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Review Article

Deep-insights: Nanoengineered gel-based localized drug delivery for arthritis management

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ABSTRACT

Arthritis is an inflammatory joint disorder that progressively impairs function and diminishes quality of life. Conventional therapies often prove ineffective, as oral administration lacks specificity, resulting in off-target side effects like hepatotoxicity and GIT-related issues. Intravenous administration causes systemic side effects. The characteristic joint-localized symptoms such as pain, stiffness, and inflammation make the localized drug delivery suitable for managing arthritis. Topical/transdermal/intra-articular routes have become viable options for drug delivery in treating arthritis. However, challenges with those localized drug delivery routes include skin barrier and cartilage impermeability. Additionally, conventional intra-articular drug delivery also leads to rapid clearance of drugs from the synovial joint tissue. To circumvent these limitations, researchers have developed nanocarriers that enhance drug permeability through skin and cartilage, influencing localized action. Gel-based nanoengineered therapy employs a gel matrix to incorporate the drug-encapsulated nanocarriers. This approach combines the benefits of gels and nanocarriers to enhance therapeutic effects and improve patient compliance. This review emphasizes deep insights into drug delivery using diverse gel-based novel nanocarriers, exploring their various applications embedded in hyaluronic acid (biopolymer)–based gels, carbopol-based gels, and others. Furthermore, this review discusses the influence of nanocarrier pharmacokinetics on the localization and therapeutic manipulation of macrophages mediated by nanocarriers. The ELVIS (extravasation through leaky vasculature and inflammatory cell-mediated sequestration) effect associated with arthritis is advantageous in drug delivery. Simply put, the ELVIS effect refers to the extravasation of nanocarriers through leaky vasculatures, which finally results in the accumulation of nanocarriers in the joint cavity.

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1. Introduction

Arthritis is an autoimmune disease affecting many people worldwide with joint disability. It is a chronic joint-inflammatory disorder characterized by joint pain, swelling, and stiffness. It is instigated that cartilage degradation and bone erosion occur mainly due to the triggering of pro-inflammatory cytokines, which eventually lead to functional disability and decrease the quality of life [1]. The body's immune system generates pro-inflammatory cytokines, a group of signaling molecules that activate in response to infections or injuries. Subsequently, these pro-inflammatory cytokines diffuse from the synovial fluid into the cartilage. It is believed that these cytokines have the potential to activate the enzymes responsible for breaking down the extracellular matrix (ECM) of the cartilage. This activation further leads to the loss of proteoglycans and collagen, the cartilage's main components. Over time, this can cause the cartilage to become thinner and weaker, leading to joint pain and stiffness [2]. The most common types include osteoarthritis (OA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), fibromyalgia, and gouty arthritis. Two types of arthritis related to joint disorders are RA and OA, which are discussed in detail in this review.

2. Rheumatoid arthritis (RA)

RA is a chronic, systemic, inflammatory, and T-cell-mediated autoimmune disease. In the people affected with RA, almost 50% of T-cells are more prevalent in the synovial fluid of hand and knee joints, which makes them even worse. It mainly affects the synovium of joints, causing inflammation (synovitis), joint cartilage lesions, and erosions in the nearby bone tissue. The condition is often progressive, and if the inflammatory process is not sufficiently controlled, joint deformity occurs, causing significant functional impairment and occupational incapacity [3]. From 1980 to 2019, there were ~460 RA cases per one lakh people worldwide [4]. It varies by area and nation, but the global incidence rate of RA each year is three new cases for 10,000 individuals with a prevalence rate of 1% [5].

2.1. Risk factors for RA

To better comprehend the complexities of the RA condition, it is required to know the diverse risk factors influencing its onset and progression. The risk factors for developing RA include age, sex, genetics and environmental factors. Women are nearly two times more likely to develop RA than males, and hormonal factors may cause this variation. The majority of those affected are in the 40–60 age range. However, it has been recently revealed that there is a rising tendency among those with joint injuries, obese people, middle-aged persons, sports, the elderly, and youngsters [6]. Individuals with certain genetic markers, such as human leukocyte antigen class II histocompatibility antigen DRB1 beta chain (HLA-DRB1) and HLA-DR4, are more susceptible to developing RA [7].

