Journal of Applied Pharmaceutical Research
Volume 14 Issue 3, Year of Publication 2026, Page 77 – 92
DOI: https://doi.org/10.69857/joapr.v14i3.1758

Check for updates

Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

TARGETED NANOCARRIERS FOR RHEUMATOID ARTHRITIS THERAPY: CURRENT EVIDENCE AND TRANSLATIONAL BARRIERS

Shishupal Kumar[1], Muneesh Kanaujaya[1], Pallavi Chand[1*], Ashish Singh Chauhan[1], Vikash Jakhmola[2]

Article Information
Received: 29th December 2025
Revised: 24th March 2026
Accepted: 27th April 2026
Published: 15th May 2026

Keywords
Rheumatoid arthritis, Nanocarriers, Active targeting, Stimuli-responsive drug delivery, Pharmacokinetics.

ABSTRACT
Background: Rheumatoid arthritis (RA) remains a debilitating autoimmune disorder characterized by chronic synovial inflammation and progressive joint destruction. Conventional systemic therapies provide symptomatic relief but often fail to achieve site-specific delivery, leading to adverse effects and limited long-term efficacy. This review appraises the available evidence for the use of targeted nanocarrier drug delivery systems in the treatment of RA and highlights the translational hurdles that hinder their clinical use. **Methodology:** A search of PubMed, Scopus, and Web of Science (2015-2025) was conducted using the keywords RA, nanocarriers, liposomes, polymeric nanoparticles, and microneedles. **Result and Discussion:** Liposomal and polymeric nanoparticle systems are emerging nanotechnologies that have demonstrated improved targeting and therapeutic outcomes in preclinical models. In addition, microneedle technologies show potential for less painful delivery through the skin. **Conclusion:** Despite encouraging results, inconsistent manufacturing reproducibility, limitations in large-scale production, and regulatory uncertainties, among others, remain factors that are slowing the transition to the clinic. Standardization of characterization procedures, validated preclinical models, and well-designed translational research are among the measures this review has identified as necessary to facilitate the transition of nanocarrier-based therapeutics to clinical application in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease that progresses gradually and is characterized by synovitis, cartilage destruction, and bone erosion, resulting in joint deformity and loss of function, as shown in Figure 1 [1]. Figure 1 illustrates the structural changes in rheumatoid arthritis, including synovial hyperplasia, immune cell infiltration, and cartilage degradation, which collectively create a microenvironment favorable for targeted nanocarrier accumulation. Although drug treatment (including disease-modifying antirheumatic (DMARDs), biologics, and Janus kinase (JK) inhibitors) has achieved significant progress, the therapeutic effect is still restricted due to systemic toxicity, poor bioavailability, and low concentration of the drug in the inflamed joints [2]. These limitations highlight

[1]*Department of Pharmaceutics, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun-248007, Uttarakhand, India.*
[2]*Department of Pharmaceutical Chemistry, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun-248007, Uttarakhand, India.*

For Correspondence: **pallavichand1990@gmail.com**

the pressing need for new drug delivery methods that not only localize the drug but also prolong its activity, thereby improving therapeutic effects and reducing side effects [3].

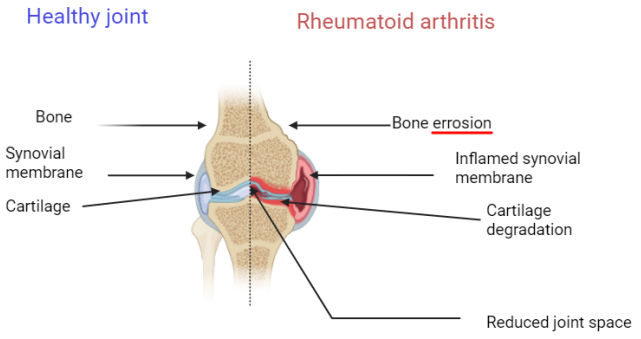

Figure 1: Inflammation in Rheumatoid Arthritis

Nanotechnology-based delivery systems have become a potentially practical solution to these limitations. Nanocarriers, including liposomes, polymer nanoparticles, solid lipid nanoparticles, and microneedles, have been shown to exhibit increased drug solubility, enhanced retention in inflamed tissue, and targeted delivery to synovial tissue [4]. Nevertheless, although several preclinical trials show promising results, translating these nanomedicine platforms into clinical practice remains difficult due to limited scalability, reproducibility, safety assessment, and regulatory standardization [5]. While several reviews have provided a general overview of nanotechnology approaches in rheumatology, there is still no focused, critical appraisal of the application of targeted nanocarriers in RA that considers preclinical evidence and translational barriers [6].

Therefore, this review aims to critically evaluate the current evidence on targeted nanocarrier-based drug delivery systems for RA, including liposomes, polymeric nanoparticles, and microneedles, and to identify the key translational challenges that impede their clinical adoption. The review excludes general epidemiological aspects and conventional drug therapies except where they directly inform the rationale for nanocarrier development.

LITERATURE SEARCH STRATEGY

A focused literature search was conducted to identify recent, high-quality studies on targeted nanocarrier-based drug-delivery systems for RA. Electronic databases, including PubMed, Scopus, and Web of Science, were searched for English-language articles published between January 2015 and December 2024, with the final search update performed in January 2025 using the keywords *"rheumatoid arthritis"*, *"nanocarriers"*, *"liposomes"*, *"polymeric nanoparticles"*, *"microneedles"*, *"targeted drug delivery"*, and *"translational barriers."*

Review articles, preclinical studies, and clinical reports describing the design, evaluation, or translational aspects of nanocarriers were included. Publications limited to conventional DMARDs or biologics without a nanocarrier component were excluded. The reference lists of relevant papers were also screened to identify additional studies. The literature was critically analyzed to (i) compare the therapeutic performance of major nanocarrier platforms (liposomes, polymeric NPs, microneedles), (ii) identify key formulation parameters influencing efficacy and safety, and (iii) highlight current translational challenges impeding clinical progression.

Although this review was not conducted as a formal systematic review, elements of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) framework were considered to ensure transparency in study selection. The included studies were critically appraised based on their experimental design, relevance to targeted nanocarrier systems, and reported therapeutic outcomes. Particular attention was given to preclinical studies demonstrating well-defined control groups, reproducibility of formulation methods, and clear evaluation of pharmacokinetics and therapeutic efficacy. Studies with insufficient methodological details or unclear outcome measures were excluded to minimize potential bias.

EPIDEMIOLOGY AND GLOBAL PREVALENCE

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that affects between 0.5-1% of the total adult population in the world, with higher prevalence among women and persons over 50 years of age, as shown in Figure 2 [7,8]. As depicted in Figure 2, the rising global prevalence and disease burden underscore the need for more efficient, targeted therapeutic strategies, thereby supporting the development of nanocarrier-based delivery systems. Recent estimates of the Global Burden of Disease (GBD 2024) indicate that the absolute number of affected patients worldwide is steadily increasing, mainly as populations age and more people with chronic inflammatory diseases survive [9]. Although there are several disease-modifying antirheumatic drugs (DMARDs), RA is still a significant cause of disability-adjusted life years (DALYs) in musculoskeletal diseases. This chronic morbidity of the world highlights the high need for

specific and sustained-release therapeutic strategies, which increase the concentration of intra-articular drugs and reduce systemic toxicity. This end goal is currently being achieved with high-technology nanocarrier systems [10]. Figure 2 is a more detailed summary of the regional prevalence.

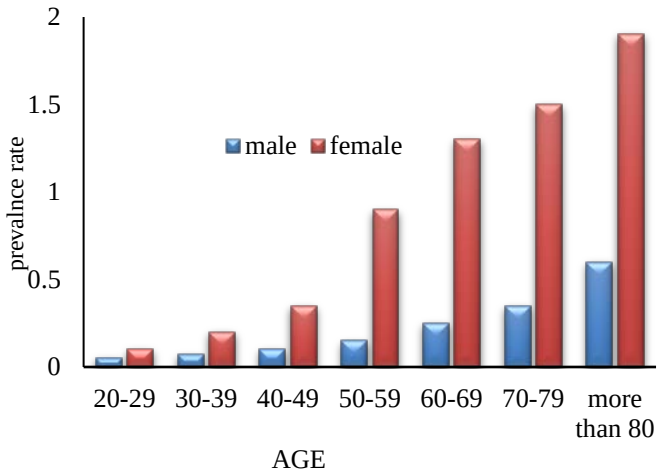

Figure 2: The charts indicate the increasing prevalence and burden of Rheumatoid Arthritis in the world.

The graphs (Figure 2) highlight worldwide prevalence growth and the effects of RA. RA had approximately 17.6 million patients worldwide in 2020, and the number is projected to rise drastically to 31.7 million in 2050, which implies that the disease is going to grow tremendously with time. There is some Epidemiological information available on the prevalence of RA in India, which indicates that this disease gradually rises with age, with the highest prevalence observed among those aged 75-79 years. This trend suggests the age risk factor of RA and the increasing healthcare needs of the aging population, as shown in Table 1 [11]. These epidemiological trends, coupled with the growing economic burden of long-term disease management, underscore the urgent need for more efficient and targeted therapeutic strategies, where nanocarrier-based delivery systems offer a promising approach to enhance treatment efficacy while reducing systemic toxicity and overall healthcare costs.

