extracellular vesicles, offer outstanding biocompatibility, targeting capability, and low immunogenicity, making them a highly promising drug delivery platform for the treatment of inflammatory diseases [57]. In recent years, researchers have developed various biomimetic exosome systems through engineering methods, such as M2 macrophage-derived exosomes loaded with IL-10 and glucocorticoids, which can synergistically promote macrophage polarization towards anti-inflammatory phenotype and markedly alleviate rheumatoid arthritis [58]. Plant-derived exosomes-like nanoparticles (such as GELNs) regulate inflammatory signaling pathways by delivering specific miRNAs (such as osa-miR164d), demonstrating good therapeutic effects in intestinal inflammation models [59]. Additionally, milk-derived exosomes are widely used for the delivery of oral anti-inflammatory drugs due to their good gastrointestinal stability, significantly improving the bioavailability and therapeutic efficacy of the drugs [60]. These studies provide important reference for the clinical application of exosomes and their biomimetic systems in the treatment of inflammation.

Despite their considerable potential and advantages, biomimetic exosomes still face numerous challenges in large-scale production, standardized preparation, purification, and precise drug loading. Future research will need to address these issues and further optimize the design and function of biomimetic exosomes, meeting the demands of personalized medicine and providing more effective and safe drug delivery solutions for the treatment of chronic inflammatory diseases.

3.2.5 Prodrug strategy

The prodrug strategy transforms active drugs into different or completely inactive forms *in vivo* via chemical modification, releasing the original drug through biotransformation processes to facilitate drug stability and solubility, or reduce drug side effects. This design can optimize the pharmacokinetic and pharmacodynamic properties of drugs, while achieving targeted drug release through specific enzymes, pH values, or other biomarkers. The prodrug strategy has shown great potential in targeted therapy for inflammatory diseases. For example, Cai et al. design a β -galactosidase-responsive prodrug SSK1, which can be specifically activated in senescent cells, release gemcitabine, selectively clear senescent cells, and mitigate age-related chronic inflammation, thereby improving physical function [61]. Similarly, Shi and Li report an engineered prodrug nanoparticle that targets activated neutrophils through pH responsive bonds, inducing their apoptosis and significantly alleviating inflammatory responses in sepsis and stroke models [62]. These studies highlight the advantages of prodrug design in promoting drug selectivity, reducing systemic toxicity, and precisely regulating inflammatory pathways.

In the field of glucocorticoids (GCs), prodrug design has also been extensively studied to overcome the serious side effects of long-term use, such as

metabolic disorders, osteoporosis, and immunosuppression. Liu et al. systematically review the design strategies and progress of GC prodrugs, pointing out that prodrugs achieve precise drug release at disease sites by introducing cleavable linkers (such as pH sensitive hydrolysis bonds, and enzyme responsive peptide chains) and functional groups (such as PEG or targeted peptides that improve water solubility). At present, various GC prodrug systems have been developed, including polymer-based prodrugs (such as HPMA-Dex, PEG-Dex), dendritic polymer prodrugs, antibody-drug conjugates (ADCs), peptide-drug conjugates (PDCs), carbohydrate-based prodrugs (such as glucoside and pectin derivatives), and long-chain fatty acid-/alcohol-based prodrugs (such as dexamethasone palmitate). These prodrugs not only enhance the accumulation of GCs in inflammatory sites (e.g. joints, kidneys, and colon) and prolong their efficacy, but also significantly reduce systemic exposure and side effects. For example, HPMA-Dex exhibits long-lasting anti-inflammatory and bone-protective effects in arthritis and lupus nephritis models. Antibody-conjugated GC prodrugs can specifically target immune cells, achieving efficient and low-toxicity treatments in animal models. Although GC prodrugs still face challenges in clinical translation, such as pharmacokinetic consistency, carrier biocompatibility, and regulatory approval, their ability to optimize drug absorption, distribution, metabolism, and excretion provides a promising direction for developing safer and more effective anti-inflammatory therapies [63]. These studies collectively confirm the broad prospects of prodrug strategies in enhancing drug targeting, reducing toxicity, and promoting precision medicine,as shown in Figure 1.

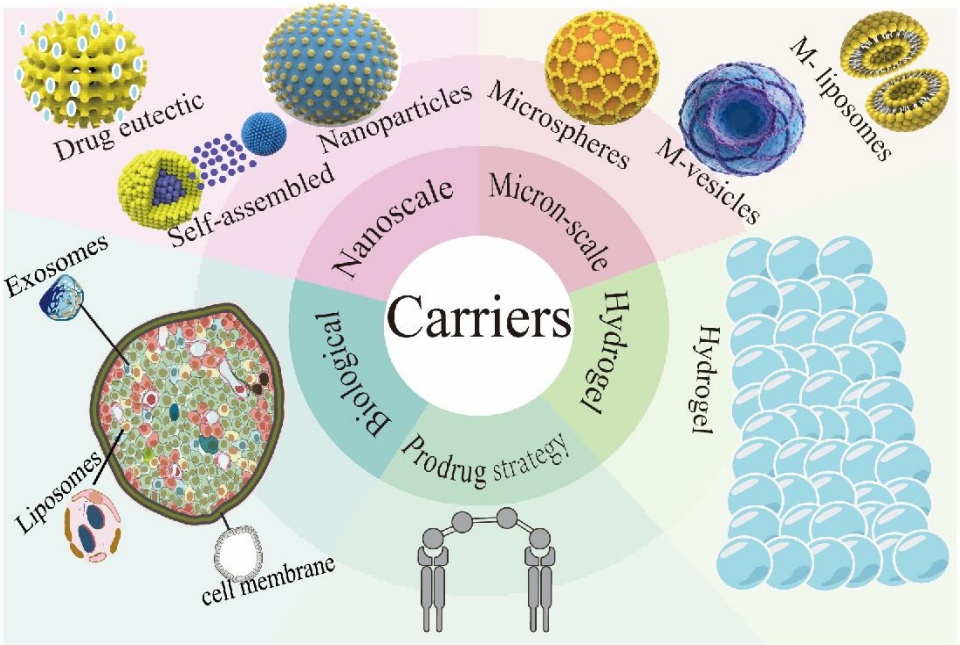

Figure 1 Drug-encapsulating carriers in IDDS.