2.2. Factors contributing to the pathogenesis of RA

The evolution of RA can be conceptualized in three distinct stages: impact of genetic and environmental factors, followed by early onset of disease (inflammatory stage), which is typically subclinical and ultimately leads to the stage of persistent synovitis along with systemic inflammatory phase. Understanding the intricate connections between the factors affecting RA provides insights into the complex nature of RA pathogenesis. The RA pathogenesis is more complex, an interplay of various factors that include genetic, environmental pollutants, immunogenic, and hormonal elements. For example, smoking, bacteria, viruses, estrogen, and epigenetic modification are some of the reasons that affect RA [8]. The body's immune system is stimulated by any of the above factors, which may encourage the loss of tolerance to its antigens. This triggers abnormal inflammatory reactions and activates the antigen-presenting cells (APC), activating other immune cells. Fig. 1 shows the dysregulation of the immune system to cause RA pathogenesis [9].

Smoking: In particular, smoking has been linked to the development of autoantibodies such as rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs) in susceptible individuals. These antibodies are associated with the immune response that targets the joints in RA. Genetics: HLA-DRB1 genes play a role in modulating the immune system, and variations may contribute to an inappropriate immune response. Infection or trauma: It is believed that an initial event such as an infection or trauma triggers an immune response in genetically predisposed individuals, generating autoantibodies and activating inflammatory pathways in the joints, leading to joint inflammation [10]. Understanding these contributing factors is crucial for developing targeted interventions and treatments for RA.

2.3. Immune response in RA

Activation of T-cells: In arthritis, autoreactive naive T-cells become activated and play a pivotal role in driving the progression of the disease towards a chronic stage [11]. Autoreactive naive T-cells refer to T-cells that possess receptors capable of recognizing self-antigens. Arthritic antigens are captured by APC and are likely presented to the T-cells through specialized interaction with molecules of major histocompatibility complex (MHC) [12,13]. There is a complex interaction of $CD4^+$ T-helper cells (Th_1, Th_{17} cells, and Th_2) with activated B cells, monocytes/macrophages, and dendritic cells in RA [13].

Activation of macrophages: Fig. 1 shows that the Th1 cells activate macrophages, causing them to release pro-inflammatory molecules like tumour necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) in the synovial joint [14]. The aberrant regulation of TNF-α and IFN-γ serves as a metaphor for RA. TNF-α stimulates the production of adhesion molecules on the endothelial cells lining blood vessels, allowing leukocytes to bind to and migrate into the inflamed tissue, which is called leukocyte influx, as shown in Fig. 1. When TNF-α is activated, it triggers the release of both interleukins (ILs) like IL-1β and IL-6 [15]. The

