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Applications of nanoparticles in targeted drug delivery for inflammatory diseases

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Abstract: Inflammatory diseases, including rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis, present significant global health challenges due to their chronic nature and complex pathophysiology. Conventional therapeutic approaches often suffer from limited efficacy, poor bioavailability, and systemic side effects arising from non-specific drug distribution. Nanoparticle-based drug delivery systems have emerged as a promising strategy to overcome these limitations by enabling targeted delivery, controlled drug release, and improved pharmacokinetics. This study aimed to evaluate the applications of nanoparticles in targeted drug delivery for inflammatory diseases, with a focus on their mechanisms, benefits, and potential clinical impact. The methodology involved a comprehensive literature review of peer-reviewed publications retrieved from databases such as PubMed, Scopus, and Google Scholar, covering studies published between 2010 and 2024. The review analyzed nanoparticle types—including liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles—highlighting their drug-loading capacities, surface modifications, and targeting mechanisms toward inflamed tissues. Findings indicate that nanoparticle-mediated delivery significantly enhances therapeutic outcomes by improving drug stability, prolonging circulation time, and facilitating site-specific accumulation via passive (enhanced permeability and retention effect) and active (ligand-receptor) targeting. Moreover, several preclinical and early clinical studies demonstrate reduced systemic toxicity and improved patient compliance compared to conventional drug administration routes. However, challenges remain in large-scale production, long-term toxicity assessment, and regulatory approval. In conclusion, nanoparticles offer substantial potential for improving the management of inflammatory diseases through precision drug delivery. It is recommended that future research prioritize the development of biocompatible, scalable, and cost-effective nanoparticle formulations, alongside robust clinical trials to validate their safety and efficacy. The integration of nanotechnology into therapeutic strategies holds promise for transforming treatment paradigms and improving quality of life for patients with inflammatory conditions.

1.0 Introduction

Nanotechnology, a multidisciplinary field, focuses on the fabrication of particles ranging from 1 to 100 nanometers in size through various synthesis methods and the manipulation of particle size and structure. In recent years, there has been a remarkable surge in the application of nanoparticles across numerous disciplines, including molecular biology, physics, organic and inorganic chemistry, medicine, and material science (Aldwayyan *et al.,* 2013; Jamkhande *et al.,* 2019; Azzaoui *et al.,* 2022; Joseph *et al.,* 2023).The term "nanoparticle" originates from the Greek word "nano," meaning "dwarf or small," referring to a scale of 10^{-9}, where one billionth of a meter corresponds to one nanometer. Nanoparticles possess both solute and distinct particle phase characteristics. Their unique surface-to-volume ratio is 35–45% higher compared to larger particles or atoms (Anselmo and Mitragotri, 2019; Joseph *et al.,* 2023). This extraordinary extrinsic feature of the nanoparticle's specific surface area impacts various intrinsic properties, such as its size-dependent strong surface reactivity, ultimately enhancing its overall value (Yu *et al.,* 2023). The unique attributes of nanoparticles are responsible for their multifunctional properties, driving the increasing interest in their application across various domains, such as energy, medicine, and nutrition (Anselmo and Mitragotri, 2019; Jamkhande *et al.,* 2019; Abouri *et al.,* 2024). Nanoparticles have significantly transformed drug delivery by facilitating targeted and precise treatment approaches for numerous diseases, including inflammatory conditions (Dou *et al.,* 2020; El Yousfi *et al.,* 2023; Eche *et al.,* 2025).

Inflammatory diseases like rheumatoid arthritis, inflammatory bowel disease, and psoriasis often involve complex pathophysiological mechanisms related to immune system dysfunction and localized or systemic inflammation (Vlachos *et al.,* 2016). Conventional therapeutic approaches for these diseases often face issues such as systemic side effects, low bioavailability, and non-specific targeting, leading to reduced treatment effectiveness and patient adherence (Campanati *et al.,* 2021). Given these limitations, this review explores the use of nanoparticles in targeted drug delivery for inflammatory diseases, focusing on the different types of nanoparticles employed, their mechanisms of action, applications, and progress in preclinical and clinical studies. Additionally, safety, toxicity, and challenges in clinical translation are addressed, along with future perspectives on this innovative technology. Nanoparticles are highly effective tools in modern drug delivery systems (DDS), offering precise, targeted delivery of therapeutic agents while minimizing side effects and improving therapeutic outcomes (Jain, 2020; Schön, 2019). Their unique properties, including nanoscale dimensions, tunable surfaces, and multifunctional designs, make them versatile carriers for treating chronic and complex diseases like inflammation, cancer, and viral infections (Saidi *et al.,* 2022; Alshahateet *et al.,* 2024). However, a drug delivery system (DDS), as defined by Jain, (2020), is a formulation or apparatus developed to enhance the safety and efficacy of a therapeutic agent by controlling its administration, the rate, timing, and location of drug release, as well as its transport across biological membranes to reach the targeted site. This multifaceted process includes the introduction of the therapeutic product into the body, the regulated release of active components, and their precise delivery to the intended site of action. Essentially, a DDS serves as the bridge between

the patient and the drug, acting either as a customized drug formulation for therapeutic applications or as a dedicated device that assists in drug delivery.