4. The delivery mechanism and response system of IDDS

4.1 Targeted delivery

Targeted delivery is one of the core features of IDDS, with the primary objective of precisely delivering therapeutic agents to disease-specific cells or tissues [64]. This precision-targeting strategy aims to minimize the distribution of drugs throughout the body and potential side effects, thus improving the efficiency and safety of treatment [65].

Targeted delivery relies on a series of sophisticated

targeting strategies. For example, antibody drug conjugates (ADCs) are a typical targeted therapy strategy that directly recognize and bind to specific molecules on the surface of cancer cells through specific antibodies, thus precisely targeting tumors,as shown in Figure 2. This strategy minimizes toxicity to normal cells by directly delivering chemotherapy drugs to cancer cells [66]. In addition, nanomedicine delivery systems are widely used in targeted delivery. By harnessing the intrinsic properties of nanomedicines, such as enhanced penetration and retention (EPR) effects, or through surface modified targeting ligands (such as receptor ligands or antibodies), the specificity of drugs to specific disease sites can be improved. For instance, in the treatment of inflammatory diseases, nanoparticles can be designed to respond to the specific biochemical environment of the inflammatory sites, thereby precisely targeting the affected tissue or organ [67]. Targeted delivery is particularly essential when treating localized inflammatory diseases such as intestinal inflammation, arthritis, or skin diseases [68]. It not only enhances the efficacy of drugs but also reduces systemic side effects, improving the treatment experience and quality of life for patients. By precisely controlling the distribution of drugs within the body, targeted delivery strategies offer a safer and more effective approach to treating inflammatory diseases.

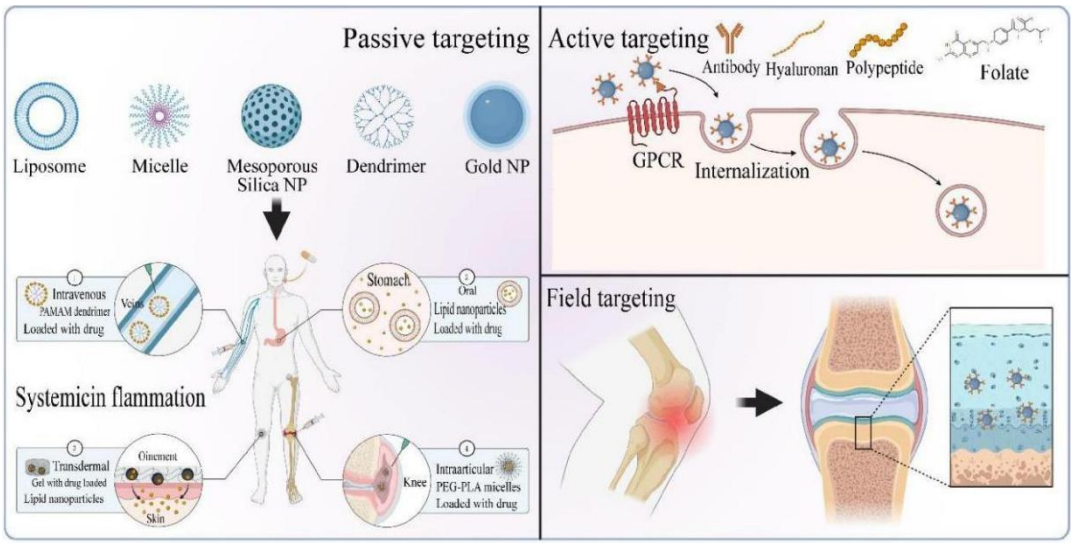

Figure 2 Targeted delivery mechanisms of IDDS for chronic inflammation.

4.2 Controlled release

Controlled release technology plays a pivotal role in the management of chronic inflammatory diseases. By integrating advanced materials science with pharmaceutical engineering design, it achieves precise regulation of drug release, ensuring that drug concentrations are maintained within the therapeutic window throughout the treatment course. This technology significantly improves treatment compliance by reducing medication frequency, which is particularly important for patients with chronic inflammatory diseases who require long-term medication management.

Specifically, biodegradable polymer microspheres or nanoparticles and other controlled release systems can precisely control drug release by mediating the degradation rate of the polymer, which allows drugs to be released at a predetermined rate and time period, providing continuous and precise treatment for patients [69]. In the treatment of chronic inflammatory diseases, this controlled release technology has exhibited its clinical advantages,

effectively improving patients' treatment experience and quality of life.

Moreover, the latest developed controlled release systems, such as implantable drug pumps or high-tech devices like microchips, provide the possibility of remote control and timed release for drug delivery [70]. These intelligent administration methods not only customize personalized treatment plans for patients, but also reduce dependence on patients or medical staff through automated control, greatly improving the efficiency and convenience of treatment.

To conclude, the controlled release technology, as a key component of IDDS, plays an important role in the treatment of chronic inflammatory diseases. This technology not only optimizes drug treatment plans and improves efficacy and patient compliance, but also provides more precise, efficient, and convenient treatment options for patients with chronic inflammatory diseases through innovative drug delivery methods.

4.3 Responsive system

In the field of inflammatory disease therapy, responsive systems, as an important component of IDDS, have demonstrated remarkable research advances and potential clinical application value. These systems trigger targeted drug release by accurately identifying physiological or environmental changes at the site of inflammation, such as specific pH changes, increased enzyme activity, or elevated local temperature. This precise responsiveness gives responsive systems unique advantages in improving the treatment efficiency of inflammatory diseases and reducing drug side effects.

For example, pH sensitive nanoparticles can utilize the acidic conditions of the inflammatory site or tumor microenvironment to automatically dissociate and release the carried anti-inflammatory or chemotherapy drugs, achieving localized therapeutic effects while minimizing the impact on normal tissues [71]. Similarly, the physical state of temperature sensitive materials changes, such as transitioning from a gel to a liquid, in response to temperature increases caused by inflammation, thus releasing pre-loaded drugs directly at the inflammatory site [72].