Table 1: Prevalence and Incidence Rates of Rheumatoid Arthritis Worldwide (Rates are expressed as the number of cases for every 100 people)

Country	Prevalence rates	Incidence Rate	Ref.
Asia			
China	0.2-0.3		
Japan	0.3		
India	0.2-0.7	0.04-0.09	[12]
Taiwan	0.1		
Philippines	0.2	0.3	
Middle East			
Turkey	0.5		
Israel	0.4		[13]
Oman	0.3		
Egypt	0.2		
Africa	0–0.4		[14]
North Europe			
Netherland	0.8	0.05	
England	0.9–1.10	0.02-0.04	
Sweden	0.6-0.9		[11]
Finland	0.03–0.05	0.03-0.04	
Denmark	0.8		
Ireland	0.4		
Norway	0.5-0.6	0.02-0.03	
South America			
Colombia	0.1		[15]
Argentina	0.2		
Brazil	0.5		
Middle -East			
Israel	0.3		
Egypt	0.2		[16]
Oman	0.4		
Turkey	0.5		

PATHOPHYSIOLOGICAL RATIONALE FOR NANOCARRIER TARGETING IN RHEUMATOID ARTHRITIS

RA is a chronic autoimmune disorder in which persistent synovial inflammation drives progressive cartilage and bone destruction. The inflamed synovium is characterized by extensive angiogenesis, increased vascular permeability, and infiltration of immune cells, including macrophages, T cells, and fibroblast-like synoviocytes (FLS) [17].

These changes transform the usually thin synovial lining into a hyperplastic, highly vascularized tissue that supports the local accumulation of nanosized drug carriers via an enhanced permeability and retention (EPR)-like effect [18].

However, this mechanism differs from the classical tumor EPR effect in several important aspects. In addition to the enhanced permeability and retention (EPR)-like phenomenon observed in inflamed synovial tissues, it is important to distinguish this process from the classical tumor EPR effect. In rheumatoid arthritis, nanocarrier accumulation is more accurately described by the ELVIS (Extravasation through Leaky Vasculature and Inflammatory cell-mediated Sequestration) effect [19]. While both mechanisms involve increased vascular permeability, the

ELVIS effect is uniquely driven by the inflammatory microenvironment, characterized by active recruitment and retention of immune cells such as macrophages and fibroblast-like synoviocytes [20]. Unlike the predominantly passive accumulation seen in tumor tissues, nanocarriers in RA are not only extravasated through leaky vasculature. Still, they are also actively internalized and retained by inflammatory cells within the synovium [19]. This cell-mediated sequestration enhances local drug concentration and prolongs therapeutic effects. Additionally, cytokine-driven vascular activation and continuous infiltration of immune cells further sustain nanocarrier retention, thereby making ELVIS a more dynamic and disease-specific targeting mechanism. Recognizing this distinction provides a more precise pathophysiological basis for the design of targeted and stimuli-responsive nanocarrier systems in rheumatoid arthritis [21]. Activated macrophages and FLSs secrete pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and degradative enzymes (MMPs, ADAMTS) that sustain inflammation and matrix breakdown, as shown in Figure 3. Also highlights the key mechanisms underlying nanocarrier targeting in rheumatoid arthritis, including enhanced vascular permeability, inflammatory cell-mediated sequestration (ELVIS effect), and stimuli-responsive drug release within the synovial microenvironment (Figure 3). Importantly, these activated cells often overexpress surface receptors amenable to active targeting (e.g., CD44, folate receptors, and scavenger receptors), providing molecular entry points for ligand-decorated nanocarriers [22]. The synovial microenvironment also exhibits elevated reactive oxygen species (ROS) levels and an acidic pH, which can be exploited by stimuli-responsive materials (e.g., pH-sensitive polymers, such as poly(β-amino esters), or ROS-cleavable linkers, such as thioketal bonds) [23].

Table 2: Comparison of Stimuli-Responsive Nanocarrier Systems in Rheumatoid Arthritis [25–27].

Trigger Type	Mechanism	Example Materials	Advantages	Limitations
pH-responsive	Drug release in an acidic synovial environment	Poly(β-amino esters), hydrazone linkers	Simple design, widely studied	Moderate specificity
ROS-responsive	Cleavage under high oxidative stress	Thioketal linkers, ROS-sensitive polymers	High specificity to inflamed tissue	Stability concerns
Enzyme-responsive	Degradation by overexpressed enzymes (e.g., MMPs)	Peptide-based linkers	Highly selective targeting	Enzyme variability
Temperature-responsive	Release triggered by local inflammation heat	PNIPAM-based polymers	Controlled release	Limited RA-specific data
Dual/multi-responsive	Combination (e.g., pH + ROS)	Hybrid nanocarriers	Improved precision and control	Complex design

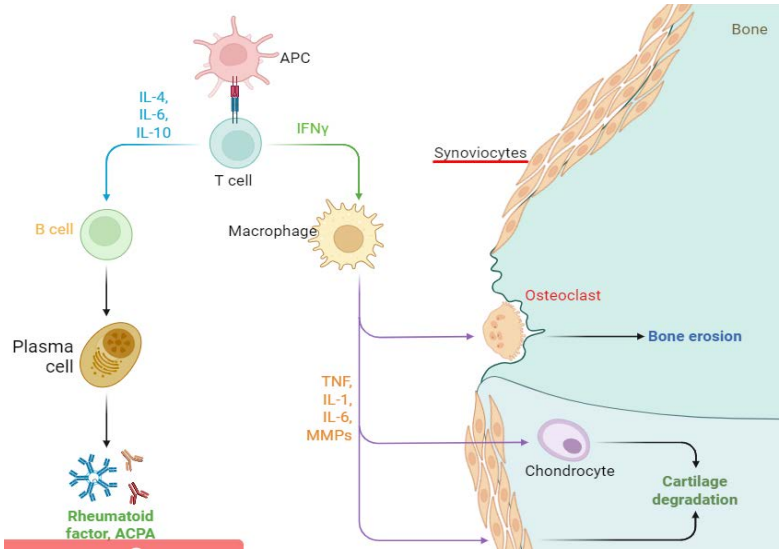

Figure 3: Pathophysiological basis of nanocarrier targeting in rheumatoid arthritis: EPR-like vascular permeability and ELVIS-mediated inflammatory cell sequestration enabling targeted and stimuli-responsive drug delivery.

Collectively, these molecular and microenvironmental abnormalities provide a mechanistic basis for targeted nanocarrier strategies that (i) enhance local drug concentration via passive accumulation (EPR-like retention), (ii) increase cell-specific uptake through ligand-mediated active targeting, and (iii) enable on-site triggered release using stimuli-responsive chemistries. Liposomal and polymeric nanoparticle systems primarily exploit passive and active targeting mechanisms to achieve sustained intra-articular retention. In contrast, microneedle-based platforms offer a minimally invasive transdermal route for local delivery [24]. In addition to passive and active targeting mechanisms, stimuli-responsive nanocarriers have gained increasing attention for rheumatoid arthritis therapy due to their ability to release drugs selectively in response to the pathological microenvironment. Various endogenous triggers, including acidic pH, elevated reactive oxygen species (ROS) levels, and overexpressed enzymes, have been investigated to achieve site-specific drug release. A comparative overview of these stimuli-responsive strategies is presented in Table 2 [25].

Emerging Biomarkers and Targeting Opportunities

Biomarkers that directly inform nanocarrier design and patient selection include circulating cytokines (TNF-α, IL-6) for disease activity, autoantibodies (anti-CCP) for early identification and stratification, and selected microRNAs (miR-146a, miR-155) that both reflect and modulate inflammatory signaling [28]. These markers can help direct the selection of therapeutic payloads, ligand targets & responsive triggers & guide biomarker-guided inclusion criteria for early translational studies. Understanding these interconnected biological processes is the mechanistic framework for the following section, a critical appraisal of current nanocarrier systems, liposomes, polymeric nanoparticles, and microneedles, and the barriers to translation preventing their clinical manifestation [29].

Present Therapeutic Strategies and Requirement for Targeted Drug Delivery

Management of RA is mainly based on the use of DMARDs, biologicals, and targeted synthetic inhibitors that suppress inflammation and slow the structural damage. Conventional DMARDs such as methotrexate, leflunomide, and hydroxychloroquine remain first-line agents, and biologics targeting TNF-alpha, IL-6, or co-stimulatory molecules, as well as newer Janus kinase (JAK) inhibitors, offer additional disease control, as shown in Table 3 [30].

Table 3: Selected Conventional Therapeutic Agents for Rheumatoid Arthritis and Their Major Delivery Limitations

Category	Representative Drug(s)	Mechanism of Action	Major Limitation / Adverse Effect	Delivery Limitation → Need for Nanocarrier	Ref.
NSAIDs	Diclofenac, Ibuprofen	Cyclooxygenase inhibition	GI bleeding, renal toxicity	Require frequent dosing; poor joint selectivity	[31]
Corticosteroids	Prednisolone, Dexamethasone	Glucocorticoid receptor activation	Systemic immunosuppression, osteoporosis	Rapid clearance; limited joint retention	[32]
csDMARDs	Methotrexate, Leflunomide	Folate/pyrimidine-pathway inhibition	Hepatotoxicity, myelosuppression	Narrow therapeutic index; systemic exposure	[33]
Biologics	Infliximab, Adalimumab	Cytokine blockade (TNF-α / IL-6)	Infection risk, infusion reactions	Require parenteral delivery; low tissue penetration	[34]
JAK Inhibitors	Tofacitinib, Baricitinib	JAK-STAT signaling inhibition	Cytopenia, lipid abnormalities	Systemic immunosuppression; no tissue specificity	[35]

Although the efficacy of these agents has been enhanced clinically, they are often limited by poor pharmacokinetic profiles, systemic immunosuppression, and non-specific tissue distribution [36]. Oral & parenteral administration often causes adverse side effects such as hepatotoxicity, myelosuppression, gastrointestinal irritation, and increased risk of infection that prevent dose escalation & long-term adherence. In addition, biologics need cold-chain storage and repeated injections, which impose logistic and economic burdens [37]. The inability of systemically delivered drugs to selectively accumulate at sites of inflammation in synovial tissues is an essential therapeutic gap. Drug molecules diffuse quickly or are cleared from the joint cavity, resulting in subtherapeutic local concentrations. This pharmacological restriction underscores the necessity of targeted, sustained-release methods that deliver anti-inflammatory agents to the diseased microenvironment while reducing systemic exposure [38]. Nanocarrier-based systems, including liposomes, polymeric nanoparticles, and microneedle platforms, have been developed to increase local retention, improve drug stability, and achieve stimuli-responsive release.