According to Ayub and Wettig, (2022), researchers have primarily focused on two major areas to create advanced therapeutic approaches, which include drug discovery and drug delivery. Drug discovery utilizes organic chemistry, biochemistry, biology, and pharmacology principles to develop new synthetic or semi-synthetic drugs. The pursuit of novel drugs has existed since ancient times, with evidence suggesting that as early as 1500 BC in ancient Egypt, a mixture of herbs, shrubs, leaves, minerals, and animal excreta was employed for medicinal purposes. Nonetheless, nano-drug-delivery systems are DDSs that function at the nanoscale and provide substantial advantages because of the essential characteristics of nanoparticles, which include their size and surface area of roughly 1–100 nm and their high surface area-to-volume ratio, which allow for improved drug loading and interaction with biological membranes. An essential component of the constantly developing field of nanomedicine is nano-delivery (Anchordoquy *et al.,* 2024). Targeted therapy for inflammatory diseases is of great importance due to its potential to address the limitations of conventional therapeutic approaches. Inflammatory diseases, such as rheumatoid arthritis, inflammatory bowel disease, and psoriasis, are characterized by a dysregulated immune response that leads to tissue damage and chronic inflammation (Jones and Jenkins, 2018; Zhao *et al.,* 2021). However, nanoparticles have emerged as a promising tool for targeted therapy in inflammatory diseases due to their unique properties and potential to address the limitations of conventional treatments (Sinha and Roy, 2024). The relevance of nanoparticles in targeted therapy for inflammatory diseases stems from their unique size and surface characteristics, which enable them to preferentially accumulate in inflamed tissues via the Enhanced Permeability and Retention (EPR) effect. The EPR effect describes a physiological process where nanoparticles and macromolecular drugs concentrate within tumor tissues due to abnormal vasculature and deficient lymphatic clearance. These vessels are often enlarged, irregular, and highly permeable, allowing therapeutic agents of suitable dimensions to infiltrate and persist in the tumor microenvironment. This passive targeting mechanism forms the basis of many nanomedicine approaches, as it enhances drug delivery efficiency, improves therapeutic outcomes, and reduces systemic toxicity. However, its applicability is limited by variations in vascular architecture across different tumor types. Furthermore, nanoparticle surface properties can be engineered to optimize cellular internalization and increase targeting precision, thereby broadening their therapeutic potential (Ejigah *et al.,* 2022; Fang *et al.,* 2022; Kalyane *et al.,* 2019). Nanoparticles' biocompatibility and biodegradability make them ideal candidates for DDS, as they can be engineered from materials that ensure minimal toxicity and safe elimination from the body after completing their therapeutic function. Additionally, their ability to encapsulate or conjugate therapeutic agents allows for high drug loading capacity and controlled release kinetics, enhancing therapeutic efficacy and reducing adverse effects (Lu *et al.,* 2019). Furthermore, their multifunctional design enables the integration of imaging and therapeutic capabilities, allowing for real-time monitoring of drug delivery and response, which is crucial for advancing personalized medicine (Wei *et al.,* 2017). In contrast, conventional treatments often result in systemic side effects, low bioavailability, and non-specific drug action, which can compromise treatment efficacy and

reduce patient adherence (Fu *et al.,* 2018). Targeted therapy addresses these challenges by focusing medications directly on inflamed tissues, improving therapeutic outcomes and minimizing off-target effects. This precision reduces systemic exposure, thereby lowering the risk of adverse reactions and enhancing patient compliance.

Moreover, targeted therapy supports personalized medicine by tailoring treatment based on individual genetic makeup or specific inflammatory pathways. By offering more effective, safer, and patient-specific treatment options, targeted therapy for inflammatory diseases has the potential to significantly improve patients' quality of life and treatment success. This review examines the types, mechanisms, and applications of nanoparticles in targeted drug delivery for inflammatory diseases, covering preclinical and clinical progress, safety, toxicity, regulatory challenges, and future innovations. The study is justified by the growing prevalence of inflammatory diseases and the shortcomings of current treatments, highlighting nanoparticle-based drug delivery systems (DDS) as promising tools for precision medicine, improved therapeutic outcomes, and reduced adverse effects. Objectives include identifying nanoparticle types used in targeted therapy, addressing clinical translation barriers, and exploring design innovations for enhanced stability, scalability, and patient-specific targeting, with scope limited to existing research on inflammatory diseases. Information was sourced from PubMed, ScienceDirect, and Google Scholar using keywords such as “nanoparticles,” “targeted drug delivery,” and “inflammatory diseases,” prioritizing recent peer-reviewed literature from the last six years alongside older foundational works, ensuring a credible and comprehensive basis for the study.

2.1 Methodology

This review was conducted through a comprehensive search of peer-reviewed publications focusing on the application of nanoparticles in targeted drug delivery for inflammatory diseases. Relevant studies published between 2010 and 2024 were retrieved from major scientific databases, including PubMed, Scopus, and Google Scholar. Keywords used in the search included *“nanoparticles,” “targeted drug delivery,” “inflammatory diseases,” “nanomedicine,”* and *“therapeutic applications.”* Articles were screened for relevance based on their titles and abstracts, and only publications written in English and providing experimental, preclinical, or clinical data were included. Review papers were also consulted to provide background and support comparative analysis. Studies were excluded if they lacked direct relevance to inflammatory disease models or did not address nanoparticle-based delivery systems. The selected literature was analyzed qualitatively to summarize nanoparticle types, mechanisms of targeting, therapeutic benefits, and challenges associated with their clinical translation. The findings presented in this paper therefore reflect current trends, innovations, and research gaps in nanoparticle-mediated drug delivery for inflammatory conditions. A bibliometric overview was also conducted to visualize research trends in nanoparticle-based drug delivery for inflammatory diseases from 2010 to 2024. Literature searches from PubMed and Scopus indicated a steady increase in publications during this period, highlighting growing global interest in nanomedicine and its clinical translation. As shown in **Figure 1**, the

number of publications rose progressively from fewer than 30 articles in 2010–2012 to over 100 studies by 2024, reflecting the expanding role of nanoparticles in precision drug delivery and inflammation-targeted therapies.