The development of responsive systems not only focuses on the intelligent design of materials, but also explores how to combine these systems with existing treatment methods to provide more personalized and precise treatment plans. For example, responsive systems that combine targeted ligands or antibodies can more accurately identify inflammatory cells or diseased tissues, further improving the targeting of drug delivery and the effectiveness of treatment [73].

With the continuous advancement of materials science, nanotechnology, and biomedicine, responsive systems are increasingly widely used in the treatment of inflammatory diseases. The new generation of responsive systems can respond to a single physiological signal, and integrate multiple signals for more complex drug release control, providing more comprehensive and detailed strategies for treatment. These innovative responsive systems bring new hope to the treatment of patients with chronic inflammatory diseases, making drug therapy more precise, efficient and convenient, significantly improving patients ' treatment experience and quality of life.

4.3.1 Magnetic response system

Magnetic response system, as a cutting-edge technology in the field of IDDS, utilizes magnetic nanoparticles as drug carriers to achieve precise positioning and release of drugs under the action of external magnetic fields, the core advantage of which lies in its high sensitivity and controllability to external magnetic fields, making the drug delivery process more precise and efficient [74]. Magnetic

nanoparticles, such as iron oxide (Fe_3O_4) nanoparticles, are widely used in the construction of magnetic response systems due to their excellent magnetic responsiveness, good biocompatibility, and ease of surface modification [75]. These nanoparticles can be obtained through various chemical synthesis methods such as co-precipitation and thermal decomposition, and functionalized through polymer encapsulation, targeted molecular modification, or direct drug loading to enhance their stability, targeting, and drug loading capacities *in vivo* [76].

The magnetic response systems are unique in their ability to guide drug carriers directly to the lesion site through precise control of an external magnetic field. By adjusting the strength, direction, and duration of the magnetic field, precise control of drug release rate and release area can be achieved, thereby elevating therapeutic efficacy and decreasing side effects. Especially in the field of tumor therapy, magnetic response systems can directly deliver chemotherapy drugs to tumor cells by targeting specific markers in the tumor microenvironment, minimizing damage to normal cells [77].

Furthermore, the magnetic response system combined with magnetic heat therapy technology can directly kill tumor cells or promote the release of drugs through the local thermal effect generated by magnetic nanoparticles under the influence of an external magnetic field [78], exerting strong therapeutic effects. This magnetic heat effect not only improves the local efficiency of tumor treatment but also provides a new strategy for multimodal treatment.

In summary, the magnetic response system provides strong technical support for precision medicine and personalized treatment through its unique working mechanism and flexible design. With the continuous advancement of nanotechnology, materials science, and biomedicine, magnetic response systems are expected to play a more important role in future drug delivery and disease treatment.

4.3.2 Electroresponsive systems

Electroresponsive systems demonstrate unique application value in the field of IDDS, particularly in precisely controlling drug release and improving therapeutic efficiency. The working principle of these systems is based on the direct effect of an electric field on the drug carriers or the drug itself, where electrical stimulation triggers drug release or alters the physicochemical properties of the drug release environment [79]. Electroresponsive materials, including conductive polymers, electrochromic materials, and specific electro-sensitive nanoparticles [80], are extensively studied for constructing electroresponsive drug delivery systems due to their high sensitivity to changes in the electric field.

The design and implementation of electroresponsive systems involve knowledge from multiple disciplines, including materials science, electrochemistry, pharmacology, and biomedical fields [81]. These systems typically include a power source, electrodes, and electrically responsive materials containing medication. Under the action of an external electric field, the drug carrier experiences structural changes or electrochemical reactions, thereby achieving targeted drug release. For example, adjusting the strength, frequency, and pulse width of the electric field can precisely control the release rate and duration of drugs to meet different therapeutic needs [82].

Electroresponsive systems hold significant potential for clinical treatment, especially in situations where rapid response and highly controlled drug release are required, such as insulin release in diabetes treatment [83], localized chemotherapeutic drug release in cancer therapy, and the management of inflammatory diseases [84]. In addition, the electroresponsive system can also be applied to develop new intelligent drug delivery devices, such as implantable or wearable

drug delivery devices, which can adjust drug release in real time according to the patient's physiological state or treatment needs, thereby achieving personalized treatment [85].

4.3.3 Thermoresponsive systems

The thermoresponsive systems are instrumental in the field of intelligent drug delivery, whose core mechanism is to trigger drug release or change the state of the drug delivery system via temperature changes [86]. These systems are typically composed of heat sensitive materials, such as poly (N-isopropylacrylamide) (PNIPAAm), which can undergo physical or chemical state changes at a specific temperature threshold, the low critical solution temperature (LCST). When the ambient temperature exceeds LCST, the thermosensitive material transitions from water solubility to lipophilicity, resulting in a change in the structure of the drug carrier, and thereby achieving rapid release of the drug [87].

The design of thermoresponsive systems is highly sophisticated and applicable in various therapeutic fields. In tumor treatment, since tumor tissues often exhibits a slightly higher temperature than the surrounding normal tissues, the thermoresponsive system can be designed to release chemotherapy drugs under these small temperature differences, achieving precise targeted treatment of tumors while minimizing damage to normal tissues. Moreover, the thermoresponsive system can also be combined with external heat sources, such as near-infrared light irradiation, magneto-thermal effect, or ultrasound heating [88], to provide more flexible and controllable treatment options.

The research on thermoresponsive drug delivery systems continues to deepen, and the development of thermosensitive materials and composite materials offers greater potential for optimizing system performance. For example, combining thermosensitive polymers with materials like gold nanoparticles or magnetic nanoparticles can produce composite materials with good thermal conversion efficiency, which can respond to temperature changes in the internal microenvironment and be controlled by external heat sources, achieving more precise and efficient drug release [89].