The present section provides a critical evaluation of the aforementioned nanotechnological methods, based on the preclinical performance of the proposed delivery systems and the translational hurdles that impede their current clinical application [38,39].

BIOLOGICS AND TARGETED THERAPIES

TNF Inhibitors: Adalimumab, Infliximab, regulation of inflammatory pathways

Tumor necrosis factor-alpha (TNF-α) is a key pro-inflammatory cytokine involved in the pathogenesis of rheumatoid arthritis (RA), contributing to immune cell recruitment, cytokine amplification, and progressive joint destruction. It promotes the production of other inflammatory mediators and plays a central role in sustaining chronic inflammation and systemic symptoms [40]. Biologic disease-modifying anti-rheumatic drugs (bDMARDs), particularly TNF inhibitors such as etanercept, infliximab & adalimumab, have been developed to neutralize TNF-α and specifically disrupt its signaling pathways. These agents effectively reduce inflammation, alleviate clinical symptoms, and slow disease progression in RA and other autoimmune disorders [41]. The mechanism of TNF-α inhibition and its downstream effects on inflammatory mediators such as IL-1 and IL-6: inhibition of TNF-α disrupts downstream cytokine signaling cascades, thereby reducing inflammation and providing a mechanistic basis for targeted therapeutic intervention (Figure 4). Despite their clinical success, TNF inhibitors face several delivery-related challenges, including the need for repeated parenteral administration, limited tissue penetration into inflamed synovial joints, and the risk of systemic immunosuppression [40]. These limitations highlight the need for improved delivery strategies that can enhance site-specific drug accumulation while minimizing systemic exposure [42]. In this context, nanocarrier-based delivery systems offer a promising approach to overcome these challenges. Encapsulation of anti-TNF agents within liposomes or polymeric nanoparticles can enhance their stability, prolong circulation time, and facilitate targeted delivery to inflamed synovial tissues via passive and active targeting mechanisms [43]. Furthermore, ligand-functionalized nanocarriers may improve uptake by activated macrophages and fibroblast-like synoviocytes, thereby increasing local therapeutic efficacy while reducing off-target effects [44,45]. Thus, integrating TNF inhibitors with nanocarrier platforms represents a rational strategy to enhance their pharmacokinetic profile and therapeutic index in rheumatoid arthritis.

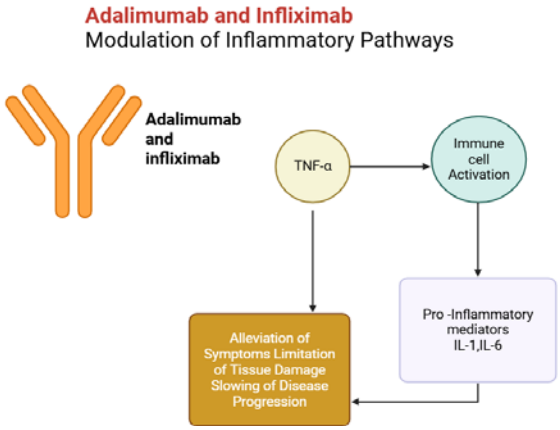

Figure 4: Mechanism of TNF-α inhibition by monoclonal antibodies (adalimumab and infliximab) and downstream suppression of pro-inflammatory cytokines (IL-1, IL-6) in rheumatoid arthritis.

JAK Inhibitors: Tofacitinib, baricitinib, novel oral immunomodulators

Janus kinase (JAK) inhibitors represent an important class of targeted synthetic DMARDs that modulate intracellular signaling pathways involved in inflammation. These small-molecule agents, including tofacitinib and baricitinib, act by inhibiting JAK enzymes and subsequently blocking the JAK–STAT signaling cascade, which is essential for the transmission of pro-inflammatory cytokine signals such as interleukin-6 (IL-6) and interferon-γ [46].

The mechanism of JAK inhibition and its downstream effects on cytokine signaling are illustrated in Figure 5. Demonstrates the inhibition of the JAK–STAT signaling pathway, highlighting how suppression of intracellular cytokine signaling contributes to reduced inflammatory responses in rheumatoid arthritis (Figure 5). Tofacitinib acts as a relatively non-selective JAK inhibitor, whereas baricitinib selectively inhibits JAK1 and JAK2. By suppressing cytokine-mediated signaling, these agents reduce immune cell activation and lower inflammatory biomarker levels, including C-reactive protein and immunoglobulins, thereby improving clinical outcomes in patients with rheumatoid arthritis [47]. Despite their therapeutic advantages and oral bioavailability, JAK inhibitors are associated with systemic adverse effects such as cytopenia, lipid abnormalities, and increased risk of infections due to non-specific immunosuppression. Additionally, their lack of tissue-specific targeting limits drug accumulation at inflamed synovial sites, which may reduce therapeutic efficiency and necessitate prolonged systemic exposure [48]. Nanocarrier-based delivery

systems offer a promising strategy to address these limitations. Encapsulation of JAK inhibitors within polymeric nanoparticles or lipid-based carriers can enable controlled and sustained drug release, improve pharmacokinetic profiles, and enhance preferential accumulation in inflamed tissues. Furthermore, surface-functionalized nanocarriers may facilitate targeted delivery to synovial macrophages and fibroblast-like synoviocytes, thereby reducing systemic toxicity while maintaining therapeutic efficacy [49]. Thus, the integration of JAK inhibitors with advanced nanocarrier systems represents a potential approach to improve site-specific delivery and optimize the safety and effectiveness of these immunomodulatory therapies in rheumatoid arthritis.

NANOCARRIER-BASED DRUG-DELIVERY SYSTEMS FOR RHEUMATOID ARTHRITIS

Nanocarrier technologies have emerged as promising strategies to overcome the pharmacokinetic limitations of conventional antirheumatic drugs [50]. By enhancing solubility, protecting labile molecules, and enabling sustained or targeted delivery, these nanosystems can improve therapeutic efficacy while minimizing systemic toxicity [51]. Their physicochemical properties, size, surface charge, composition, and ligand functionalization determine biodistribution and interaction with the inflamed synovium [52].

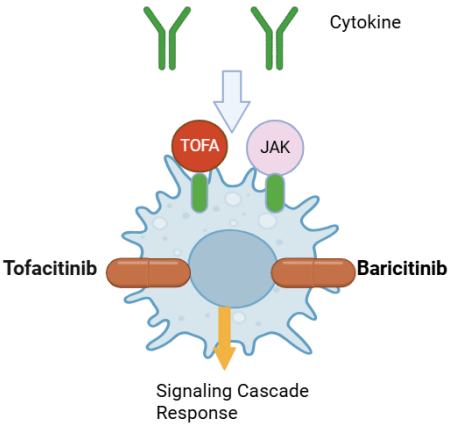

Figure 5: Mechanism of JAK–STAT pathway inhibition by JAK inhibitors (tofacitinib and baricitinib) and its impact on pro-inflammatory cytokine signaling in rheumatoid arthritis.

Classification of Nanocarriers Used in RA

Nanocarrier systems used in rheumatoid arthritis (RA) can be broadly classified into lipid-based, polymeric, and hybrid delivery systems based on their composition and structural characteristics. Lipid-based carriers include liposomes and nanostructured lipid carriers (NLCs), which offer high biocompatibility and efficient drug encapsulation. Polymeric nanoparticles, typically composed of biodegradable materials such as PLGA or PEG, provide controlled release and tunable surface properties. Hybrid systems, including lipid–polymer nanoparticles and surface-functionalized vesicles such as hyalurosomes, combine the advantages of both lipid and polymeric systems to enhance stability, targeting efficiency, and therapeutic performance [53,54].

Comparative Analysis of Nanocarrier Systems

As summarized in Table 4, a wide range of nanocarrier systems have been investigated to improve drug delivery and therapeutic outcomes in RA [55]. Lipid-based systems such as liposomes have demonstrated improved drug retention and reduced systemic toxicity, as observed in methotrexate formulations with encapsulation efficiencies greater than 30% and a suitable nanoscale size (<150 nm) [56]. Similarly, nanostructured lipid carriers co-loaded with leflunomide and resveratrol exhibited a particle size of 188.2 ± 0.85 nm and high encapsulation efficiencies of 92.16 ± 0.41% and 82.82%, respectively, thereby enabling sustained drug release and reducing joint inflammation [57].

Hybrid nanocarrier systems further enhance therapeutic performance by combining lipid and polymer components. For instance, folate-modified lipid–polymer hybrid nanoparticles co-delivering dexamethasone and curcumin exhibited a particle size of 287.8 ± 1.32 nm with encapsulation efficiencies of 89.12 ± 0.087% and 98.27 ± 0.110%, respectively, resulting in enhanced cellular uptake and synergistic anti-inflammatory effects [58]. PEG-decorated hyalurosomes loaded with fluocinolone acetonide demonstrated a particle size of 169.00 ± 1.41 nm & encapsulation efficiency of 83.58 ± 0.69%, enabling effective transdermal delivery and cytokine modulation [59].