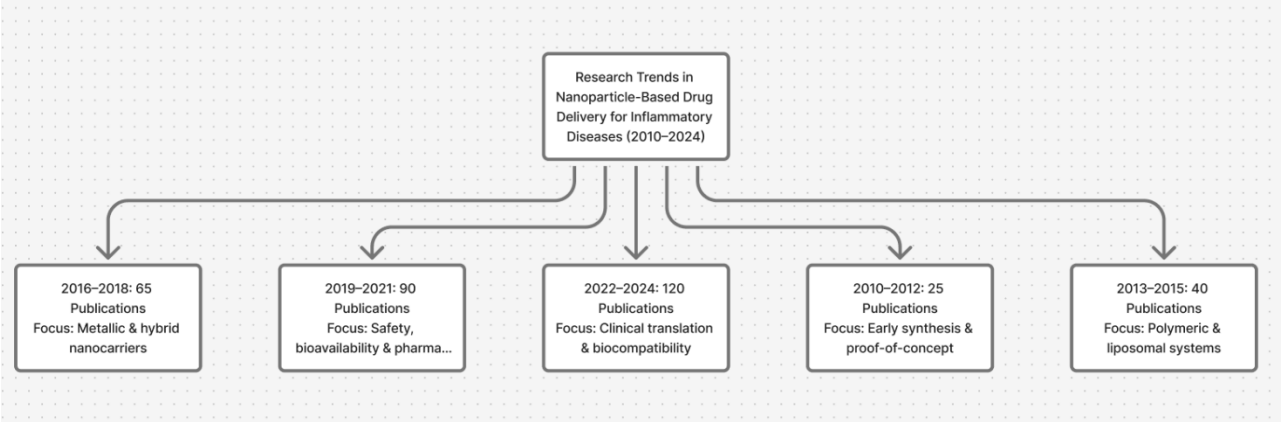

Fig. 1. Bibliometric overview of publication trends on nanoparticle-based drug delivery for inflammatory diseases between 2010 and 2024, showing progressive growth in research output and evolving thematic focus from basic synthesis to clinical translation

2.2 Nanoparticle Types and Their Properties

Over time, nanotechnology has attracted a lot of interest and focus (Shaibu *et al.,* 2014). Compared to their larger-scale counterparts such as bulk materials, and nanoparticles, the fundamental component of this subject, exhibits distinct physical, chemical, and biological properties at the nanoscale. Improved mechanical strength, enhanced reactivity or stability in chemical reactions, and an increased surface area-to-volume ratio are some of the causes of this unusual behavior. These remarkable qualities of nanoparticles have thus made it possible for them to be used in a wide range of industries and applications (Shaibu *et al.,* 2014; Ealias and Saravanakumar, 2017; Tabaght *et al.,* 2021; Eche *et al.,* 2025). Nanoparticles exhibit diverse characteristics, ranging from dimensions and shapes to sizes and materials. They can be classified into different dimensional categories, such as zero-dimensional nanoparticles with fixed dimensions like nanodots, one-dimensional nanoparticles with a single parameter like graphene, two-dimensional nanoparticles possessing length and breadth like carbon nanotubes, and three-dimensional nanoparticles with all dimensions like gold nanoparticles. Additionally, nanoparticles can have uniform or irregular surfaces with variations (Joudeh and Linke, 2022). Some nanoparticles are crystalline or amorphous, with single or multi-crystal solids that may be loose or agglomerated. The wide variety of properties displayed by nanoparticles makes them suitable for numerous applications across various industries (Ijaz *et al.,* 2020).

2.3 Types and potentials

2.3.1 Lipid-Based Nanoparticles

Drug development and cancer treatment have focused a lot of attention on lipid-based nanoparticles (LBNPs), including liposomes, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC). Because of their extended half-life and regulated release of the medication, these nanoparticles may carry both hydrophobic and hydrophilic molecules, exhibit very little or no toxicity, and extend the duration of pharmacological action (García-Pinel *et al.,* 2019). By modifying the chemical composition of lipid nanosystems, such as gangliosides or polyethylene glycol (PEG), the drug's solubility can be enhanced, and immune system detection can be prevented. However, pH-sensitive formulations can be developed to promote drug release in acidic environments. These systems can also be conjugated with antibodies that target tumor cells or their receptors, like folic acid (FoA). Various antitumor agents have been studied in nanoformulations, including doxorubicin (DOX), oxaliplatin, cisplatin, irinotecan (IRI), paclitaxel (PTX), daunorubicin, cytarabine, and vincristine. A few of these agents have undergone clinical trials and/or are commercially available for treating patients in clinical settings (Burdușel and Andronescu, 2022).

2.3.1.1 Liposomes

Liposomes' biocompatibility and biodegradability make them the most researched delivery mechanism. Because of their amphipathic characteristics, phospholipids—the primary constituents of these nanoparticles—are arranged in a bilayer form. Once anticancer medications are put into their structure, they improve their solubility and stability by forming vesicles when water is present. They have the ability to encapsulate medications that are hydrophilic or hydrophobic (García-Pinel *et al.,* 2019). In addition to phospholipids, other substances can be added to their formulations, such as cholesterol, which improves the stability of these nanoparticles in blood by decreasing their fluidity and increasing the permeability of hydrophobic drugs through the bilayer membrane. Cholesterol-modified liposomes can display a single bilayer with sizes above 100 nm, known as Large Unilamellar Vesicles (LUVs); a multiple bilayer with sizes between 0.5 and 10 nm, known as Multilaminar Vesicles (MLVs); and intermediate sizes (10–100 nm), known as Small Unilamellar Vesicles (SUVs). Recent years have seen a surge in research on the synthesis and development of novel liposomes. A prominent trend involves the use of Fe_3O_4 cores to functionalize various nanoparticles. In 2014, a combination of chemotherapy and hyperthermia treatment was achieved using liposome-encapsulated doxorubicin (DOX) with citric acid-coated magnetic nanoparticles. Additionally, in 2014, DOX was co-encapsulated with Magnevist®, a contrast agent, within a liposome modified with amphiphilic hyaluronic acid and cholesterol, demonstrating the potential for multifunctional liposomal DDS (Alavi and Hamidi, 2019; Burdușel and Andronescu, 2022; Samimi *et al.,* 2018).

2.3.1.2 Solid Lipid Nanoparticles (SLN)

Solid lipid nanoparticles (SLNs) are a novel innovation in colloidal DDS that have emerged in recent years as shown in **Figure 1** (Alsaad *et al.,* 2020). These particles comprise physiological lipids that maintain a solid state at both room and body temperatures, with a size range of 50 to 1000 nm (Alsaad *et al.,* 2020; García-Pinel *et al.,* 2019; Shaibu *et al.,* 2023). The solid lipid matrix facilitates drug encapsulation and typically consists of mono-, di-, or triglycerides, fatty acids, and complex glyceride mixtures. To ensure stability, surfactants or polymers are utilized. SLNs offer several advantages, including targeted drug delivery, long-term physical stability, controlled release of lipophilic and hydrophilic drugs, protection of sensitive drug compounds, cost-effective production, straightforward preparation methods, and biocompatibility, making them an attractive option for various therapeutic applications (García-Pinel *et al.,* 2019; Shaibu *et al.,* 2024).