Despite great potential, the practical application of thermoresponsive systems still faces some challenges, such as the biocompatibility of thermosensitive materials, long-term stability, and technical difficulties in accurately controlling the temperature of the treatment area [90]. In the future, through interdisciplinary research combined with advanced achievements in materials science, pharmacology, and biomedical fields, thermoresponsive systems are expected to play a more important role in improving treatment efficiency and patient comfort.

4.3.4 Photoresponsive system

Photoresponsive systems occupy a position in intelligent drug delivery technology, with core advantage presenting as the ability to control the release behavior of drugs via light signals (including ultraviolet light, visible light, and near-infrared light). This system is particularly suitable for situations that require high spatial and temporal control of drug release, as light signals can be accurately located and triggered instantaneously, enabling precise regulation of the drug release process [91].

The working principle of photoresponsive systems is based on specific photosensitive materials or molecules that can undergo chemical structural changes under light irradiation, leading to changes in the physical state of drug carriers or directly triggering drug release [92]. Such materials include photosensitive polymers, optical switch molecules and photosensitive nanoparticles, which can be designed into different forms, such as nanoparticles, nanocapsules or micro gel, to meet different drug

delivery needs [93].

In terms of clinical applications, the photoresponsive system provides new treatment methods for local chemotherapy, photodynamic therapy, and tissue engineering. For instance, in photodynamic therapy, the photoresponsive system can precisely deliver photosensitive drugs to tumor tissues, and then activate the drugs through specific wavelengths of light to cause toxic reactions and kill tumor cells, while minimizing damage to the surrounding normal tissues [94]. Moreover, the near-infrared light has attracted particular attention in photoresponsive systems because of its deep tissue-penetrating ability. The near-infrared light-activated system can enable the treatment of tissues at greater depths, thereby expanding the application scope of the photoresponsive system [95].

Despite their tremendous therapeutic promise, photoresponsive systems also face some challenges in practical applications, including the selection of light sources, optimization of light irradiation conditions, biocompatibility and long-term stability of photosensitive materials. Additionally, how to improve the therapeutic efficiency of photosensitive systems for deep tissues is also one of the current research hotspots [96]. Future research requires in-depth collaboration in multiple fields such as materials science, photochemistry, and biomedical sciences to overcome existing challenges and further enhance the application value of photoresponsive systems in precision medicine.

4.3.5 Ultrasonic response system

Ultrasonic response system, as an innovative technology in the field of intelligent drug delivery, utilizes the physical properties of ultrasound, such as mechanical vibration and thermal effects, to achieve targeted drug release and enhance transdermal absorption. The prominent advantage of this system lies in its non-invasiveness and ability to treat deep tissues, allowing drugs to reach the disease site more accurately and effectively.

Ultrasonic response systems are typically based on ultrasonic sensitive materials or carriers, including microbubbles, nanoparticles, and certain specific polymers, which can undergo structural changes or local temperature increases under the action of ultrasound, triggering drug release. The frequency, intensity, and duration of ultrasound can be adjusted according to treatment needs to control the rate and range of drug release [97].

In clinical applications, the ultrasound response system is particularly suitable for tumor treatment, pain management, and wound healing promotion. For instance, in tumor treatment, ultrasound can guide ultrasound-sensitive drug carriers to precisely accumulate in tumor tissues and directly destroy tumor cells or promote the penetration and distribution of drugs in tumor tissues through the thermal or mechanical effects. Moreover, ultrasound can also be used to facilitate drug permeation through the skin or other biological barriers, enhancing the bioavailability of the drugs and the therapeutic effect [98].

Although ultrasound response systems have broad application prospects in theory, their practical implementation still requires addressing several technical and safety challenges, including the biocompatibility and long-term stability of ultrasound sensitive materials, as well as the possible effects of ultrasound irradiation on normal tissues [99]. Future research requires further optimization of the design of ultrasound responsive materials, precise control of ultrasound parameters, and in-depth study of the interaction mechanism between ultrasound and biological tissues, so as to promote the widespread application of ultrasound responsive systems in the medical and health field and provide patients with safer and more effective treatment plans.

4.3.6 Enzyme-responsive systems

Enzyme-responsive systems are an important component of intelligent drug delivery, and their core design concept is to use specific enzymes overexpressed in lesion areas (such as tumors and inflammatory sites) as biological trigger signals to achieve precise spatiotemporal control over drug release. Such systems are usually composed of enzyme-sensitive "linkers" or "protective groups", which are integrated into the structure of drug delivery carriers (such as nanoparticles, hydrogels or prodrugs) as "molecular switches". Under normal physiological conditions, the system remains stable with minimal drug leakage. However, when the carriers accumulate at the target site via blood circulation and comes into contact with the abnormally high concentrations of specific enzymes (such as matrix metalloproteinases, cathepsins, or phospholipases in the tumor microenvironment), the enzymes efficiently hydrolyze or cleave these sensitive bonds, leading to carrier structure dissociation, surface charge reversal or increased membrane permeability, and triggering rapid and specific drug release. This "lock-key" response mechanism endows the drug delivery system with excellent targeting precision and biosafety, not only significantly increasing the local drug concentration in the lesion to enhance efficacy, but also effectively reducing toxic side effects on normal tissues [100].

In recent years, enzyme-responsive nanosystems have shown great potential in inflammation regulation. For example, Qiao et al. develop a cascade enzyme system based on Ti_3C_2Tx MXene (TPDMGP), which not only possesses peroxidase like activity and can decompose H_2O_2 into O_2 to enhance hunger therapy, but also responds to high concentrations of glutathione in tumor cells to release the anti-inflammatory drug Phloretin. This system has been experimentally confirmed to effectively clear reactive oxygen, apparently reduce expressions of pro-inflammatory cytokines (e.g. TNF-α, IL-6 and IL-1 β), suppress inflammatory reactions in photothermal therapy, and provide new ideas for combined treatment of inflammation-related diseases [101]. Similarly, Li et al. found that vitamin E evidently inhibits inflammatory responses and enhances immune capacity in green crabs by activating antioxidant enzyme systems and regulating the expressions of apoptosis- and inflammation-related genes [102]. These studies collectively reveal the multifunctionality and potential applications of enzyme-responsive nanosystems in inflammation regulation.