Polymeric and vesicular systems also contribute to improved therapeutic outcomes. Curcumin-loaded hyalurosomes exhibited a particle size of 189 nm with approximately 88% encapsulation efficiency and demonstrated significant modulation of inflammatory cytokines in synovial cells [60]. Additionally, PLGA-based nanoliposomes co-loaded with diclofenac sodium and celecoxib showed a particle size of 218.36 ± 6.27 nm and encapsulation efficiencies of 95.18 ± 4.43% and 93.63 ± 5.11%, supporting sustained release and synergistic anti-inflammatory effects [61].

Overall, these findings demonstrate that nanocarrier systems significantly improve drug targeting, enhance pharmacokinetic profiles, and reduce systemic toxicity in RA therapy. Among them, hybrid systems appear particularly promising due to their ability to integrate multiple functionalities, including controlled release, active targeting, and combination therapy. However, challenges related to large-scale manufacturing, reproducibility, and long-term safety remain key barriers to clinical translation.

Table 4: Liposome- and Polymer-Based Drug Delivery Systems in Rheumatoid Arthritis: Limitations Addressed and Therapeutic Advantages

Drug	Carrier Type	Route	Particle Size (nm)	Encapsulation Efficiency (%)	Key Advantage	Ref.
Methotrexate	Liposomes (ethanol injection method)	In vivo (mice)	NR (target <150 nm)	>30%	Improved therapeutic efficacy with reduced toxicity	[56]
Leflunomide + Resveratrol	CHS-modified NLCs (in situ hydrogel)	Localized (in situ gel, arthritis model)	188.2 ± 0.85 nm	92.16 ± 0.41% (LEF); 82.82% (RSV)	Sustained release, targeted delivery, reduced joint inflammation	[57]
Dexamethasone + Curcumin	Folate lipid–polymer hybrid nanoparticles	In vitro (RAW 264.7 cells)	287.8 ± 1.32 nm	89.12 ± 0.087% (Dex); 98.27 ± 0.110% (Cur)	Targeted delivery, synergistic anti-inflammatory effect, enhanced uptake	[58]
Fluocinolone acetonide	PEG-decorated hyalurosomes (nanofiber system)	Transdermal (in vivo)	169.00 ± 1.41 nm	83.58 ± 0.69%	Sustained delivery, reduced systemic toxicity, cytokine modulation	[59]
Curcumin	Hyalurosomes (phospholipid vesicles)	In vitro (synovial cells)	189 nm	~88%	Anti-inflammatory modulation and improved synovial targeting	[60]
Diclofenac sodium + Celecoxib	PLGA-based nanoliposomes	In vivo (rat model)	218.36 ± 6.27 nm	95.18 ± 4.43% (DS); 93.63 ± 5.11% (CEL)	Sustained release, synergistic effect, improved biosafety	[61]

Microneedle-Based Delivery Systems

Microneedles are unique drug delivery systems that enable drug administration through the skin without compromising patient comfort and are ranked the least invasive among all delivery modes due to their mechanism of action. To achieve a local effect without systemic pain or side effects, the tiny needle tips are applied to the skin, creating temporary openings in the stratum corneum [62]. Preclinical studies on microneedles made of both metals and polymers, loaded with methotrexate, tacrolimus, or anti-inflammatory peptides, have shown high local bioavailability and patient acceptance. The combination with either nanoparticles or hydrogels provides additional control over drug release rates. Still, the microneedles are hindered in their clinical translation by a lack of human data, differences in insertion force, and challenges in mass manufacturing, despite promising results [63]. The mechanical performance of microneedles is critically dependent on the material properties of the polymers used. Effective skin penetration requires an optimal balance between mechanical strength and flexibility to prevent needle fracture or bending during insertion. Polymers such as polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and hyaluronic acid are commonly employed due to their favorable biocompatibility and sufficient mechanical integrity. Additionally, factors such as needle geometry, aspect ratio, and polymer crosslinking density influence insertion efficiency and drug release behavior [64].

TRANSLATIONAL BARRIERS AND REGULATORY CONSIDERATIONS

Although nanocarrier platforms have demonstrated considerable therapeutic potential, their clinical application remains limited and not yet established, as shown in Table 5.

Reproducibility of the formulation and scale-up: It is challenging to maintain the same size distribution and drug loading during large-scale manufacturing [65].

Sterilization and stability: Many nanosystems are more fragile to heat and radiation than others; thus, those methods would complicate the sterilization process [66].

Safety evaluation: It is necessary to carry out long-term biodistribution, immunogenicity, and off-target effects studies using standardized methods to their full extent [65,66]. In addition to drug-related toxicity, the safety profile of the

nanocarrier materials themselves is an important consideration for clinical translation. While biodegradable polymers such as PLGA, chitosan, and lipid-based carriers are generally regarded as safe because they degrade into biocompatible metabolites, non-biodegradable or poorly cleared materials may accumulate in organs such as the liver, spleen, or lymphatic system, potentially leading to long-term toxicity [67]. Factors including particle size, surface charge & composition influence biodistribution, cellular uptake & clearance pathways. Therefore, a comprehensive evaluation of carrier metabolism, biodegradability, and long-term safety is essential to ensure the clinical applicability of nanocarrier-based drug delivery systems in rheumatoid arthritis [68].

Regulatory and cost barriers

The absence of a common standard for nanomedicine leads to a lengthy approval process and complex manufacturing, which increases production costs [69]. Although no dedicated regulatory pathway exists exclusively for nanomedicines, agencies such as the U.S. Food and Drug Administration and the European Medicines Agency have issued guidance documents addressing nanomaterial-based products. The FDA's guidance on drug products containing nanomaterials emphasizes detailed physicochemical characterization, manufacturing controls, and evaluation of pharmacokinetics and safety profiles [70]. Similarly, the EMA has published reflection papers outlining requirements for quality, safety, and efficacy assessment of nanotechnology-based medicinal products. However, both agencies currently evaluate nanomedicines on a case-by-case basis under existing drug regulatory frameworks, contributing to variability in approval pathways and delays in clinical translation [71].

Table 5: Comparative Summary of Nanocarrier Systems for Rheumatoid Arthritis.

Nanocarrier Type	Representative Drugs	Targeting Strategy	Key Outcomes	Translational Status	Ref.
Liposomes	Methotrexate, Prednisolone	Passive + Folate ligand	Enhanced synovial accumulation, prolonged release	Preclinical / Early clinical	[72]
Polymeric NPs / NLCs	Curcumin, Genistein, MTX	CD44, folate receptor targeting	Improved bioavailability, reduced toxicity	Preclinical	[73]
Microneedles	Methotrexate, Tacrolimus	Local transdermal	Non-invasive, sustained effect	Prototype / Preclinical	[74]

GENE- AND STEM-CELL-BASED APPROACHES: INTEGRATION WITH NANOCARRIER TECHNOLOGY

New gene and cell therapies can reduce inflammation by directly modulating inflammatory mediators and promoting tissue regeneration, enabling long-term RA management [75]. Among these, the gene therapy approach of delivering anti-inflammatory cytokines, such as IL-1 receptor antagonist (IL-1Ra) and IL-10, or small interfering RNAs (siRNAs) targeting TNF-α and IL-6, has shown promising results in preclinical RA models. Nanocarrier platforms, especially cationic liposomes, polymeric nanoparticles, and hydrogels, are efficient non-viral vectors that enhance gene stability, cellular uptake, and targeted transfection in inflamed synovial tissues [76].

For instance, liposomal IL-1Ra plasmids have been shown to prolong IL-1Ra expression and reduce joint swelling in collagen-induced arthritis models. In contrast, siRNA-loaded PLGA nanoparticles targeting TNF-α have been shown to suppress TNF-α for prolonged periods with minimal systemic toxicity. Besides, gene delivery systems assisted by nanocarriers have overcome the safety issues associated with viral vectors and have also enabled controlled, localized gene modulation [77,78]. The stem cell-related methods, especially those using mesenchymal stem cells (MSCs), are promising & achieve this through immunomodulatory cytokine secretion & cartilage repair [79].

The incorporation of nanomaterials into MSC treatment through different methods, such as nanoparticle marking, guiding magnets, or covering with nano-hydrogels, improves the retention, survival, and directional migration of the cells specifically to the inflamed joints [80]. On the other hand, although these advanced methods showed great promise, their translation is still hindered by challenges related to vector reproducibility, transfection efficiency, biosafety, and regulatory complexity. Working together to optimize nanocarrier design and gene-editing technologies (e.g., CRISPR/Cas9) could lead to precisely controlled, long-lasting therapeutic effects with minimized risk of insertional mutagenesis [79,81]. The combination of gene and stem-cell

approaches, mediated by nanocarriers, thus represents a new direction for RA and the broader realm of medical science toward long-term disease remission and joint regeneration [82].

CARRIER-RELATED TOXICITY AND METABOLIC FATE

While nanocarrier systems are designed to reduce systemic toxicity of therapeutic agents, the safety profile of the carrier materials themselves remains an important consideration. Biodegradable polymers such as PLGA and lipid-based systems are generally regarded as safe due to their ability to degrade into non-toxic metabolites. However, concerns persist regarding the potential accumulation of non-biodegradable or slowly degradable materials, which may lead to long-term tissue retention and unintended biological effects [83]. In addition, nanoparticle surface properties, size, and charge can influence biodistribution, cellular uptake, and immunogenic responses. Limited long-term in vivo studies and variability in degradation kinetics further complicate safety evaluation. Therefore, a comprehensive assessment of carrier-related toxicity, biodegradation pathways, and clearance mechanisms is essential to ensure the safe clinical translation of nanocarrier-based therapies in rheumatoid arthritis [84].