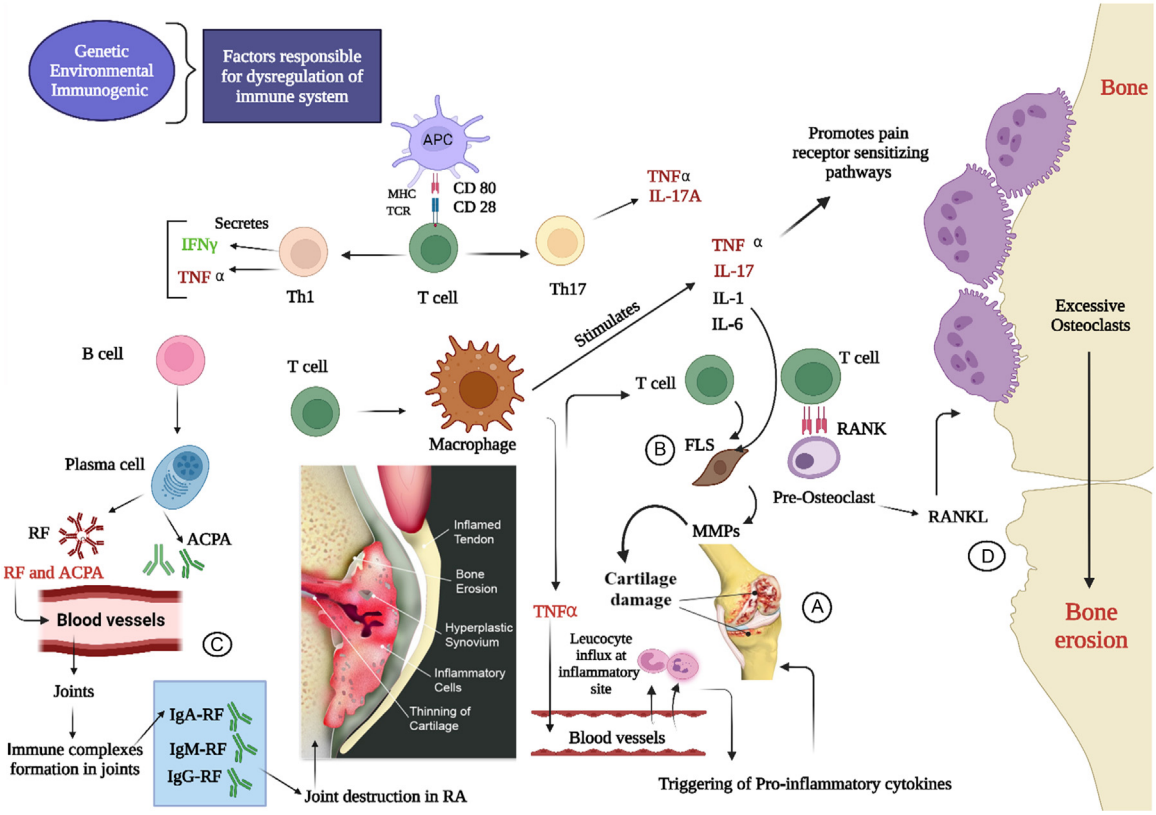

Fig. 1 – A schematic diagram of the pathogenesis of RA is explained in the series of events. (A) Activation of macrophages followed by triggering proinflammatory cytokines leading to leucocyte influx and cartilage damage. (B) Inflammatory cascade and T-cells stimulate FLS, generating MMPs causing cartilage damage. (C) B cells produce RF and ACPAs, which form ICs with IgA, IgG, and IgM. (D) T-cells, when interacting with the RANK receptor on pre-osteoclasts, induce the production of RANKL. This leads to osteoclast activation, resulting in bone erosion due to more bone resorption.

TNF-α is overproduced by macrophage stimulation in RA, which, in turn, leads to a persistent influx of leukocytes, including neutrophils, monocytes, and lymphocytes, to the inflamed joint sites [16]. These immune cells become major contributors to the chronic inflammation in RA joints. Th_{17} subset secretes TNF-α and IL-17A. Pro-inflammatory cytokines produced from M1-macrophages include TNF-α, IL-1, IL-6, IL-8, IL-18 [17]. The inflammatory cascade and T-cells further stimulate the fibroblast-like synoviocytes (FLS) interaction with immune cells [18]. As a result, FLS generates matrix metalloproteinases (MMPs) that cause severe cartilage damage and joint degradation, as shown in Fig. 1 [19]. MMP-1 is anticipated to act as the primary proteinase responsible for degrading the collagenous cartilage matrix. The degradation of cartilage is evident through the presence of joint-space narrowing on radiographs of RA patients [18]. The IL-1β, IL-6 and TNF-α can all induce NO production [20]. This NO plays a role as an apoptosis regulator in arthritis disease; thereby, apoptotic cells were significantly elevated in the synovium as well as cartilage, leading to joint inflammation and tissue damage in RA patients [15].

Activation of B-cells: In both patients and mouse models of RA, there were numerous antigens, including autoantibodies such as RF and ACPA, within the joint synovium [21,22]. These autoantibodies production is a hallmark of RA [23], caused by interactions between the innate and adaptive immune responses, as shown in Fig. 1. Citrullination is an inflammation-associated process in RA, where arginine amino acids are deiminated to citrullines by peptidyl arginine deiminase enzymes during the posttranslational alteration [24,25]. The activated B-cells stimulate the plasma cells to produce serum autoantibodies like RF and APCP against the citrullinated peptides. RF forms immune complexes (ICs) with antibodies in the blood like IgG (IgG-RF-ICs), IgM (IgM-RF-ICs), and IgA (IgA-RF-ICs) [22], The IgM-RF-ICs and IgG-RF-ICs activate the classical complement pathway, but IgA-RF-ICs activate the alternate complement pathway in RA patients [22]. ACPA also forms ICs with IgA-RF or IgM-RF, thereby triggering inflammation and promoting complement cascade activation in RA joints [26]. These ICs can then deposit in the outermost layers of articular cartilage in joints [22,26], causing inflammation and damage to the surrounding tissues and thereby causing joint pain, as shown in Fig. 1. FLS and T-lymphocytes are responsible for the increased expression of RANKL [27]. The IL-6 and IL-1 induce the production of RANKL by synoviocytes and T-cells in the RA synovium [28]. RANKL (Receptor activator of nuclear factor κB ligand) is a cytokine belonging to the TNF superfamily, and it is highly expressed in fibroblasts, T cells, and B cells. The RANK receptor is expressed on pre-osteoclasts and