4.3.7 pH-responsive systems

The pH-responsive system is an intelligent strategy based on the specific response of materials to changes in hydrogen ion concentration, which mainly leverages carriers or probes containing pH-sensitive groups (such as carboxyl and amino groups) that experience controllable changes in structure, charge, or degradation behavior upon triggering by specific pH conditions. This characteristic is highly compatible with the unique acidic microenvironment (pH 6.0-7.0) of the inflammatory site, providing innovative ideas for precise diagnosis and treatment of inflammatory diseases [103]. At present, this strategy has been widely applied in the fields of inflammation targeted drug delivery, lesion specific imaging, and intelligent anti-inflammatory system development, which significantly improves treatment efficiency and reduces systemic side effects by controllable drug release and efficient enrichment at the lesion site. Although there are challenges in sensitivity and clinical translation, pH-responsive methods, as one of the key technologies in precision medicine, have shown great potential for application in the diagnosis and treatment of diseases such as arthritis and inflammatory bowel disease. Wang et al. develop a pH- and

ROS-responsive mesoporous silica nanoparticle (MSN) system for targeted delivery of 5-demethylated saponin (5-DN) for the treatment of psoriasis like inflammation. This nanocarrier exhibits controlled drug release under acidic conditions (pH < 6.0), simulating the inflammatory microenvironment of psoriasis lesions. This pH-responsive behavior, combined with ROS sensitivity, enables site-specific drug delivery, enhances anti-inflammatory efficacy, reduces off-target effects, and highlights the potential of microenvironment-responsive nanocarriers in the treatment of inflammatory skin diseases [104]. The pH-responsive drug delivery system utilizes the acidic microenvironment of pathological tissues, such as tumors and inflammatory areas, to achieve targeted drug release and enhance therapeutic efficacy. The design strategy mainly includes introducing pH-sensitive chemical bonds (such as hydrazone bonds and imine bonds) or protonated groups (such as amino groups and imidazoles) to respond to local pH changes. In the treatment of inflammation, such systems have been widely used in models of arthritis, colitis, vascular and skin inflammation, etc., which release anti-inflammatory drugs through acidic triggering, signally improve efficacy and reduce systemic toxicity, demonstrating good clinical translational potential [103].

5 Application of IDDS in chronic inflammatory diseases and the pathogenesis of inflammation

Chronic inflammatory diseases refer to the chronic stress response of the body ' s immune system triggered by pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), or hereditary periodic diseases caused by abnormal activation of the autoimmune system due to genetic or environmental factors. It can generally be classified into two categories: chronic autoimmune inflammatory diseases and chronic non-autoimmune inflammatory diseases. These diseases have a wide coverage and involve multiple organ systems, including the respiratory system, digestive system, cardiovascular system, liver and kidney tissues, joints, and skin, with long disease course and recurrent attacks. Among them, chronic autoimmune diseases still lack effective treatment methods in clinical practice, which has a significant impact on the quality of life of patients [5]. Now I have reviewed the following intelligent drug system treatments for these diseases, as shown in Figure 3.

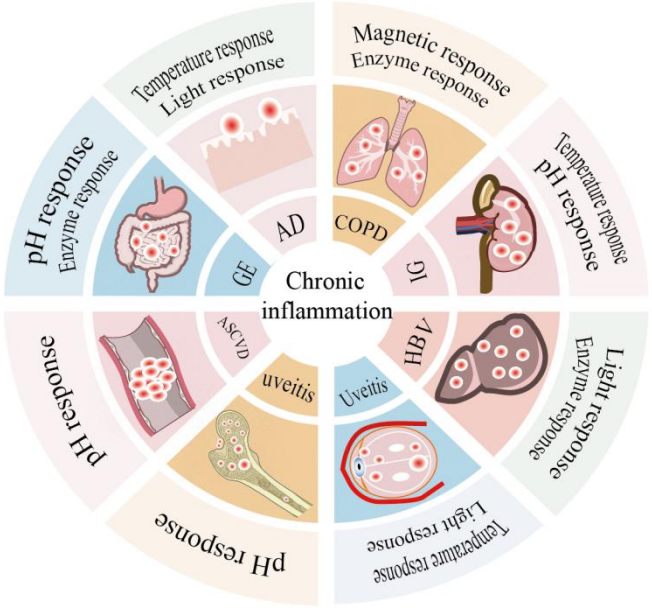

Figure 3 Application of responsive systems in IDDS for chronic inflammatory diseases.

5.1 Chronic inflammatory digestive tract disease

Chronic inflammatory digestive tract diseases are characterized by long-term inflammation, mucosal damage, and functional disorders, mainly including inflammatory bowel disease (IBD, such as Crohn's disease and ulcerative colitis) [105], irritable bowel syndrome (IBS), gastroesophageal reflux disease (GERD), chronic gastritis, and colorectal cancer [106]. They not only manifest as chronic recurrent inflammation of the inner wall of the digestive tract, but may also lead to sustained damage to the colon and small intestine, inducing symptoms such as abdominal pain, diarrhea, weight loss, and fatigue [107]. Crohn's disease can affect the entire digestive tract, with transmural inflammation and common granuloma formation. The pathogenesis of such chronic digestive diseases primarily stems from the interaction of genetic, immune, microbial, and environmental factors, with the core mechanisms of mucosal barrier disruption, immune dysfunction, and microbial dysbiosis. Pathologically, these diseases are characterized by sustained activation of immune cells such as macrophages and dendritic cells, which are intimately related to an imbalance in gut microbiota [108]. The key to treating chronic inflammatory digestive tract diseases lies in regulating immune abnormalities, repairing mucosal barriers, controlling contributors, blocking the "inflammation-fibrosis-carcinogenesis" process, and ultimately achieving immune regulation and microecological balance [109]. IDDS, such as pH-responsive formulations, can alter their release behavior when reaching the site of digestive tract inflammation, thereby reducing the impact on healthy tissues, improving drug treatment efficiency, and diminishing systemic side effects. Enzyme-responsive dosage forms utilize the unique enzyme activity of the inflammatory site, such as intestinal specific enzymes, to precisely release drugs, target inflammation treatment, and improve treatment compliance by reducing unnecessary drug exposure [110].