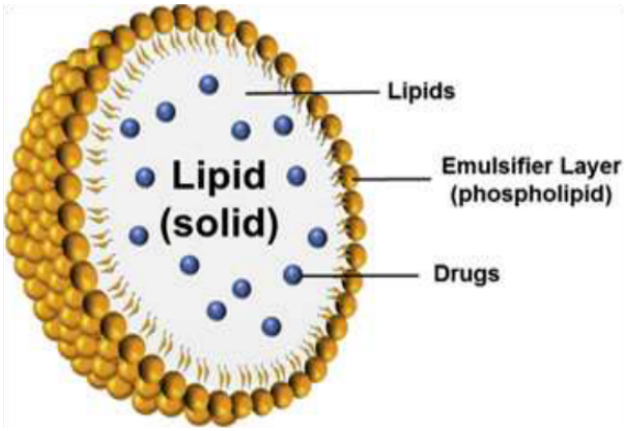

Fig. 1: Chemical structure of SLN (Alsaad *et al.,* 2020)

However, solid lipid nanoparticles (SLNs) possess several benefits in the realm of DDS, as highlighted by (Alsaad *et al.,* 2020). SLNs minimize the risk of chronic and acute toxicity and prevent the use of organic solvents in the production process by utilizing biodegradable physiological lipids. The bioavailability of poorly water-soluble molecules is improved, and site-specific distribution of drugs allows for enhanced medication penetration into the skin through dermal application. Additionally, SLNs enable controlled drug release and targeting. They protect chemically labile reducing agents in the intestine and shield delicate molecules from external factors. In comparison to liposomes, SLNs demonstrate higher stability. Furthermore, there are some drawbacks associated with SLNs, such as low drug loading capacity, drug expulsion during storage due to polymer transition, a comparatively high volume of dispersed water (70-99.9%), and limited loading capacity for water-soluble drugs during the manufacturing process, which can be attributed to partitioning effects.

2.3.1.3 Nanostructured Lipid Carriers (NLC)

An improved version of lipid-based nanocarriers as shown in **Figure 2** called Nanostructured Lipid Carriers (NLCs) was created to overcome the drawbacks of Solid Lipid Nanoparticles (SLNs).

Glyceryl tricaprylate, ethyl oleate, isopropyl myristate, and glyceryl dioleate are examples of solid and liquid lipids that are included in NLCs as opposed to SLNs, which are made entirely of solid lipids (Alavi and Hamidi, 2019; García-Pinel *et al.,* 2019). This composition minimizes lipid crystallization, preventing drug expulsion during storage and increasing drug-loading capacity. NLCs typically have particle sizes ranging from 10 to 1000 nm, similar to SLNs, with size influenced by the lipid type and manufacturing process. Their key advantages include the ability to encapsulate both hydrophilic and hydrophobic drugs, surface modification potential, site-specific targeting, controlled drug release, and low in vivo toxicity. However, challenges persist, such as drug expulsion caused by polymorphic transitions in the lipid matrix during storage and a relatively low loading capacity (Khan *et al.,* 2023).

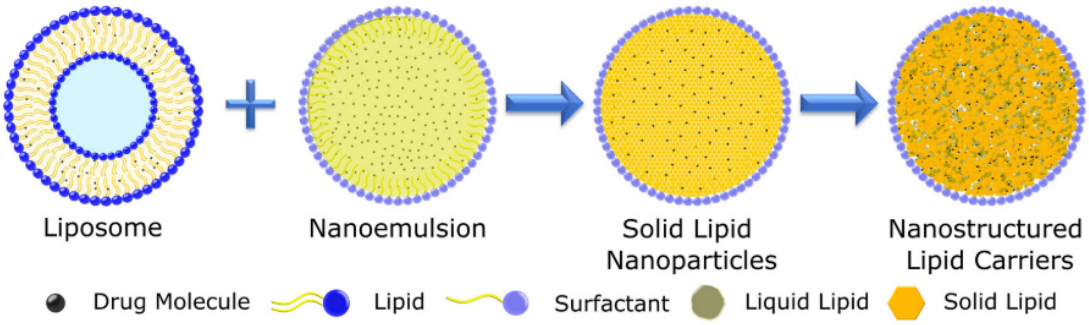

Fig. 2: Lipid-based nanocarrier evolution (Khan *et al.,* (2023)

Khan *et al.,* (2023) did, however, corroborate those multiple approaches to NLC preparation have been documented. The hot high-pressure homogenization, cold high-pressure, high speed/shear, microemulsion, solvent diffusion and evaporation, hot melt extrusion, and solvent injection techniques are some of the different preparation techniques. Additionally, the benefits of NLC in drug administration include its intrinsic capacity to deliver medications safely and effectively via a variety of routes, such as oral, transdermal, and nasal (Grassiri *et al.,* 2021; Khan *et al.,* 2023).

2.4 Polymeric Nanoparticles

Drug delivery has so far made use of a range of DDSs, including liposomes, micelles, and mesoporous silica nanoparticles. Among them, polymeric nanoparticles (NPs) as shown in Figure 3 have been suggested as significant platforms that are controlled by either synthetic or natural polymers. Numerous polymeric nanoparticles have been employed to date, each with its own set of pros and cons (Zu *et al.,* 2021). However, these nanoparticles can be categorized into two main types: nanospheres and nanocapsules. Nanospheres are matrix systems in which the drug is uniformly distributed, while nanocapsules possess a core-shell structure where the drug is encapsulated within a polymeric shell. Each type offers distinct advantages and disadvantages depending on the specific drug delivery application.