TRANSLATIONAL DISCUSSION AND FUTURE OUTLOOK

Key Translational Insights from Current Evidence

Preclinical investigations have shown that nanocarrier-based systems, including liposomes, polymeric nanoparticles, and microneedle platforms, can provide significant local drug retention and improved therapeutic outcomes in rheumatoid arthritis models [85]. Enhanced and sustained effects have been observed with liposomal formulations of methotrexate and prednisolone. At the same time, ligand-modified polymeric nanoparticles have enabled targeted delivery to macrophages and fibroblast-like synoviocytes via receptor-mediated mechanisms. Microneedle-mediated delivery offers a minimally invasive approach, improves patient compliance, and bypasses first-pass metabolism [86].

However, these promising outcomes are predominantly derived from small-animal models and have not consistently translated into clinical success. This limitation can be attributed to differences between animal models and human disease pathology, heterogeneity of the synovial microenvironment in patients, and challenges in achieving reproducible large-scale manufacturing. In addition, concerns about long-term safety, immunogenicity, and regulatory uncertainties further impede clinical translation, highlighting the need for more predictive models and standardized evaluation strategies.

Regulatory, Manufacturing, and Safety Barriers

The foremost challenge remains scaling laboratory formulations to clinical-grade production. Quality control has been made more difficult by batch-to-batch differences in particle size, drug loading, and release kinetics. The usual sterilization methods, such as heat, radiation, and filtration, have the potential to alter nanostructural integrity, while there is little information available on long-term biodistribution & immuno- genicity [87]. At present, regulatory authorities are treating nanomedicines on a case-by-case basis due to the lack of standardized guidelines, resulting in delays in approvals & discouraging industry investment. Moreover, high costs of production and storage make it even harder to access the products [88,89].

Emerging Technological Trends

The incorporation of AI-driven formulation design enables the prediction of optimal lipid/polymer combinations and in vivo drug-release profiles. Nanosystems that combine lipids, polymers, and inorganic materials not only receive better support but also can release their contents in a controlled manner when pH, temperature, or the presence of certain species changes [90,91]. The combination of different delivery methods, including the use of nanocarriers for small-molecule drugs together with gene or stem-cell therapy, is promising not only for disease modulation but also for tissue restoration. The use of real-time imaging and theranostic nanocarriers would help monitor treatments and adjust drug doses for individual patients [92].

Strategic Roadmap and Future Outlook

The deviation from the use of distributor characterization protocols, validated animal models, and single-center preclinical consortia, which will yield unrepeatable data on both efficacy and safety, will be the main factor determining the success of translation. The medical research community, regulators, and pharmaceutical companies need to work together to enable the use of quality-by-design methods in drug development and to fast-track approval [93,94]. Moreover, biomarker-assisted patient stratification in early-phase trials could enhance the

treatment's effectiveness. The combination of nanotechnology, regenerative medicine, and AI-driven analytics will undoubtedly be one of the most critical aspects of RA management, enabling a shift from merely controlling symptoms to personalized, disease-modifying, and even regenerative therapies [95,96].

CONCLUSION

Rheumatoid arthritis remains a challenging autoimmune disease to manage, with conventional therapies limited by systemic toxicity, poor tissue specificity, and suboptimal long-term outcomes. Nanocarrier-based drug delivery systems, including liposomes, polymeric nanoparticles, solid lipid nanoparticles, and hybrid platforms, have demonstrated significant potential to enhance synovial targeting, improve pharmacokinetics, and prolong therapeutic effects while minimizing adverse reactions. These systems offer a promising strategy to overcome key limitations of conventional treatments and enable more precise, site-specific therapy.

However, despite encouraging preclinical outcomes, clinical translation remains constrained by formulation complexity, scale-up challenges, long-term safety concerns, and the lack of standardized regulatory frameworks. Addressing these barriers requires not only improved experimental models and harmonized regulatory guidelines but also robust strategies to ensure reproducibility and consistency in manufacturing.

In this context, emerging approaches such as artificial intelligence (AI)-driven formulation design and Quality by Design (QbD) frameworks are expected to play a critical role. AI can facilitate the prediction of optimal nanocarrier compositions, drug-release behavior, and in vivo performance, thereby reducing empirical trial-and-error. Simultaneously, QbD enables systematic identification and control of critical material attributes and process parameters, ensuring batch-to-batch reproducibility and scalable manufacturing. The integration of these approaches has the potential to bridge the gap between laboratory innovation and clinical application significantly.

Future research should also emphasize biomarker-guided patient stratification, multifunctional and stimuli-responsive nanocarriers, and the integration of gene or regenerative therapies. Together, these advancements will support the transition from conventional disease management toward precision and personalized medicine in rheumatoid arthritis.

In summary, while targeted nanocarriers represent a highly promising platform, their successful clinical adoption will depend on the convergence of advanced design strategies, standardized manufacturing processes, and translationally relevant validation models. Such integrated efforts will be essential to realize the full potential of nanomedicine in delivering safer, more effective, and patient-specific therapeutic solutions for rheumatoid arthritis.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Shishupal Kumar, Muneesh Kanaujaya, and Ashish Singh Chauhan contributed to the conceptualization of the review, conducted the formal analysis and methodology development, and prepared the original draft and subsequent revisions. Pallavi Chand and Vikash Jakhmola contributed to the investigation and visualization of the content, as well as to the review and editing of the manuscript. Pallavi Chand and Ashish Singh Chauhan further contributed to the conceptualization and validation of the scientific content. In contrast, Pallavi Chand and Vikash Jakhmola provided overall supervision and additional support in drafting, reviewing, and editing the final version. All authors read and approved the final manuscript.

ABBREVIATIONS

RA: Rheumatoid arthritis; NSAIDs: Nonsteroidal anti-inflammatory drugs; COX: Cyclooxygenase; csDMARDs: Conventional synthetic disease-modifying antirheumatic drugs; DMARDs: Disease-modifying antirheumatic drugs; TNF: Tumor necrosis factor; IL: Interleukin; JAK: Janus kinase; FLSs: Fibroblast-like synoviocytes; MMPs: Matrix metalloproteinases; ADAMTs: A disintegrin and metalloproteinase with thrombospondin motifs; RF: Rheumatoid factor; ACPAs: Anti-citrullinated protein antibodies; RANKL: Receptor activator of nuclear factor kappa-B ligand; GM-CSF: Granulocyte-macrophage colony-stimulating factor; MIF: Macrophage migration inhibitory factor; PSA: Psoriatic arthritis; HLA: Human leukocyte antigen; PTPN22: Protein tyrosine phosphatase non-receptor type 22; STAT4: Signal transducer and activator of transcription 4; IFN-γ: Interferon gamma; MSU: Monosodium urate; NLRP3: NOD-

like receptor family pyrin domain-containing 3; DAMPs: Danger-associated molecular patterns; miRNA: MicroRNA; MBDA: Multi-biomarker disease activity; CRP: C-reactive protein; SAA: Serum amyloid A; VCAM-1: Vascular cell adhesion molecule-1; VEGF-A: Vascular endothelial growth factor A; EGF: Epidermal growth factor; MMP-1 / MMP-3: Matrix metalloproteinases 1 and 3; CTX: C-terminal telopeptide of type I collagen; COMP: Cartilage oligomeric matrix protein; AI: Artificial intelligence; ROS: Reactive oxygen species; AS: Ankylosing spondylitis; SPA: Spondylarthritis; MTX: Methotrexate; ADA: Anti-drug antibodies; PML: Progressive multifocal leukoencephalopathy; CVD: Cardiovascular disease; PEG: Polyethylene glycol; PEGylation: Polyethylene glycol surface modification; SLNs: Solid lipid nanoparticles; NLCs: Nanostructured lipid carriers; CHS: Chondroitin sulfate; LEF: Leflunomide; RSV: Resveratrol; Dex: Dexamethasone; Cur: Curcumin; FLA: Fluocinolone acetonide; PHs: Hyalurosomes; DS: Diclofenac sodium; CEL: Celecoxib; PLGA: Poly(lactic-co-glycolic acid); DCFLPs: Dexamethasone–Curcumin folate lipid–polymer hybrid nanoparticles; EE: Encapsulation efficiency; PDI: Polydispersity index; ZP: Zeta potential; QbD: Quality by Design; EPR: Enhanced permeability and retention; ELVIS: Extravasation through leaky vasculature and inflammatory cell-mediated sequestration; FDA: Food and Drug Administration; EMA: European Medicines Agency; NR: Not reported.