5.2 Chronic skin inflammatory diseases

Chronic skin inflammatory diseases are skin diseases characterized by persistent inflammatory reactions, barrier dysfunction, and immune dysregulation, with a vicious cycle of barrier defects, immune dysregulation, and microbial imbalance as core pathogenesis. The main inflammatory diseases include atopic dermatitis (AD) [111], psoriasis [112], lupus erythematosus, chronic eczema, contact dermatitis [113], and other inflammatory skin diseases that not only affect patients' skin health, but may also lead to serious psychological and social burdens. Psoriasis has complex pathogenesis, involving immune dysfunction, excessive proliferation and angiogenesis, which is a multifactorial disease influenced by environmental and genetic factors, and the pathological process of these diseases involves abnormal regulation of T cells and Langerhans cells, as well as chronic inflammatory responses [114]. The chronic skin inflammatory disease treatment should focus on repairing skin barrier function and regulating immune imbalance [115]. Temperature-responsive IDDS can trigger drug release in areas of skin inflammation where local body temperature is elevated, accurately intervening in the affected area. Photoresponsive IDDS can achieve local treatment of skin inflammation by controlling external light sources, reduce the damage of drugs to healthy skin, and alleviate the problem of drug tolerance in long-term treatment [116].

5.3 Chronic respiratory inflammatory disease

Chronic respiratory inflammatory diseases are characterized by chronic inflammation, structural remodeling, and progressive functional impairment of the airway or lung parenchyma, mainly including chronic obstructive pulmonary disease (COPD) [117], bronchial asthma [118], pulmonary fibrosis, and bronchiectasis. Pathologically, the primary mechanisms of these chronic diseases involve the

interplay among multiple factors such as genetic susceptibility, environmental exposure, immune inflammatory response, oxidative stress, and abnormal tissue repair. The pathogenesis of bronchial inflammation results from the combined effects of environmental factors and genetic susceptibility, involving epithelial barrier disruption, immune imbalance, and neural regulation disorders [119]. The key treatment challenge for respiratory diseases such as bronchial asthma and COPD is to precisely regulate the local release of anti-inflammatory and immunomodulatory drugs to alleviate persistent airway inflammation, reduce mucus secretion, and improve airflow limitation [120]. These conditions not only weaken lung function, but also significantly reduce the quality of life of patients [121]. In this field, enzyme-responsive IDDS show their progressiveness and professionalism, which can achieve fine control of drug release behavior through targeted activation of specific biomarkers in the inflammatory microenvironment or in response to stimuli like magnetic fields. Enzyme-responsive drug delivery systems are especially well-suited to respiratory diseases, as they can recognize enzymes specific to the inflammatory environment of the airway, such as elastase and matrix metalloproteinases, whose expression is markedly up-regulated in the pathological states of asthma and COPD [122]. The drug carrier in the drug delivery system undergoes structural changes under the action of these enzymes, and triggers the release of drugs that directly act on the inflammatory site, reducing the impact on healthy tissues and systemic side effects.

5.4 Chronic inflammatory kidney disease

Chronic inflammatory kidney diseases are conditions with renal immune inflammatory response as the dominant pathological change, mainly including glomerulonephritis (such as IgA nephropathy and lupus nephritis), interstitial nephritis, and vasculitis related nephropathy (such as ANCA related vasculitis), which are inflammatory kidney diseases resulting from immune complex-mediated renal glomerular injury. These diseases can cause proteinuria, hematuria, hypertension, and renal dysfunction. The pathogenesis of IgA nephropathy is representative, as the deposition of IgA1 immune complexes in the glomerular mesangial area induces mesangial cell proliferation, matrix expansion, and inflammatory response. The core mechanisms of these chronic inflammatory kidney diseases include immune complex deposition, complement activation, inflammatory cell infiltration, and fibrosis [123]. The disease progression also involves complex interactions between T cells, B cells, and macrophages, leading to sustained inflammatory responses and kidney damage [124]. To treat chronic inflammatory kidney disease, therapy must be based on multi-target intervention of immune inflammatory response, protection of renal function, and delay of fibrosis progression. IDDS, especially pH-responsive and temperature-responsive IDDSs, can identify changes in the microenvironment of chronic inflammatory areas, such as changes in pH value or local temperature elevation, as triggering conditions to accurately release drugs directly to the damaged area. This targeted approach can significantly reduce the side effects of drugs, improve treatment efficacy, and meet the needs of long-term management [4].

5.5 Chronic liver injury inflammatory disease

Chronic liver injury inflammation is a common pathological process of various liver diseases, such as chronic viral hepatitis [125], alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD/NASH), autoimmune hepatitis, etc. Chronic liver injury involving immune mediators is manifested as hepatocyte damage, inflammation, and fibrosis, the essence of which is also a vicious cycle of " damage-inflammation-fibrosis " [126]. The core

pathogenesis of chronic liver injury diseases mentioned above is persistent hepatocyte damage, inflammatory cell infiltration, fibrosis, and abnormal regeneration and repair. The treatment challenge lies in slowing the inflammatory process while avoiding drug-related liver toxicity [127]. Chronic viral hepatitis refers to a chronic inflammatory disease of the liver caused by persistent infections (> 6 months) of hepatitis B virus (HBV), hepatitis C virus (HCV), etc. From a pathological perspective, this disease can lead to a vicious cycle of persistent hepatocyte damage, immune-mediated inflammatory responses, and fibrosis. The key to treating liver injury and inflammation lies in multi-target comprehensive intervention, which not only controls the etiology and progression of inflammation, but also promotes liver cell repair and regeneration, while preventing fibrosis and complications. IDDS, such as enzyme-responsive and photoresponsive IDDSs, leverages liver-specific biochemical characteristics, such as the expressions of specific enzymes or photosensitivity, to achieve localized drug release tailored to various liver diseases. This can not only reduce further damage to the liver, but also improve the targeting and efficiency of treatment, reduce the side effects of long-term treatment, and achieve a transition from a vicious cycle of fibrosis to a benign cycle, gradually minimizing the harm of chronic liver injury inflammation to the body [4].