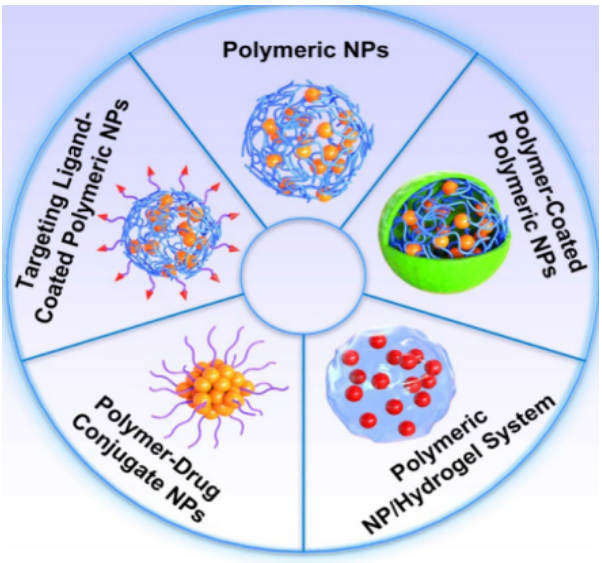

Fig. 3: Schematic representation of several polymeric nanoparticles (Zu *et al.,* 2021)

For instance, several biodegradable polymers have been employed as NP matrices, including gelatin, chitosan, dendrimer, poly(lactide-co-glycolide) (PLGA), and poly(D,L-lactic acid) (PLA). All of these biocompatible materials have Food and Drug Administration (FDA) approval for drug delivery (Verma *et al.,* 2021; Zu *et al.,* 2021). Numerous strategies for their use in drug delivery are made possible by the large spectrum of drug encapsulation efficiencies, targeting moieties, and stimuli-responsive features that these polymer-based NPs offer. Furthermore, NPs are frequently surface functionalized with polyethylene glycol (PEG), which gives oral NPs the ability to penetrate mucus and enhances medication penetration in inflammatory intestinal tissues (Hadji and Bouchemal, 2022).

Psoriasis, inflammatory bowel disease (IBD), and rheumatoid arthritis are examples of inflammatory illnesses that result from dysregulated immune responses that cause tissue damage and chronic inflammation. The overall effectiveness of conventional treatments is typically diminished by their limitations, which include non-specific action, limited bioavailability, and systemic adverse effects. In order to overcome these obstacles, polymeric nanoparticles (PNPs) have become cutting-edge vehicles for targeted drug delivery. They guarantee accurate administration of therapeutic drugs to inflammatory tissues with increased effectiveness and fewer adverse effects (Kumar *et al.,* 2018). In managing inflammatory diseases like rheumatoid arthritis, which involves chronic inflammation of the joints mediated by hyperactive immune cells such as macrophages and T cells, polymeric nanoparticles loaded with methotrexate or biologics like Tumor Necrosis Factor-alpha (TNF-α) inhibitors have shown promising results. TNF-α inhibitors are a class of drugs that treat inflammatory and autoimmune conditions by inhibiting the proinflammatory cytokine TNF-α. These nanoparticles have demonstrated improved targeting to inflamed synovial tissues, thus enhancing therapeutic efficacy while reducing systemic toxicity (Ahn *et al.,* 2020).

Inflammatory Bowel Disease (IBD), specifically Ulcerative Colitis (UC) as shown in **Figure 4**, is a prevalent chronic and incurable inflammatory bowel condition causing symptoms such as diarrhea, bloody stools, and mucosal damage. This disease is characterized by inflammation of the intestinal

mucosa, which poses challenges for drug delivery due to rapid gastrointestinal transit and enzymatic degradation. To overcome this issue, mucoadhesive polymeric nanoparticles have been developed to transport corticosteroids and immunosuppressants directly to the inflamed colon. This targeted approach results in localized drug effects and minimized systemic exposure, offering a promising solution for more effective and safer treatment of UC (Verma *et al.,* 2021; Xie *et al.,* 2022; Zu *et al.,* 2021). Moreover, psoriasis is a chronic autoimmune skin disorder characterized by inflammation, which affects 1-3% of the global population and significantly impacts patients' quality of life. This condition involves excessive keratinocyte proliferation and immune activation. Polymeric nanoparticles encapsulating anti-inflammatory drugs or siRNA targeting inflammatory pathways have demonstrated improved drug penetration into the skin and sustained therapeutic effects, enhancing the treatment of this chronic disease (Yadav *et al.,* 2021).

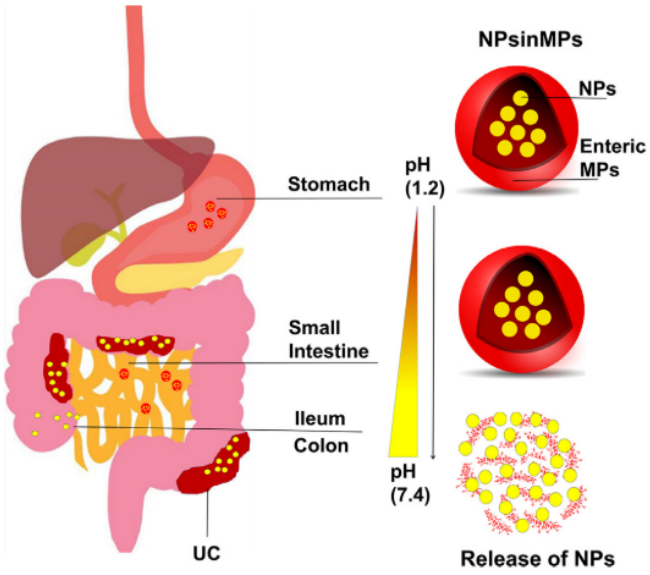

Fig. 4: Diagrammatic representation of the suggested technique for delivering nanoparticles (NPs) (Naeem *et al.,* 2020)

2.4.1 Synthetic polymer-based NPs

Synthetic polymer-based nanoparticles (NPs) are fabricated using artificially created polymers as shown in Table 1. These polymers can be tailored to possess specific properties and functionalities, allowing for greater control over the characteristics of the resulting NPs (Shaibu *et al.,* 2023*; Zu et al.,* 2021*)*. Some common synthetic polymers used for NP synthesis include poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(lactic-co-glycolic acid) (PLGA), and poly(caprolactone) (PCL). These biodegradable polymers can encapsulate drugs, proteins, or other bioactive molecules for targeted drug delivery, imaging, and diagnostic applications. Furthermore, compared to natural polymers, synthetic polymers are typically more homogeneous and pure, which helps with high reproductivity (Minakshi *et al.,* 2020; Singh and Nayak, 2023). As a result, the biomedical profession has seen an exponential increase in interest in synthetic polymers in recent

years. Scientists suggested a number of changes to create effective NPs, including matrix composition, shape, zeta potential, particle size, and size distribution. Despite the advantages of synthetic polymer-based NPs which include controlled drug release, tunable size and surface properties, and the ability to incorporate various targeting ligands. However, potential disadvantages may include toxicity concerns and batch-to-batch variability in production. Overall, synthetic polymer-based NPs offer a versatile platform for developing advanced biomedical applications. In addition, Synthetic polymer-based nanoparticles (NPs) hold great promise for treating inflammatory diseases such as psoriasis, inflammatory bowel disease (IBD), and rheumatoid arthritis.