REFERENCES

[1] Díaz-González F, Hernández-Hernández MV. Rheumatoid arthritis. *Medicina Clínica (English Edition)*, **161**, 533–42 (2023) https://doi.org/10.1016/J.MEDCLE.2023.07.008

[2] An X, Yang J, Cui X, Zhao J, Jiang C, Tang M, Dong Y, Lin L, Li H, Wang F. Advances in local drug delivery technologies for improved rheumatoid arthritis therapy. *Adv. Drug Deliv. Rev.*, **209**, 115325 (2024) https://doi.org/10.1016/J.ADDR.2024.115325

[3] Chelliah R, Rubab M, Vijayalakshmi S, Karuvelan M, Barathikannan K, Oh DH. Liposomes for drug delivery: Classification, therapeutic applications, and limitations. *Next Nanotechnology*, **8**, 100209 (2025) https://doi.org/10.1016/J.NXNANO.2025.100209

[4] Sultana A, Zare M, Thomas V, Kumar TSS, Ramakrishna S. Nano-based drug delivery systems: Conventional drug delivery routes, recent developments and future prospects. *Med. Drug Discov.*, **15**, 100134 (2022) https://doi.org/10.1016/J.MEDIDD.2022.100134

[5] Kurul F, Turkmen H, Cetin AE, Topkaya SN. Nanomedicine: How nanomaterials are transforming drug delivery, bio-imaging, and diagnosis. *Next Nanotechnology*, **7**, 100129 (2025) https://doi.org/10.1016/J.NXNANO.2024.100129

[6] Islam S, Ahmed MMS, Islam MA, Hossain N, Chowdhury MA. Advances in nanoparticles in targeted drug delivery: A review. *Results in Surfaces and Interfaces*, **19**, 100529 (2025) https://doi.org/10.1016/J.RSURFI.2025.100529

[7] Dixit T, Vaidya A, Ravindran S. Polymeric nanoparticles-based targeted delivery of drugs and bioactive compounds for arthritis management. *Future Sci. OA*, **11** (2025) https://doi.org/10.1080/20565623.2025.2467591

[8] Di Matteo A, Bathon JM, Emery P. Rheumatoid arthritis. *The Lancet*, **402**, 2019–33 (2023) https://doi.org/10.1016/S0140-6736(23)01525-8

[9] Dai F, Cai Y, Yang S, Zhang J, Dai Y. Global burden of gallbladder and biliary diseases (1990–2021) with healthcare workforce analysis and projections to 2035. *BMC Gastroenterology*, **25**, 249 (2025) https://doi.org/10.1186/S12876-025-03842-X

[10] Su QY, Yang L, Qi XY, Wang MY, Cheng JW, Niu H, Zhang SX. Global, regional, and national burdens of rheumatoid arthritis among people aged 60 years and older from 1990 to 2021: a trend analysis for the Global Burden of Disease Study 2021. *Front. Public Health*, **13**, 1527680 (2025) https://doi.org/10.3389/FPUBH.2025.1527680/BIBTEX

[11] Black RJ, Cross M, Haile LM, Culbreth GT, Steinmetz JD, Hagins H et al. Global, regional, and national burden of rheumatoid arthritis, 1990–2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. *Lancet Rheumatol.*, **5**, e594–610 (2023) https://doi.org/10.1016/S2665-9913(23)00211-4

[12] Cao M, Li C, Li M, Lu K, Wu C, Wang J et al. Prevalence and incidence of rheumatoid arthritis in urban China: A national population-based study. *Int. J. Rheum. Dis.*, **28** (2025) https://doi.org/10.1111/1756-185X.70184

[13] Mousavi SE, Nejadghaderi SA, Khabbazi A, Alizadeh M, Sullman MJM, Kaufman JS, Collins GS, Safiri S. The burden of rheumatoid arthritis in the Middle East and North Africa region, 1990–2019. *Sci. Rep.*, **12**, 19297 (2022) https://doi.org/10.1038/S41598-022-22310-0

[14] Dowman B, Campbell RM, Zgaga L, Adeloye D, Chan KY. Estimating the burden of rheumatoid arthritis in Africa: A systematic analysis. *J. Glob. Health*, **2**, 020406 (2012) https://doi.org/10.7189/JOGH.02.020406

[15] Germano JL, Reis-Pardal J, Tonin FS, Pontarolo R, Melchiors AC, Fernandez-Llimos F. Prevalence of rheumatoid arthritis in South America: A systematic review and meta-analysis. *Ciencia e Saude Coletiva*, **26**, 5371–82 (2021) https://doi.org/10.1590/1413-812320212611.3.05152020

[16] Bakri FG, Mollin M, Beaumel S, Vigne B, Roux-Buisson N, Al-Wahadneh AM, Alzyoud RM et al. Second report of chronic granulomatous disease in Jordan: Clinical and genetic description of 31 patients from 21 different families, including families from Libya and Iraq. *Front. Immunol.*, **12**, 639226 (2021) https://doi.org/10.3389/FIMMU.2021.639226/FULL

[17] Tran CN, Lundy SK, Fox DA. Synovial biology and T cells in rheumatoid arthritis. *Pathophysiology: The Official Journal of the International Society for Pathophysiology / ISP*, **12**, 183 (2005) https://doi.org/10.1016/J.PATHOPHYS.2005.07.005

[18] Hao G, Han S, Xiao Z, Shen J, Zhao Y, Hao Q. Synovial mast cells and osteoarthritis: Current understandings and future perspectives. *Heliyon*, **10**, e41003 (2024) https://doi.org/10.1016/J.HELIYON.2024.E41003

[19] Yuan F, Quan L Dong, Cui L, Goldring SR, Wang D. Development of macromolecular prodrug for rheumatoid arthritis. *Adv. Drug Deliv. Rev.*, **64**, 1205–19 (2012) https://doi.org/10.1016/j.addr.2012.03.006

[20] Wu J. The enhanced permeability and retention (EPR) effect: The significance of the concept and methods to enhance its application. *Journal of Personalized Medicine*, **11**, 771 (2021) https://doi.org/10.3390/jpm11080771

[21] Nasra S, Bhatia D, Kumar A. Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. *Nanoscale Adv.*, **4**, 3479–94 (2022) https://doi.org/10.1039/d2na00229a

[22] Damerau A, Gaber T. Modeling rheumatoid arthritis in vitro: From experimental feasibility to physiological proximity. *International Journal of Molecular Sciences*, **21**, 7916 (2020) https://doi.org/10.3390/IJMS21217916

[23] Hitchon CA, El-Gabalawy HS. The synovium in rheumatoid arthritis. *Open Rheumatol. J.*, **5**, 107 (2011) https://doi.org/10.2174/1874312901105010107

[24] Bustamante MF, Garcia-Carbonell R, Whisenant KD, Guma M. Fibroblast-like synoviocyte metabolism in the pathogenesis of rheumatoid arthritis. *Arthritis Research & Therapy*, **19**, 110 (2017) https://doi.org/10.1186/S13075-017-1303-3

[25] Bhowmik S, Ghosh R, Dev A. Advanced disease-responsive materials as intelligent drug delivery systems for rheumatoid arthritis. *J. Drug Deliv. Sci. Technol.*, **115**, 107787 (2026) https://doi.org/10.1016/j.jddst.2025.107787

[26] Bai L, Su P. Nanocarrier-based delivery of siRNA therapeutics in rheumatoid arthritis: Immune mechanisms and translational perspectives. *Front. Immunol.*, **16**, 1718256 (2025) https://doi.org/10.3389/fimmu.2025.1718256

[27] Wang Q, Qin X, Fang J, Sun X. Nanomedicines for the treatment of rheumatoid arthritis: State of art and potential therapeutic strategies. *Acta Pharm. Sin. B*, **11**, 1158–74 (2021) https://doi.org/10.1016/j.apsb.2021.03.013

[28] Chauhan K, Jandu JS, Brent LH, Al-Dhahir MA. Rheumatoid arthritis. *Rosen and Barkin's 5-Minute Emergency Medicine Consult: Fifth Edition* (2023) https://doi.org/10.1017/chol9780521332866.074

[29] Kim M, Shin M, Zhao Y, Ghosh M, Son YO. Transformative impact of nanocarrier-mediated drug delivery: Overcoming biological barriers and expanding therapeutic horizons. *Small Science*, **4**, 2400280 (2024) https://doi.org/10.1002/SMSC.202400280

[30] Ben Mrid R, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. *Biomedicine & Pharmacotherapy*, **151**, 113126 (2022) https://doi.org/10.1016/J.BIOPHA.2022.113126

[31] Haley RM, von Recum HA. Localized and targeted delivery of NSAIDs for treatment of inflammation: A review. *Exp. Biol. Med.*, **244**, 433–44 (2019) https://doi.org/10.1177/1535370218787770

[32] Butoescu N, Seemayer CA, Palmer G, Guerne PA, Gabay C, Doelker E, Jordan O. Magnetically retainable microparticles for drug delivery to the joint: Efficacy studies in an antigen-induced arthritis model in mice. *Arthritis Research & Therapy*, **11**, R72 (2009) https://doi.org/10.1186/AR2701

[33] Infante M, Padilla N, Alejandro R, Caprio M, Della-morte D, Fabbri A, Ricordi C. Diabetes-modifying antirheumatic drugs: The roles of DMARDs as glucose-lowering agents. *Medicina*, **58**, 571 (2022) https://doi.org/10.3390/MEDICINA58050571

[34] Aljabri A, Soliman GM, Ramadan YN, Medhat MA, Hetta HF. Biosimilars versus biological therapy in inflammatory bowel disease: Challenges and targeting strategies using drug delivery systems. *Clinical and Experimental Medicine*, **25**, 107 (2025) https://doi.org/10.1007/S10238-025-01558-6

[35] Herrera-deGuise C, Serra-Ruiz X, Lastiri E, Borruel N. JAK inhibitors: A new dawn for oral therapies in inflammatory bowel diseases. *Front. Med. (Lausanne)*, **10**, 1089099 (2023) https://doi.org/10.3389/FMED.2023.1089099/BIBTEX

[36] Garcia-Melendo C, Cubiró X, Puig L. Janus kinase inhibitors in dermatology: Part 1 — general considerations and applications in vitiligo and alopecia areata. *Actas Dermosifiliogr.*, **112**, 503–15 (2021) https://doi.org/10.1016/J.ADENGL.2021.03.012