osteoclasts. Osteoclast differentiation is aided by RANKL and RANK interaction [27]. Fig. 1 shows increased bone erosion in the case of RA patients due to the increased production of RANKL, leading to excessive activation of osteoclasts (the cells that break down bone cells) [29]. Chronic synovitis leads to hyperplasia in synovium and the development of pannus, a thickened, hypertrophied synovial membrane [27]. This pannus invades the adjacent cartilage and bone, contributing to cartilage degradation and bone erosions. Chronic synovitis and pannus promote osteoclast differentiation, which in turn causes bone erosion [27], as shown in Fig. 1. Therefore, the RF, ACPAs, proinflammatory cytokines, and high production of RANKL are the major precipitating factors that increase bone erosion in RA as they stimulate osteoclastogenesis. It was observed that alteration in apoptosis sensitivity of FLS and T-lymphocytes causes synovial hyperplasia and chronic inflammation in RA [30].

In summary, through various molecular signaling pathways, RA disease progresses initially from joint inflammation to synovitis, followed by cartilage damage and, ultimately, bone erosion.

3. Osteoarthritis (OA)

OA is the most prevalent disease in older people and is characterized by secondary synovitis, osteophyte growth, subchondral bone sclerosis and cartilage degradation [31]. According to estimates, 40% of people over the age of 70 years have OA, which is more prevalent as people age [32,33]. The most typical symptom of an OA-affected joint is pain. The patient observes a reduction in range of motion as the condition worsens because of abnormal joint space, muscular spasm and contracture, capsular shrinkage, and mechanical block caused by osteophytes or loose bodies [34].

3.1. *Progression of OA*

The progression of OA typically involves a series of stages marked by changes in joint structures and increasing symptoms. The general steps involved in the progression of osteoarthritis are 4 stages: Pre-OA stage (Stage 0): Microscopic changes occurring at the cellular level without noticeable effects or symptoms [35]. Early stage (Stage 1): Cartilage begins to change with some loss of cartilage integrity [35]. Bone spurs are the osteophytes that emerge from the periosteal surface close to the joints [36]. The joint space does not significantly narrow at this stage, but doubtful symptoms such as occasional stiffness may be present [35]. Mild stage (Stage 2): Cartilage in the affected area begins to erode. joint space starts to narrow, leading to increased friction. Stiffness after periods of inactivity becomes more noticeable. Moderate stage (Stage 3): Cartilage loss continues, and joint space further narrows. Symptoms become more pronounced, including pain, swelling, and tenderness. Daily activities may become more challenging due to joint dysfunction. Severe stage (Stage 4): Advanced cartilage loss leads to significant joint damage. Joint space is severely narrowed, and bone-on-bone contact may occur. Severe pain, swelling, and tenderness are common symptoms. Functional limitations are pronounced, impacting daily activities.

3.2. *Risk factors of OA*

The risk factors associated with OA can be categorized into two groups, namely joint-level factors (such as abnormal loading of the joints and injury) and person-level factors (such as age, gender, obesity, heredity, metabolic conditions, and hormonal factors) [37]. OA has a genetic component, suggesting that certain genes may influence an individual's susceptibility to the disease. No gene has yet been identified. The risk of osteoarthritis increases with age. Joint tissues experience natural wear and tear, leading to a gradual breakdown of cartilage. According to the Centre for Disease Control and Prevention, more than one-third of adults over the age of 65 have symptoms of OA. About 13% of women and 10% of men aged 60 years and older have symptomatic knee OA. Previous knee trauma, such as a dislocation or fracture, increases the risk of knee OA by 3.86 times [38].

3.3. *Factors contributing to the pathogenesis of oa*

To gain a deeper understanding of OA pathogenesis, it is crucial to investigate the diverse risk factors influencing it. OA develops and progresses due to complex genetic, biomechanical, biochemical, and environmental interactions. Inflammatory mediators can contribute to cartilage degradation and synovial inflammation, followed by subchondral changes in the bone.