These NPs facilitate targeted drug delivery and controlled release, minimizing side effects and enhancing therapeutic effectiveness. In psoriasis, they encapsulate anti-inflammatory drugs or small interfering RNA (siRNA) targeting inflammatory pathways, improving skin penetration, and ensuring sustained therapeutic outcomes, thereby managing this chronic autoimmune disorder more effectively (Bodnár *et al.,* 2024). For IBD, synthetic NPs are tailored to deliver drugs directly to inflamed colonic regions, reducing systemic exposure and enhancing treatment efficacy. In rheumatoid arthritis, these NPs transport anti-inflammatory drugs like methotrexate or biologics such as Tumor Necrosis Factor-alpha (TNF-α) inhibitors directly to inflamed synovial tissues, boosting therapeutic results while lowering systemic toxicity. Overall, synthetic polymer-based NPs represent a versatile and innovative approach to managing inflammatory diseases (Yang and Merlin, 2019). Nevertheless, in spite of their potential, the clinical translation of polymeric nanoparticles faces a number of obstacles, including scalability, which can be argued because it is still difficult and expensive to synthesize polymeric nanoparticles at an industrial scale with consistent quality, and stability, which is the ability of the nanoparticles to aggregate or degrade during storage, thereby compromising their effectiveness, the immune response, which involves the Although most PNPs are biocompatible, some may cause unexpected immune reactions, which calls for more immunogenicity research and regulatory clearances. One of the main obstacles to regulatory approval is the absence of standardized procedures for nanoparticle characterisation and testing.

2.4.2 Natural polymer-based NPs

Prior to their clinical applications, it is crucial to thoroughly assess the potential toxicities of synthetic polymers. On the other hand, natural polymers sourced from biological materials, such as proteins and polysaccharides, are generally regarded as safer and more cost-effective alternatives as shown in **Table 2** (Ajibola *et al.,* 2020; Zu *et al.,* 2021; Saidi *et al.,* 2022). However, several common natural polymers used in nanomedicine include chitosan, alginate, gelatin, and silk fibroin (SF). Notably, SF, an FDA-approved natural polymer, has been employed as a suture material in clinical settings for over a century. Remarkably, silk fibroin-based nanoparticles (SFNPs) have demonstrated intrinsic anti-inflammatory activity and wound-healing properties, qualifying them as bioactive nanotherapeutics in their right (Ejigah *et al.,* 2022; Zu *et al.,* 2021). Gelatin, a biocompatible, hydrophilic, and biodegradable polymer derived from partially hydrolyzed collagen, has been widely utilized as a drug delivery medium, as noted by Zu *et al.,* (2021). Gelatin-based nanoparticles have been shown to effectively deliver 5-ASA molecules to colon tissues in a DSS-induced UC mouse

model, offering protective benefits against colitis. Another promising material for drug delivery and wound healing is chitosan, a polysaccharide obtained from chitin, a natural substance found in crustacean shells. Chitosan possesses excellent biocompatibility, biodegradability, and mucoadhesive properties, making it a suitable choice for these applications. In addition, both gelatin and chitosan have demonstrated potential as DDS due to their desirable properties and effectiveness in targeted drug delivery. While gelatin-based nanoparticles have shown protective benefits against colitis in a mouse model, chitosan's unique characteristics make it an attractive option for drug delivery and wound healing (Zu *et al.,* 2021).

Table 1: FDA-Approved Synthetic and Natural Nanoparticle-Based Drugs Synthetic Nanoparticles (Agrahari and Agrahari, 2018)

Name and Type of Nanomaterial	Year Approved	Indication	Mechanism of Delivery and Targeting
Copaxone1 (polymer conjugate)	1996	Multiple sclerosis	Mimics myelin for autoimmune decoying via controlled molecular weight polymers.
Renagel1 (polymer conjugate)	2000	Chronic kidney disease	Binds phosphate ions in the gastrointestinal tract to reduce phosphate levels.
PegIntron1 (polymer conjugate)	2001	Hepatitis C	Uses PEG conjugation for sustained drug release and enhanced therapeutic action.
Pegasys1 (polymer conjugate)	2002	Hepatitis B and C	Extends drug half-life through PEG conjugation for improved delivery and sustained effects.
Neulasta1 (polymer conjugate)	2002	Febrile neutropenia (nonmyeloid malignancies)	Facilitates sustained release of filgrastim to stimulate white blood cell production.
Eligard1 (polymer conjugate)	2002	Prostate cancer	Provides controlled leuprolide acetate release for hormone-dependent cancer treatment.
Somavert1 (polymer conjugate)	2003	Acromegaly	PEGylated somatropin enhances therapeutic effect and reduces drug degradation.

Macugen1 (polymer conjugate)	2004	Age-related macular and neovascular degeneration	Targets VEGF to prevent neovascularization in macular degeneration.
Abraxane1 (polymer–drug conjugate)	2005 (breast cancer), 2012 (lung cancer), 2013 (pancreatic cancer)	Cancer therapy	Uses albumin-conjugated paclitaxel for improved solubility and passive tumor targeting.
Mircera1 (polymer conjugate)	2007	Anemia associated with chronic renal failure	PEGylated erythropoietin ensures prolonged action and reduces dosing frequency.
Cimzia1 (polymer conjugate)	Crohn's disease (2008), rheumatoid arthritis (2009), psoriatic arthritis (2012), ankylosing spondylitis (2013)	Autoimmune diseases	PEGylated certolizumab pegol neutralizes TNF-α to reduce inflammation in autoimmune conditions.