5.6 Chronic inflammatory eye disease

Chronic inflammatory ocular disease refers to the inflammatory response of the eyes ascribed to infection, autoimmune, trauma, or other factors, which may endanger structures such as eyelids, conjunctiva, cornea, choroid, retina, optic nerve and eye sockets, and may develop into conditions including blepharitis, conjunctivitis, keratitis, uveitis, and endophthalmitis in some cases [128]. Chronic non-infectious anterior chamber inflammation, mainly manifested as persistent intraocular inflammation [129], may trigger visual impairment and ocular discomfort [130]. The core mechanisms of such ocular inflammation primarily involve dysregulated autoimmune responses, disruption of the blood-ocular barrier, and direct or indirect infections by microorganisms. The challenge in treating such diseases is to effectively deliver drugs directly to the affected area of the eye while minimizing systemic side effects [131]. IDDS, especially temperature-responsive and photoresponsive IDDSs, provides an innovative solution. These systems can automatically trigger the release of drugs under specific conditions in the eye, such as a slight increase in local temperature or specific light exposure, ensuring that the drugs reach the inflammatory area accurately. This method enhances the local efficacy of drug treatment, and reduces the impact on the patient's entire body, while elevating the convenience of treatment and patient comfort [4].

5.7 Chronic joint inflammatory disease

Chronic arthritis includes various forms such as purulent arthritis, osteoarthritis, rheumatoid arthritis [132], gouty arthritis, ankylosing spondylitis, metabolic arthritis, etc., commonly involving joint inflammation, pain, and functional impairment [133]. The primary mechanism of their onset comprises immune homeostasis imbalance, self-reactive T/B cells, innate immune activation, genetic environmental interaction, and abnormal tissue repair. For example, rheumatoid arthritis is a chronic, symmetrical, and erosive autoimmune arthritis that mainly affects small joints but potentially involves multiple systemic processes throughout the body. Its pathogenesis mainly involves genetic susceptibility, environmental triggers, autoimmune abnormalities, and chronic inflammation, ultimately leading to synovial hyperplasia, cartilage destruction, and bone erosion [134]. Effective chronic arthritis therapy

hinges on suppressing inflammation, relieving pain and protecting joint mobility [135]. The IDDS can accurately release anti-inflammatory or analgesic drugs at the joint site based on biomarkers of joint inflammation response or specific environmental changes within the joint cavity (such as pH changes). This localized drug delivery can not only effectively alleviate symptoms, but also decrease the systemic side effects of drugs. Especially for diseases that require long-term management such as rheumatoid arthritis, this method can significantly improve the quality of life of patients. By adjusting the drug release rate and dosage [136], IDDS can also optimize efficacy, reduce the risk of treatment interruption, and improve patient compliance.

5.8 Chronic cardiovascular inflammatory disease

Chronic cardiovascular diseases are conditions characterized by cardiac and vascular dysfunction resulting from long-term effects such as inflammation, metabolic abnormalities, and hemodynamic changes, and also include related diseases like atherosclerosis, rheumatic heart disease [137], and chronic pericarditis. The core pathogenesis of such diseases is sustained low-grade inflammatory reaction that leads to vascular or myocardial damage, cardiac function decline, and ultimate heart failure and arrhythmia [138]. Atherosclerosis (AS) frequently occurs in the middle-aged and elderly population, initiated by endothelial dysfunction, lipid accumulation, smooth muscle cell migration and fiber cap formation, which ultimately causes thrombosis, cerebral infarction or myocardial infarction. The corresponding treatment should focus on preventing hypertension and hyperlipidemia, controlling metabolism, stabilizing vascular and myocardial structures, and achieving lifelong management [139]. IDDS, especially pH-responsive ones, can react to cardiovascular changes or early manifestation of inflammation. pH-responsive nanocarriers represent a breakthrough in the treatment of chronic cardiovascular inflammation. This type of IDDS can accurately identify the acidic environment (pH 6.5-7.0) of the lesion site, enabling precise drug release in atherosclerotic plaques or areas of myocardial inflammation [140]. This dosage form can also selectively distinguish between lesions and normal tissues through microenvironmental response mechanisms, significantly improving the targeted therapeutic effect of anti-inflammatory drugs while minimizing impacts of drugs on healthy tissues. This precise delivery method avoids the systemic side effects of traditional drug administration, such as immune suppression and liver damage, while optimizing treatment efficacy and improving patient treatment compliance via combining pathological features to achieve multi-stage, controlled drug release.

5.9 Subsection

At present, despite various drug treatment methods, there often exist problems such as unsatisfactory treatment effects, significant drug side effects, and poor patient medication compliance. Noteworthily, such diseases generally have the characteristics of long course, complex pathological changes, and prolonged treatment cycles. In this context, IDDSs, as innovative drug delivery systems, demonstrate unique clinical value: on the one hand, they can greatly improve drug treatment efficacy, and on the other hand, through real-time monitoring and feedback of pharmacokinetic parameters, they provide objective medication compliance evaluation basis for clinical doctors, thereby optimizing personalized treatment plan. Therefore, this IDDS presents great potential in addressing these challenges in chronic inflammatory diseases

In conclusion, the research and development of IDDS provide new directions for treating various chronic inflammatory diseases,as shown in Table 1. IDDS

enables precise drug release based on specific biomarkers or environmental conditions, thereby improving therapeutic efficacy, reducing side effects, and enhancing patient compliance. Future research will focus on further optimizing these delivery systems and exploring their application potential in a broader range of disease treatments.

Table 1 An Overview of the immune mechanisms of common chronic inflammatory diseases and the application of intelligent drug delivery response systems.