Metabolic factors: Metabolic conditions, such as obesity and metabolic syndrome, are linked to OA [39,40]. Excess body weight puts additional stress on weight-bearing joints, such as the knees and hips, increasing the risk of OA. White adipose tissue is associated with obesity [41]. Activated adipocytes of white adipose tissue enhance the secretion of signaling protein factors called adipokines, which in turn synthesizes the generation of IL-1β, IL-6, IL-8 IL-10 and TNF-α leading to the damage of the cartilage [41,42]. Therefore, obesity can further enhance inflammation and contribute to OA [38]. Biomechanical factors: Excessive joint loading, repetitive stress, joint trauma, joint injuries, or abnormal joint alignment can alter biomechanical factors and accelerate wear and tear on cartilage [43]. Ormonal factors: Hormonal changes, especially in postmenopausal women, may influence the development of OA. Estrogen deficiency has been associated with cartilage loss and increased susceptibility to OA [44]. Biochemical factors: Imbalance in the production and breakdown of cartilage components, such as proteoglycans and collagen, can contribute to cartilage degradation. Abnormalities in the synthesis of lubricating synovial fluid may affect joint function [43]. Joint tissue homeostasis: Disruptions in the balance between cartilage synthesis and degradation, known as joint tissue homeostasis, contribute to OA progression. Inadequate repair mechanisms and an imbalance in the activity of enzymes involved in cartilage breakdown (MMPs) play a role [43]. Understanding these factors is crucial for developing targeted interventions and treatments for OA.

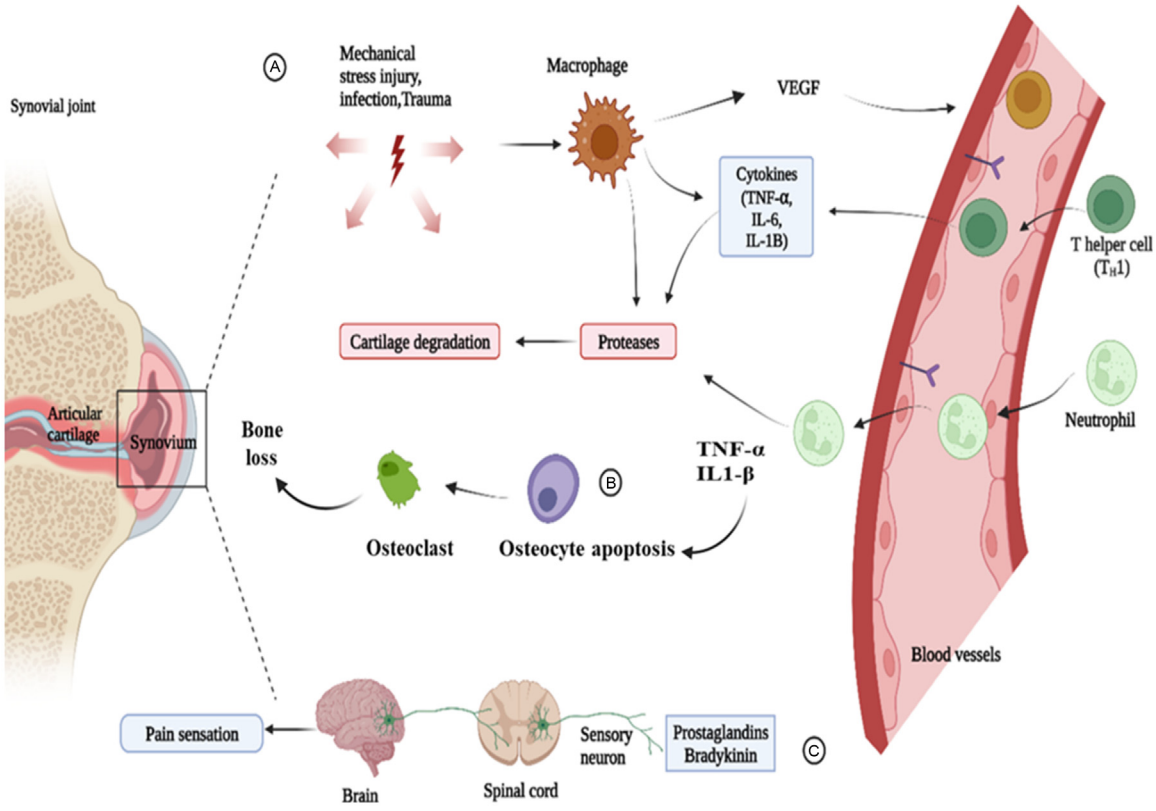

Fig. 2 – A schematic diagram of the pathogenesis of OA is discussed in a series of events. (A) Neutrophils, macrophages and proinflammatory cytokines induce protease production, causing cartilage degradation. (B) Inflammatory cytokines directly impact the apoptosis of osteocytes, which in turn causes the activation of osteocytes and leads to bone loss. (C) Pain-sensing prostaglandins and bradykinins are produced in association with subchondral bone lesions.