Table 2: FDA-Approved Synthetic and Natural Nanoparticle-Based Drugs Natural Nanoparticles (Arahari and Agrahari, 2018)

Name and Type of Nanomaterial	Year Approved	Indication	Mechanism of Delivery and Targeting
Doxil1 (liposome)	1995	AIDS/Kaposi's sarcoma	Accumulation of liposomes by passive targeting for enhanced drug delivery.
Abelcet1 (lipid–drug conjugate)	1995	Fungal infections	Selective release of Amphotericin B to fungal cells reduces toxicity.
DaunoXome1 (liposome)	1996	AIDS/Kaposi's sarcoma	Passive targeting via sustained daunorubicin release.
AmBisome1 (liposome)	1997	Systemic fungal infections	Ensures targeted delivery with minimal cellular uptake for reduced systemic toxicity.
DepoCyt1 (liposome)	1999, 2007	Lymphomatous malignant meningitis	Releases drugs into cerebrospinal fluid for extended half-life and prolonged effect.
Visudyne1 (liposome)	2000	Age-related macular degeneration	Targets damaged retinal tissue for localized treatment.

Venofer1 (magnetic)	2000	Iron deficiency in chronic kidney disease	Uses magnetic properties of iron oxide nanoparticles for targeted iron replenishment.
DepoDur1 (liposome)	2004	Chronic pain treatment	Controlled drug release for prolonged analgesic effects.

2.5 Metallic Nanoparticles

Metallic nanoparticles are nanoscale particles made from various metals, such as gold, silver, iron, and platinum. These nanoparticles exhibit unique physical, chemical, and optical properties that make them attractive for various applications in fields like medicine, electronics, and catalysis (Xie *et al.,* 2022). Various physical and chemical methods, including electrochemical alterations, chemical reduction, and photochemical reduction, are frequently utilized for the synthesis and stabilization of metallic nanoparticles. Choosing an appropriate preparation method is critical because factors such as the kinetics of metal ion interaction with reducing agents, the adsorption of stabilizing agents onto the nanoparticles, and experimental conditions significantly impact their morphology (size and structure), stability, and physicochemical properties (Jamkhande *et al.,* 2019).

Metallic nanoparticles are increasingly incorporated into products that interact directly with humans, including cosmetics, detergents, toothpaste, soaps, shampoos, medicines, and pharmaceuticals. Gold nanoparticles, widely used in medicine and Ayurvedic preparations in India and China, are employed for diagnostic purposes and drug delivery (Jamkhande *et al.,* 2019). Similarly, silver nanoparticles are extensively applied in biomedical fields, such as separation science and advanced DDS (Nene *et al.,* 2021). Renowned for their antimicrobial and anti-inflammatory properties, silver nanoparticles promote faster wound healing and are commercially used in wound dressings, pharmaceutical formulations, and medical implant coatings. Platinum nanoparticles have also been explored for their health benefits and are effectively used in biomedical applications, either in pure form or alloyed with other metals. The growing use of metallic nanoparticles, particularly in biomedicine and related fields, reflects their versatile applications and potential to transform healthcare globally (Jeyaraj *et al.,* 2019).

2.6 Hybrid Nanoparticles

Hybrid polymer-based nanoparticles (NPs) have shown significant potential in the treatment of various autoimmune and inflammatory disorders, such as rheumatoid arthritis, inflammatory bowel disease (IBD), and psoriasis. These conditions are characterized by chronic inflammation and often require targeted DDS to improve treatment efficacy and minimize side effects (Fang *et al.,* 2019; Zu *et al.,* 2021). In the case of rheumatoid arthritis, hybrid NPs can be designed to specifically target inflamed synovial joints, allowing for the targeted delivery of anti-inflammatory drugs such as methotrexate or glucocorticoids. This targeted approach can help reduce drug dosage and minimize systemic side effects associated with conventional treatments (Ren *et al.,* 2024). For IBD, including Crohn's disease and ulcerative colitis, hybrid NPs can be engineered to selectively deliver anti-

inflammatory agents like 5-aminosalicylic acid (5-ASA) or TNF-alpha inhibitors to the inflamed regions of the gastrointestinal tract. This can help alleviate symptoms and promote mucosal healing while minimizing systemic exposure to the drug (Naeem *et al.,* 2020). In psoriasis treatment, hybrid NPs can be utilized to deliver anti-psoriatic drugs such as corticosteroids or vitamin D analogs to the affected skin areas. The enhanced penetration and targeted delivery of these drugs using hybrid NPs can improve treatment outcomes and reduce the adverse effects associated with conventional topical therapies (Bodnár *et al.,* 2024). Overall, the application of hybrid polymer-based NPs in the treatment of rheumatoid arthritis, IBD, and psoriasis holds great promise for improving drug delivery efficiency, enhancing treatment efficacy, and minimizing side effects associated with conventional therapies.

3.1. Encapsulation Efficiency and Drug Loading

Encapsulation efficiency (EE) and drug loading (DL) are critical parameters in nanoparticle formulation for DDS targeting inflammatory diseases (Yalcin *et al.,* 2018). EE measures the proportion of the drug successfully entrapped within the nanoparticles relative to the initial drug amount, while DL refers to the quantity of drug loaded per unit weight of nanoparticles. These parameters influence therapeutic efficacy, drug release kinetics, and toxicity profiles. Techniques such as solvent evaporation, nanoprecipitation, and emulsification-solvent diffusion are commonly used for nanoparticle formulation, with modifications tailored to specific drugs and delivery goals (Castro *et al.,* 2022). High-performance liquid chromatography (HPLC) and UV-spectrophotometry are standard analytical techniques employed to quantify EE and DL (Hameedat *et al.,* 2022; Hanafy *et al.,* 2019). For example, polymeric nanoparticles encapsulating methotrexate for rheumatoid arthritis have demonstrated enhanced EE due to their hydrophobic polymer matrices (Syed *et al.,* 2023). Optimizing EE and DL can enhance targeted delivery, minimize systemic side effects, and improve patient compliance (Zafar *et al.,* 2020).