Organ System	Representative Diseases	Key Pathological Features	Core Therapeutic Challenges	Smart Drug Delivery Strategies	Reference
Digestive System	Inflammatory Bowel Disease (IBD), Irritable Bowel Syndrome (IBS)	Mucosal barrier disruption, Transmural inflammation (e.g., Crohn's), Dysbiosis	Repair mucosa, Regulate immunity, Halt the "inflammation-fibrosis-cancer" progression	pH-Responsive Enzyme-Responsive	[105]
Skin System	Psoriasis, Atopic Dermatitis (AD)	Skin barrier defect, Keratinocyte hyperproliferation, Immune cell infiltration	Restore skin barrier, Correct immune imbalance, Reduce drug tolerance	Temperature-Responsive Light-Responsive	[111]
Respiratory System	Asthma, Chronic Obstructive Pulmonary Disease (COPD)	Airway inflammation, Mucus hypersecretion, Airflow limitation, Tissue remodeling	Precise local pulmonary delivery of anti-inflammatory/immunomodulatory drugs to reduce systemic side effects	Enzyme-Responsive Magnetic-Responsive	[117]
Renal System	IgA Nephropathy, Lupus Nephritis	Immune complex deposition, Complement activation, Mesangial cell proliferation, Fibrosis	Multi-target intervention in immune inflammation, Protect renal function, Delay fibrosis	pH-Responsive Temperature-Responsive	[123]
Hepatic System	Viral Hepatitis, Non-alcoholic Steatohepatitis (NASH)	Hepatocyte injury, Inflammatory cell infiltration, Vicious cycle of fibrosis	Control etiology and inflammation, Avoid drug-induced liver toxicity, Promote repair/regeneration	Enzyme-Responsive Light-Responsive	[127]
Ocular System	Uveitis, Chronic Anterior Chamber Inflammation	Blood-ocular barrier breakdown, Autoimmune response, Infection	Effective drug delivery to intraocular sites while minimizing systemic exposure	Temperature-Responsive Light-Responsive	[128]
Joint System	Rheumatoid Arthritis (RA), Gout	Synovial hyperplasia, Cartilage/bone erosion, Autoimmunity	Reduce inflammation, Control pain, Preserve joint function, Long-term management	pH-Responsive Biomarker-Responsive	[132]
Cardiovascular System	Atherosclerosis (AS)	Endothelial dysfunction, Lipid accumulation, Plaque formation, Thrombosis	Stabilize plaques, Control metabolism, Lifelong management, Reduce systemic side effects	pH-Responsive	[137]

6 Discussion

The chronic inflammatory microenvironment, characterized by acid-base imbalance, overexpressed specific enzymes, redox dysregulation and aberrant thermo-mechanics, provides precision-targeting "biological beacons" for IDDS. By integrating multidisciplinary technologies and focusing on targeting, controlled release and environmental responsiveness, IDDS have emerged as a key direction for overcoming therapeutic challenges in chronic inflammatory diseases.

At the carrier design level, IDDS forms a multi-scale, multi-source technology matrix. Nanoscale carriers, by dint of their high specific surface area and environmental responsiveness, solve the problem of delivering poorly soluble drugs. For instance, nanocrystals achieve precise drug release through solubility enhancement and self-assembling micelles. Micro-scale carriers, represented by microspheres and micron-sized liposomes, optimize the treatment cycle of chronic diseases through long-term controlled release. The hydrogel relies on the three-dimensional network structure to achieve sustained drug release and microenvironment regulation in local inflammatory sites. Biologically derived carriers utilize the natural biocompatibility and targeted homing ability of cells (neutrophils, stem cells) and extracellular vesicles to break through the limitations of biological barriers. The prodrug strategy activates drugs specifically at the lesion site through chemical modification and significantly reduces systemic toxicity. These diverse carriers complement each other's strengths, covering therapeutic needs ranging from local to systemic, and from short-term intervention to long-term management.

From the perspective of delivery mechanism, targeted delivery achieves "precise navigation" of drugs through EPR effect, ligand modification and other strategies. Controlled release technology leverages polymer degradation and intelligent devices to maintain stable drug concentration, while responsive systems are the core highlight of IDDS, where physical response systems (such as magnetic, electric, thermal, optical, and ultrasonic waves) combine with biological response systems (such as pH and enzymes) to construct a drug release mode of "internal and external signal linkage". This mode can respond to endogenous signals in the inflammatory microenvironment and achieve on-demand drug delivery through exogenous regulation, significantly improving the controllability and accuracy of treatment.

In clinical application, IDDS has developed differentiated solutions for chronic inflammatory diseases across multiple systems, including the digestive tract, skin, respiratory tract, kidneys, liver, eyes, joints, and cardiovascular system. For example, pH-responsive carriers adapt to the pH gradient of the digestive tract, enzyme-responsive carriers target highly expressed enzymes in respiratory inflammation, and temperature-responsive carriers adapt to local warming in joint inflammation. These methods effectively solve the shortcomings of traditional drug delivery, such as "poor targeting, significant side effects, and low compliance", and provide new treatment routes for refractory diseases such as Crohn's disease, psoriasis, asthma, and rheumatoid arthritis.

Currently, although IDDS has made great progress in carrier materials optimization, response mechanisms innovation, and animal experiment-based verification, it still faces bottlenecks in clinical translation, such as standardization of large-scale preparation, long-term biosafety assessment, and collaborative regulation of multiple response systems that urgently need to be addressed. Looking ahead, with the deep integration of materials science, nanotechnology, and biomedicine, IDDS is poised to evolve toward "multi-signal integrated response", "personalized customization"

and "integrated diagnosis and treatment". It is expected to further improve the treatment efficiency of chronic inflammatory diseases, promote the clinical implementation of precision medicine in this field, and provide patients with safer, more efficient, and convenient treatment options.

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Conflicts of Interest

The authors declare that there is no conflict of interests.

Author Contributions

C.Z.: Methodology, Software, Validation, Data curation, Writing – original draft, Formal analysis. C.Z.: Validation, Data curation. Q.S.: Validation, Data curation. Q.S.: Writing – original draft. Q.S.: Data curation, Investigation. Q.S.: Data curation, Visualization. Q.S.: Data curation, Investigation. X.X.: Investigation. X.X.: Conceptualization, Writing–review & editing. All authors read and approved the final manuscript.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary

Not applicable.

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