3.4. *Immune responses in OA*

The pathological mechanisms involved in OA significantly impact the damage of synovium, bone and cartilage. Fig. 2 shows the pathogenesis of OA.

Exacerbation of pro-inflammatory cytokines: In the early stages of OA, the collagen matrix undergoes more disorganization, accompanied by a reduction in the proteoglycan content in the ECM of cartilage, resulting in the loss of collagen [45]. The cytokines released by the synovium and chondrocytes, particularly IL-1β and TNF-α, mediate cartilage destruction. The OA-affected cartilage releases IL-1β readily, whereas healthy cartilage does not. Cytokines like IL-1β and TNF-α can promote their production as well as the production of prostaglandin E2 (PGE2), proteases, IL-8, and IL-6, which all together contribute to cartilage degradation in OA patients [46,47]. Along with prostaglandins, cytokines (particularly IL-1β), and substance P, bradykinin can be considered one of the most significant molecules that cause pain [48]. These molecules act through the various receptors in peripheral sensory neurons and the spinal cord, as shown in Fig. 2 [49]. Pain in a joint affected by OA has been associated with synovial membrane thickening and lesions in the subchondral bone [50,51]

Activation of macrophages: In OA, inflammatory cells like macrophage activation leads to the release of proinflammatory cytokines and proteases (MMPs), which induce cartilage damage, as shown in Fig. 2. In addition to secreting pro-angiogenic substances, macrophages also secrete substances that stimulate the production of vascular endothelial growth factor (VEGF), which in turn promotes angiogenesis in endothelial and fibroblast cells, as shown in Fig. 2 [52].

Activation of neutrophils: Neutrophils are the first cell types to be recruited to the sites of inflammation, and IL-17 encourages their recruitment and activation [28]. The OA is characterized by an increased leukocyte influx in the synovium, particularly within the subintimal layer. The activated neutrophils produce degradative proteases (mainly serine proteases), including neutrophil elastase (NE), cathepsin G, and proteinase 3, which can cause damage to joint cartilage, as shown in Fig. 2 [53]. In OA pathogenesis, activated neutrophils, M1-macrophages, and interleukins like IL-6 and IL-1β are involved in protease production, which aggravates cartilage damage, as shown in Fig. 2. For example, MMP9 and neutrophil gelatinase-associated lipocalin form a complex in OA synovial fluid that is relevant to cartilage degradation [54]

Osteoblasts and osteoclasts in OA: osteoblasts are the cells responsible for bone formation, whereas osteoclasts are cells responsible for bone resorption, meaning they break down and absorb bone tissue. In OA, an imbalance occurs between

the activities of osteoclasts and osteoblasts that leads to the net loss of bone tissue, finally contributing to the degradation of the joint.

The fate of osteocytes in OA: Osteocytes are mature bone cells embedded in the mineralized bone matrix, crucial for maintaining bone homeostasis, sensing mechanical stress, and regulating bone remodeling. In the case of OA, osteocyte death was observed in the subchondral bone. In the later stages of OA, there is an increased subchondral bone volume, coupled with a decrease in mineralization (hypomineralization) attributed to osteocyte apoptosis [55]. Substantial evidence indicates that pro-inflammatory cytokines, such as TNF-α, IL-1β, etc., directly induce osteocyte apoptosis in cell culture models. This induction subsequently triggers the release of cytokines that affect bone turnover [56]. Osteocyte apoptosis, which in turn signals an increase in the osteoclast, driving targeted bone resorption and leading to bone loss, as shown in Fig. 2. The RANKL signaling is majorly responsible for causing excessive osteoclast formation [57].

4. Conventional treatment for arthritis and its drawbacks

Conventional treatment for arthritis typically involves a combination of medications, physical therapy, lifestyle modifications, and surgical interventions, which are also carried out in some cases. While these treatments can effectively manage symptoms and improve the quality of life for many individuals, they also have drawbacks and limitations. Corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying anti-rheumatic drugs (DMARDs) are the conventional drugs used in RA and OA [32]. Opioids and NSAIDs both relieve pain in OA and RA patients in a similar manner. Orally given NSAIDs are the most usually recommended treatment for OA. However, drawbacks of these orally administered drugs include non-specificity, off-target side effects, first-pass effect, poor bioavailability, drug degradation by gastrointestinal tract (GIT) enzymes, food interactions, burst release, and destruction of significant numbers of normal cells [20,58,59].