[37] Ezike TC, Okpala US, Onoja UL, Nwike CP, Ezeako EC, Okpara OJ, Okoroafor CC, Eze SC, Kalu OL, Odoh EC, Nwadike UG, Ogbodo JO, Umeh BU, Ossai EC, Nwanguma BC. Advances in drug delivery systems, challenges and future directions. *Heliyon*, **9** (2023) https://doi.org/10.1016/J.HELIYON.2023.E17488

[38] Colella F, Garcia JP, Sorbona M, Lolli A, Antunes B, D'Atri D, Barré FPY, Oieni J, Vainieri ML, Zerrillo L, Capar S, Häckel S, Cai Y, Creemers LB. Drug delivery in intervertebral disc degeneration and osteoarthritis: Selecting the optimal platform for the delivery of disease-modifying agents. *Journal of*

Controlled Release, **328**, 985–99 (2020) https://doi.org/10.1016/J.JCONREL.2020.08.041

[39] Hua S, de Matos MBC, Metselaar JM, Storm G. Current trends and challenges in the clinical translation of nanoparticulate nanomedicines: Pathways for translational development and commercialization. *Front. Pharmacol.*, **9**, 790 (2018) https://doi.org/10.3389/FPHAR.2018.00790/EPUB

[40] Andretto V, Dusi S, Zilio S, Repellin M, Kryza D, Ugel S, Lollo G. Tackling TNF-α in autoinflammatory disorders and autoimmune diseases: From conventional to cutting edge in biologics and RNA-based nanomedicines. *Adv. Drug Deliv. Rev.*, **201**, 115080 (2023) https://doi.org/10.1016/J.ADDR.2023.115080

[41] Jang DI, Lee AH, Shin HY, Song HR, Park JH, Kang TB, Lee SR, Yang SH. The role of tumor necrosis factor alpha (TNF-α) in autoimmune disease and current TNF-α inhibitors in therapeutics. *International Journal of Molecular Sciences*, **22**, 2719 (2021) https://doi.org/10.3390/IJMS22052719

[42] Evangelatos G, Bamias G, Kitas GD, Kollias G, Sfikakis PP. The second decade of anti-TNF-a therapy in clinical practice: New lessons and future directions in the COVID-19 era. *Rheumatology International*, **42**, 1493–511 (2022) https://doi.org/10.1007/S00296-022-05136-X

[43] Chen Y, Zhang G, Yang Y, Zhang S, Jiang H, Tian K, Arenbaoligao, Chen D. The treatment of inflammatory bowel disease with monoclonal antibodies in Asia. *Biomedicine & Pharmacotherapy*, **157**, 114081 (2023) https://doi.org/10.1016/J.BIOPHA.2022.114081

[44] Tanaka Y. Rheumatoid arthritis. *Inflammation and Regeneration*, **40**, 20 (2020) https://doi.org/10.1186/S41232-020-00133-8

[45] McInnes IB, Schett G. Pathogenetic insights from the treatment of rheumatoid arthritis. *Lancet.*, **389**, 2328–37 (2017) https://doi.org/10.1016/s0140-6736(17)31472-1

[46] Mayence A, Eynde JJ Vanden. Baricitinib: A 2018 novel FDA-approved small molecule inhibiting Janus kinases. *Pharmaceuticals*, **12**, 37 (2019) https://doi.org/10.3390/PH12010037

[47] Shi JG, Chen X, Lee F, Emm T, Scherle PA, Lo Y, Punwani N, Williams WV, Yeleswaram S. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. *J. Clin. Pharmacol.*, **54**, 1354–61 (2014) https://doi.org/10.1002/jcph.354

[48] Tanaka Y. Recent progress in treatments of rheumatoid arthritis: An overview of developments in biologics and small molecules, and remaining unmet needs. *Rheumatology (Oxford)*, **60**, vi12 (2021) https://doi.org/10.1093/RHEUMATOLOGY/KEAB609

[49] Kiełbowski K, Plewa P, Bratborska AW, Bakinowska E, Pawlik A. JAK inhibitors in rheumatoid arthritis: Immunomodulatory properties and clinical efficacy. *International Journal of Molecular Sciences*, **25**, 8327 (2024) https://doi.org/10.3390/IJMS25158327

[50] Kurul F, Turkmen H, Cetin AE, Topkaya SN. Nanomedicine: How nanomaterials are transforming drug delivery, bio-imaging, and diagnosis. *Next Nanotechnology*, **7**, 100129 (2025) https://doi.org/10.1016/J.NXNANO.2024.100129

[51] Mirkin CA, Langer R, Mrksich M, Margolin AA, Petrosko SH, Artzi N. Blueprints for better drugs: The structural revolution in nanomedicine. *ACS Nano*, **19**, 18889–901 (2025) https://doi.org/10.1021/acsnano.5c06380

[52] Chen M, Daddy KA, Xiao Y, Ping Q, Zong L. Advanced nanomedicine for rheumatoid arthritis treatment: Focus on active targeting. *Expert Opin. Drug Deliv.*, **14**, 1141–4 (2017) https://doi.org/10.1080/17425247.2017.1372746

[53] Chuang SY, Lin CH, Huang TH, Fang JY. Lipid-based nanoparticles as a potential delivery approach in the treatment of rheumatoid arthritis. *Nanomaterials*, **8**, 42 (2018) https://doi.org/10.3390/nano8010042

[54] Anita C, Munira M, Mural Q, Shaily L. Topical nanocarriers for management of rheumatoid arthritis: A review. *Biomedicine & Pharmacotherapy*, **141**, 111880 (2021) https://doi.org/10.1016/j.biopha.2021.111880

[55] Dejeu IL, Vicaș LG, Marian E, Ganea M, Frenț OD, Maghiar PB, Bodea FI, Dejeu GE. Innovative approaches to enhancing the biomedical properties of liposomes. *Pharmaceutics*, **16**, 1525 (2024) https://doi.org/10.3390/PHARMACEUTICS16121525

[56] Guimarães D, Noro J, Loureiro A, Lager F, Renault G, Cavaco-Paulo A, Nogueira E. Increased encapsulation efficiency of methotrexate in liposomes for rheumatoid arthritis therapy. *Biomedicines*, **8**, 630 (2020) https://doi.org/10.3390/biomedicines8120630

[57] Sahu A, Rathee S, Saraf S, Raikwar S, Das Bidla P, Pawar RS, Jain SK. Development and characterization of leflunomide and resveratrol loaded nanostructured lipid carrier based in-situ hydrogel system for effective management of rheumatoid arthritis. *Journal of Pharmaceutical Innovation*, **20**, 107 (2025) https://doi.org/10.1007/s12247-025-09976-5

[58] Panchal E, Yadav SK, Jain N, Chauhan M, Sharma A. Design and optimization of folate-targeted lipid-polymer hybrid nanoparticles co-encapsulating dexamethasone and curcumin for synergistic anti-inflammatory efficacy in rheumatoid arthritis. *Journal of Applied Pharmaceutical Research*, **13**, 91–113 (2025) https://doi.org/10.69857/joapr.v13i5.1176

[59] ELhabal SF, El-Nabarawi MA, Hassanin SO, Hassan FE, Abbas SS, Gebril SM, Albash R. Transdermal fluocinolone acetonide loaded decorated hyalurosomes cellulose acetate/polycaprolactone nanofibers mitigated Freund's adjuvant-induced rheumatoid arthritis in rats. *Journal of Pharmaceutical Investigation*, **55**, 113–32 (2024) https://doi.org/10.1007/s40005-024-00693-8

[60] Manca ML, Lattuada D, Valenti D, Marelli O, Corradini C, Fernàndez-Busquets X, Zaru M, Maccioni AM, Fadda AM, Manconi M. Potential therapeutic effect of curcumin loaded hyalurosomes against inflammatory and oxidative processes involved in the pathogenesis of rheumatoid arthritis: The use of fibroblast-like synovial cells cultured in synovial fluid. *European Journal of Pharmaceutics and Biopharmaceutics*, **136**, 84–92 (2019) https://doi.org/10.1016/j.ejpb.2019.01.012

[61] Chu B, Chen D, Ma S, Yang Y, Shang F, Lv W, Li Y. Novel poly(lactic-co-glycolic acid) nanoliposome-encapsulated diclofenac sodium and celecoxib enable long-lasting synergistic treatment of osteoarthritis. *J. Biomater. Appl.*, **39**, 221–34 (2024) https://doi.org/10.1177/08853282241258311

[62] Li Y, Chen Q, Wang T, Ji Z, Regmi S, Tong H, Ju J, Wang A. Advances in microneedle-based drug delivery system for metabolic diseases: Structural considerations, design strategies, and future perspectives. *Journal of Nanobiotechnology*, **23**, 350 (2025) https://doi.org/10.1186/S12951-025-03432-9

[63] Guillot AJ, Cordeiro AS, Donnelly RF, Montesinos MC, Garrigues TM, Melero A. Microneedle-based delivery: An overview of current applications and trends. *Pharmaceutics*, **12**, 569 (2020) https://doi.org/10.3390/PHARMACEUTICS12060569

[64] Makvandi P, Kirkby M, Hutton ARJ, Shabani M, Yiu CKY, Baghbantaraghdari Z, Jamaledin R, Carlotti M, Mazzolai B, Mattoli V, Donnelly RF. Engineering microneedle patches for improved penetration: Analysis, skin models and factors affecting needle insertion. *Nano-Micro Letters*, **13**, 93 (2021) https://doi.org/10.1007/s40820-021-00611-9