3.2. Particle Size and Surface Charge Analysis

The size and surface charge of nanoparticles significantly affect their biodistribution, cellular uptake, and drug release profile. Nanoparticles for drug delivery typically range from 10 to 200 nm, enabling them to evade renal clearance and enhance permeability and retention (EPR) in inflamed tissues (Mitchell *et al.,* 2021). Smaller particles penetrate deeper into inflamed tissues, while larger particles may exhibit prolonged circulation. Dynamic light scattering (DLS) is widely employed to determine particle size distribution, while zeta potential analysis is used to assess surface charge. A high absolute zeta potential value, typically ±30 mV, enhances colloidal stability by preventing nanoparticle aggregation. Positively charged nanoparticles, such as chitosan-based systems, interact strongly with negatively charged cell membranes, facilitating cellular uptake in inflamed tissues (Rashki *et al.,* 2021).

3.3 Stability and Biocompatibility

Nanoparticle stability and biocompatibility are essential for their safe and effective application in targeted drug delivery. Stability ensures that nanoparticles maintain their physicochemical properties during storage and biological circulation. Techniques such as freeze-drying and surface modification with stabilizers like polyethylene glycol (PEG) improve nanoparticle stability (Paul and Sharma, 2020). Biocompatibility is crucial to minimize adverse immune responses. Polymeric nanoparticles, including those made from PLGA and chitosan, are biodegradable and well-tolerated in biological systems, reducing toxicity risks (Kyriakides *et al.,* 2021). Preclinical studies have shown that lipid-based nanoparticles delivering corticosteroids for inflammatory bowel disease achieve high biocompatibility and localized therapeutic effects, minimizing systemic toxicity (Chuang *et al.,* 2018). Together, stability and biocompatibility are pivotal in advancing nanoparticle-based therapies for inflammatory diseases.

4.1. Preclinical Evaluation of Nanoparticle DDS

Preclinical studies play a crucial role in assessing the safety, efficacy, and pharmacokinetics of nanoparticle DDS for inflammatory diseases. Animal models, such as murine models of rheumatoid arthritis or inflammatory bowel disease (IBD), are widely used to evaluate the therapeutic potential of nanoparticle formulations (Ahn *et al.,* 2020). These studies focus on biodistribution, drug release kinetics, and toxicity profiles to ensure nanoparticles effectively target inflamed tissues while minimizing systemic exposure. For example, polymeric nanoparticles encapsulating methotrexate demonstrated enhanced targeting to synovial tissues in arthritic mice, reducing inflammation without significant off-target effects (Lamprecht *et al.,* 2018). Lipid-based nanoparticles delivering corticosteroids in IBD models have shown localized drug release, leading to reduced colonic inflammation and systemic side effects (Wei *et al.,* 2017). Preclinical evaluations provide critical data that inform the design of clinical trials.

4.2. Success Stories in Clinical Trials

Several nanoparticle-based DDS have progressed to clinical trials, showcasing promising outcomes for inflammatory disease treatment. Liposomal formulations, such as Doxil® (liposomal doxorubicin), have set the foundation for translating nanotechnology into clinical practice. In IBD, nanoparticles encapsulating biologics like TNF-α inhibitors have demonstrated improved therapeutic outcomes by reducing systemic toxicity and enhancing drug stability (Anchordoquy *et al.,* 2024). Clinical studies involving mucoadhesive nanoparticles in Crohn's disease have shown enhanced drug retention in the inflamed intestinal mucosa, improving patient outcomes (Anchordoquy *et al.,* 2024). Additionally, gold nanoparticles functionalized with anti-inflammatory drugs have entered early-phase trials for rheumatoid arthritis, displaying superior efficacy compared to conventional therapies. These success stories highlight the potential of nanoparticles to address the unmet needs in managing chronic inflammatory conditions.

4.3. Challenges and Limitations in Translating to Clinical Use

Despite the promising results, translating nanoparticles from preclinical studies to clinical applications faces significant challenges. One major hurdle is the scalability of nanoparticle production while maintaining uniformity and quality. Manufacturing techniques must comply with Good Manufacturing Practices (GMP) to ensure reproducibility and safety (Türeli and Türeli, 2020). Regulatory approvals are another challenge, as nanoparticles often require extensive toxicological evaluations due to their unique physicochemical properties. Additionally, patient-specific factors, such as variations in immune responses and disease progression, complicate the generalizability of nanoparticle-based treatments. Cost is also a limiting factor, as the synthesis of certain nanoparticles, such as those incorporating gold or carbon nanotubes, remains expensive (Rahman *et al.,* 2019). Furthermore, long-term safety data are limited, necessitating extended follow-up in clinical trials. Addressing these challenges is critical to fully realizing the potential of nanoparticles in targeted drug delivery.

Conclusion

Nanoparticles, with their unique physicochemical properties, have revolutionized DDS, particularly for inflammatory diseases. Their small size, high surface area, and tunable surface characteristics enable precise and targeted drug delivery to inflamed tissues, minimizing systemic side effects and enhancing therapeutic efficacy. Various types of nanoparticles, such as lipid-based, polymeric, and metallic nanoparticles, have demonstrated significant potential in preclinical and clinical studies for diseases like rheumatoid arthritis, inflammatory bowel disease (IBD), and psoriasis. Despite notable success stories, challenges in scalability, regulatory approval, and cost remain barriers to widespread clinical translation. The application of nanoparticles in targeted drug delivery represents a groundbreaking advancement in treating inflammatory diseases. Their ability to deliver drugs directly to inflamed tissues, coupled with controlled release and biocompatibility, highlights their superiority over conventional therapies. While the potential is immense, addressing the existing limitations in production, regulatory pathways, and long-term safety is crucial for their successful integration into routine clinical practice. Future research should focus on optimizing nanoparticle design for enhanced stability, scalability, and patient-specific targeting. Collaborative efforts between academia, industry, and regulatory bodies are essential to streamline approval processes and reduce production costs. Expanding clinical trials with diverse populations will provide robust safety and efficacy data, paving the way for nanoparticles to become a cornerstone of modern therapeutic strategies.

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