Moreover, systemic delivery of drugs through the parenteral administration is used to reduce the adverse effects caused by oral route drugs. However, these parenteral drugs also face a problem due to the possibility of undesirable side effects in organs other than the target organs, leading to non-specific tissue toxicity. This underscores the need for alternative administration routes to mitigate adverse effects. Intra-articular administration, involving direct drug delivery to the site of joint damage in arthritic patients, is gaining preference as an alternative route. This localized approach minimizes systemic side effects and boosts bioavailability. However, a significant drawback of intra-articular administration is the rapid clearance from the synovial joint tissue through the lymphatic system. For instance, the intra-articularly injected steroids can be cleared from joints within 1 to 4 h [60,61]. This rapid clearance, in turn, results in the need for frequent drug dosing [34]. This drug dosing frequency poses challenges in terms of treatment adherence and convenience. Even though conventional treatments for arthritis offer valuable therapeutic options, the drawbacks associated with orally and parenterally administered drugs highlight the importance of exploring alternative approaches to optimize treatment outcomes and minimize adverse effects.

5. Rationale behind the use of gel-based drug-loaded nanocarrier systems in arthritis

Arthritis progresses initially from joint inflammation. Therefore, if the inflammation process is not controlled, it leads to joint deformity and bone erosion within one year after diagnosis. RA is a systemic disease due to the triggering of pro-inflammatory mediators and their release into the blood. Despite its systemic nature, the signs and symptoms of inflammation (associated with arthritis) are majorly topical (inflammatory redness and swelling on the hand and knee joints). Additionally, the other symptoms related to arthritis are primarily localized to the joints (like pain and stiffness). Hence, gel-based therapies are suitable for localized action.

Even though gel-based conventional topical formulations are available in the market for the management of arthritis, certain issues exist, including higher doses, side effects, poor efficacy, poor skin permeation, and poor penetration into the synovial capsule of the joint. As a result, these issues make them less efficient dosage forms. The rationale behind exploring alternative formulations for arthritis treatment is grounded in the limitations observed with conventional gel-based formulations. Moreover, the stratum corneum (SC), the skin's outermost layer, acts as an effective barrier. This barrier can pose challenges for drugs to be absorbed via the skin through typical percutaneous absorption. While certain gels are effective for topical applications, achieving intra-cartilage penetration at therapeutic concentrations remains challenging. The complex structure of cartilage and its composition pose a significant hurdle for the intra-cartilage penetration of drugs when administered using conventional gels. This challenge hinders the attainment of therapeutic drug concentrations within inflamed joints. All the above limitations restrict the clinical application of conventional gels and have prompted the search for more efficient dosage forms. Nanocarriers are efficient in overcoming the above limitations and hence become the superior mode for transdermal [62] or topical [63] drug delivery systems to manage local inflammatory diseases [64,65]

Ensuring the therapeutic effectiveness of a pharmaceutical dosage form primarily relies on delivering the drug to the target site at the desired concentration [66]. Nanoengineered therapy is a therapeutic approach that involves designing, developing, and applying nanoscale structures or devices to diagnose, treat, or prevent diseases. Nanoscale structures are objects or features that exist on the nanometer size scale. This cutting-edge field integrates nanotechnology principles into the development of therapeutic interventions, often employing nano-sized materials to enhance drug delivery, improve treatment specificity, and provide novel solutions for medical challenges [67,68]. Gel-based nanoengineered therapy refers to embedding drug-loaded nanocarriers in

any gel-based formulations. This helps deliver the drugs to specific inflammation sites of local inflammatory diseases like OA, RA, gouty arthritis, PsA, scleroderma, lupus, uveitis, periodontal diseases and atopic dermatitis. Bringing together nanocarriers and gels as one system opens new therapeutic avenues by capitalizing on the synergies between these technologies [69]. This gel-based nanoengineered therapy approach improves the fine-tuning of spatiotemporal drug release, as both the nanocarrier and gel components can be optimized [70] Spatiotemporal drug release involves the precise and controlled release of drugs at specific sites with specific time intervals.

5.1. *Topical or transdermal drug delivery*

The nanocarriers are nanosized, which allows them to penetrate the SC more effectively. Additionally, the water present in the gel-based systems moisturizes the skin. This causes the expansion of cells in the SC layer and the drug's channel to widen, thereby increasing overall penetration. They also provide a larger surface area for interaction with the skin. This increased surface area facilitates better contact and absorption through the skin barrier.