[65] Abdullah KM, Sharma G, Singh AP, Siddiqui JA. Nanomedicine in cancer therapeutics: Current perspectives from bench to bedside. *Molecular Cancer*, **24**, 169 (2025) https://doi.org/10.1186/S12943-025-02368-W

[66] Mohan N, Nair RPAN, Narayanasamy D. Nanoparticle-integrated transdermal patches: A platform for next-generation drug delivery. *Drug Dev. Res.*, **86**, e70164 (2025) https://doi.org/10.1002/DDR.70164

[67] Elumalai K, Srinivasan S, Shanmugam A. Review of the efficacy of nanoparticle-based drug delivery systems for cancer treatment. *Biomedical Technology*, **5**, 109–22 (2024) https://doi.org/10.1016/j.bmt.2023.09.001

[68] Addissouky T. Nanocarrier-mediated drug delivery in rheumatoid arthritis: Overcoming therapeutic limitations through targeted approaches. *Clinical Orthopaedics and Trauma Care*, **6**, 1–8 (2024) https://doi.org/10.31579/2694-0248/108

[69] Mühlebach S. Regulatory challenges of nanomedicines and their follow-on versions: A generic or similar approach? *Adv. Drug Deliv. Rev.*, **131**, 122–31 (2018) https://doi.org/10.1016/J.ADDR.2018.06.024

[70] Bi Y, Xie S, Li Z, Dong S, Teng L. Precise nanoscale fabrication technologies, the "last mile" of medicinal development. *Acta Pharm. Sin. B*, **15**, 2372–401 (2025) https://doi.org/10.1016/j.apsb.2025.03.040

[71] Hussian T, Nagar L, Saini A, Gulati N, Gupta VK, Dua G, Tripathy S, Dureja H. Regulatory requirements and clinical trials for nanotechnology-based drug delivery systems for the management of COPD. *Nanotechnology-Based Innovations in Chronic Obstructive Pulmonary Disease (COPD) Treatment and Management*, 443–63 (2026) https://doi.org/10.1016/B978-0-443-43946-9.00024-0

[72] Huang Y, Guo X, Wu Y, Chen X, Feng L, Xie N, Shen G. Nanotechnology's frontier in combatting infectious and inflammatory diseases: Prevention and treatment. *Signal Transduction and Targeted Therapy*, **9**, 34 (2024) https://doi.org/10.1038/s41392-024-01745-z

[73] Su S, Kang PM. Recent advances in nanocarrier-assisted therapeutics delivery systems. *Pharmaceutics*, **12**, 837 (2020) https://doi.org/10.3390/PHARMACEUTICS12090837

[74] Crintea A, Dutu AG, Sovrea A, Constantin AM, Samasca G, Masalar AL, Ifju B, Linga E, Neamti L, Tranca RA, Fekete Z, Silaghi CN, Craciun AM. Nanocarriers for drug delivery: An overview with emphasis on vitamin D and K transportation. *Nanomaterials*, **12**, 1376 (2022) https://doi.org/10.3390/NANO12081376

[75] Zhao L, Huang J, Fan Y, Li J, You T, He S, Xiao G, Chen D. Exploration of CRISPR/Cas9-based gene editing as therapy for osteoarthritis. *Ann. Rheum. Dis.*, **78**, 676–82 (2019) https://doi.org/10.1136/annrheumdis-2018-214724

[76] Wang S, Wang Y, Chen Q. Nanotechnology-driven strategies for gene therapy of arthritis. *Mater. Today Bio*, **35**, 102301 (2025)https://doi.org/10.1016/J.MTBIO.2025.102301

[77] Wen J, Li H, Dai H, Hua S, Long X, Li H, Ivanovski S, Xu C. Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management. *Mater. Today Bio*, **19**, 100597 (2023) https://doi.org/10.1016/J.MTBIO.2023.100597

[78] Song P, Yang C, Thomsen JS, Dagnæs-Hansen F, Jakobsen M, Brüel A, Deleuran B, Kjems J. Lipidoid-siRNA nanoparticle-mediated IL-1β gene silencing for systemic arthritis therapy in a mouse model. *Molecular Therapy*, **27**, 1424–35 (2019) https://doi.org/10.1016/j.ymthe.2019.05.002

[79] Han X, Liao R, Li X, Zhang C, Huo S, Qin L, Xiong Y, He T, Xiao G, Zhang T. Mesenchymal stem cells in treating human diseases: Molecular mechanisms and clinical studies. *Signal Transduction and Targeted Therapy*, **10**, 262 (2025) https://doi.org/10.1038/s41392-025-02313-9

[80] Mahla RS. Stem cells applications in regenerative medicine and disease therapeutics. *Int. J. Cell Biol.*, **2016**, 6940283 (2016) https://doi.org/10.1155/2016/6940283

[81] Trapana J, Weinerman J, Lee D, Sedani A, Constantinescu D, Best TM, Hornicek FJ, Hare JM. Cell-based therapy in the treatment of musculoskeletal diseases. *Stem Cells Transl. Med.*, **13**, 959–78 (2024) https://doi.org/10.1093/STCLTM/SZAE049

[82] Garg P, Singhal S, Kulkarni P, Horne D, Malhotra J, Salgia R, Singhal SS. Advances in non-small cell lung cancer: Current insights and future directions. *Journal of Clinical Medicine*, **13**, 4189 (2024) https://doi.org/10.3390/JCM13144189

[83] Kim M, Shin M, Zhao Y, Ghosh M, Son YO. Transformative impact of nanocarrier-mediated drug delivery: Overcoming biological barriers and expanding therapeutic horizons. *Small Science*, **4**, 2400280 (2024) https://doi.org/10.1002/smsc.202400280

[84] Xu Z, Xie Y, Chen W, Deng W. Nanocarrier-based systems for targeted delivery: Current challenges and future directions. *MedComm (Beijing)*, **6**, e70337 (2025) https://doi.org/10.1002/mco2.70337

[85] Basak A, Ghosh S, Ganguly D, Garain S, Ghosh R, Choudhury A, Deka H, Sarmah J. Current trends and future perspectives of natural polymer loaded nanoparticle based drug delivery system for the management of inflammatory bowel disease. *Journal of Applied Pharmaceutical Research, 11*(4), 01-09 (2023) https://doi.org/10.18231/j.joapr.2023.11.4.1.9

[86] Rahman MM, Islam MR, Akash S, Harun-Or-Rashid M, Ray TK, Rahaman MS, Islam M, Anika F, Hosain MK, Aovi FI, Hemeg HA, Rauf A, Wilairatana P. Recent advancements of nanoparticles application in cancer and neurodegenerative disorders: At a glance. *Biomedicine & Pharmacotherapy*, **153**, 113305 (2022) https://doi.org/10.1016/J.BIOPHA.2022.113305

[87] Jiang Y, Zhou Y, Tian Y, Nabavi N, Ashrafizadeh M, Conde J, Li Z, Guo L. Conductive polymers in smart wound healing: From bioelectric stimulation to regenerative therapies. *Mater. Today Bio*, **34**, 102114 (2025) https://doi.org/10.1016/J.MTBIO.2025.102114

[88] Zahmanova G, Aljabali AAA, Takova K, Minkov G, Tambuwala MM, Minkov I, Lomonossoff GP. Green biologics: Harnessing the power of plants to produce pharmaceuticals. *International Journal of Molecular Sciences*, **24**, 17575 (2023) https://doi.org/10.3390/IJMS242417575

[89] Sairam AB, Sanmugam A, Pushparaj A, Mahesh Kumar G, Sundarapandian N, Balaji S, Nallal M, Park KH. Toxicity of polymeric nanodrugs as drug carriers. *ACS Chemical Health & Safety*, **30**, 236–50 (2023) https://doi.org/10.1021/ACS.CHAS.3C00008

[90] Dalbanjan NP, Korgaonkar K, Eelager MP, Gonal BN, Kadapure AJ, Arakera SB, Kumar SKP. In-silico strategies in nano-drug design: Bridging nanomaterials and pharmacological applications. *Nano TransMed*, **4**, 100091 (2025) https://doi.org/10.1016/J.NTM.2025.100091

[91] Bae H, Ji H, Konstantinov K, Sluyter R, Ariga K, Kim YH, Kim JH. Artificial intelligence-driven nanoarchitectonics for smart targeted drug delivery. *Advanced Materials*, **37**, e10239 (2025) https://doi.org/10.1002/ADMA.202510239

[92] Siddique S, Chow JCL. Recent advances in functionalized nanoparticles in cancer theranostics. *Nanomaterials*, **12**, 2826 (2022) https://doi.org/10.3390/NANO12162826

[93] Sangshetti JN, Deshpande M, Zaheer Z, Shinde DB, Arote R. Quality by design approach: Regulatory need. *Arabian Journal of Chemistry*, **10**, S3412–25 (2017) https://doi.org/10.1016/J.ARABJC.2014.01.025

[94] Dienstmann R, Rodon J, Tabernero J. Biomarker-driven patient selection for early clinical trials. *Curr. Opin. Oncol.*, **25**, 305–12 (2013) https://doi.org/10.1097/CCO.0B013E32835FF3CB

[95] Davis KD, Aghaeepour N, Ahn AH, Angst MS, Borsook D, Brenton A et al. Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: Challenges and opportunities. *Nature Reviews Neurology*, **16**, 381–400 (2020) https://doi.org/10.1038/s41582-020-0362-2

[96] Hassan YM, Wanas A, Ali AA, El-Sayed WM. Integrating artificial intelligence with nanodiagnostics for early detection and precision management of neurodegenerative diseases. *Journal of Nanobiotechnology*, **23**, 668 (2025) https://doi.org/10.1186/S12951-025-03719-X