5.1.1. *Nanocarriers delivery through the percutaneous absorption*

Nanocarriers can encapsulate hydrophobic drugs, improving their solubility in the skin's lipid-rich environment. This enhanced solubility increases the likelihood of drug molecules permeating through the skin. The penetration of nanocarriers is most likely along three possible routes: the transcellular route, the intercellular route, and the appendage route [71]. Nanocarriers can interact with cellular structures in the skin, such as keratinocytes and fibroblasts. This interaction may enhance drug transport by promoting cellular uptake and intracellular (transcellular) delivery, which can modulate the properties of the skin barrier, making it more permeable for nanocarriers. This modulation may involve temporarily disrupting the lipid bilayers of the SC, allowing for increased drug permeation. The fastest way for nanocarriers to permeate through the skin is the transcellular route, which is favourable for amphiphilic nanocarriers.

The intercellular route is the primary pathway for the penetration of nanocarriers [71]. Through the intercellular route, flexible nanocarriers penetrate through the flexible lipid channels (that exist between the corneocytes) and finally reach the deeper skin layers by diffusion processes [72]. Highly rigid nanocarriers penetrate the appendage or follicular pathway through hair follicles and sweat glands [73]. Permeation enhancers, on the other hand, can temporarily alter the structural arrangement of the skin barrier, thereby improving the transport of drugs. They can be used in combination with the nanocarriers further to enhance the transport of drugs through the skin. When nanocarriers are incorporated into gels containing permeation enhancers, the permeation through the skin barrier is greatly improved. For example, to treat arthritis, Garg et al. [74] developed a transdermal hydrogel of methotrexate (MT) embedded nanostructured lipid carriers (NLCs) with added chemical enhancers (CEs). The formulation process began with a preparation of primary emulsion using MT, solid lipids (stearic acid and gelucire), liquid lipid (transcutol), an ethanolic solution of phospholipid, and the primary surfactant (Tween 80), mixed with water. Subsequently, secondary surfactants, specifically CEs like Kolliphor® P188, Kolliphor® P338 and Kolliphor® P407, were incorporated to finalize the MT NLCs. Among these, Kolliphor® P188 was the most effective, as it reduced the particle size (PS) of the MT-NLCs and increased the entrapment efficiency (EE) of MT. The inclusion of CEs significantly improved the skin penetration capabilities of the NLCs, resulting in enhanced permeation rates. Specifically, the use of NLCs with CEs achieved a permeation enhancement ratio of 28 times for NLCs+CEs and 26 times for the gel containing NLCs+CEs, compared to 21 and 18 times, respectively, for formulations NLCs and NLCs gel without CEs. Due to their nano-sized structure and lipid matrix composition, NLCs are in close contact with keratinocytes, forcing the drug MT into the skin. Thus, the synergistic effect of the CEs and lipid components enhanced the flux and facilitated percutaneous absorption.

The effectiveness of therapy has been improved by attaining a high concentration of a drug at the specific target area where the gel is applied. Therefore, enhancing therapy through the successful delivery of therapeutic agents remains the primary objective for any research in drug delivery [75].

5.1.2. *Role of polymeric network of gels*

Generally, the polymeric network in gels has a crucial role in ensuring stability and a controlled release of drugs within the gel matrix.

Stability: A polymeric network of gels helps prevent drug aggregation (in the case of drug-loaded gels) and nanocarrier aggregation (in the case of gel-based nanocarriers). This is possible because these polymeric networks play a role in maintaining stability by forming a three-dimensional structure within the gel matrix [76]. They ensure the uniform dispersion of the drug or nanocarriers throughout the gel without being aggregated.

Controlled release: Additionally, they contribute to the controlled release of drugs in gels by regulating the diffusion of drug molecules through the network. Nanocarriers, such as liposomes or polymeric nanoparticles (NPs), can be incorporated into gel matrices to create nanocomposite gels. The mechanism involved in nanocomposite gels helps prevent sudden bursts of drug release and promotes the sustained release of drugs for a longer time [77]. The extensive intermolecular voids within hydrogel networks function as homing for numerous nanocarriers [78]. Polymeric hydrogels play the role of a "host," providing a habitat for various types of nanocarriers, which act as "guests," resulting in the formation of nanocomposite hydrogels [79].

Enhanced gel strength: Polymeric gel, when embedded with nanocarriers, also provides high gel strength. Nanocarriers can serve as mechanical reinforcing agents as they cross-link with the polymer chains of hydrogels [80–84]. This interaction establishes a network type within the gel matrix, enhancing the nanocarrier's stability and gel strength. This physical crosslink interaction between nanocarriers and polymer chains of the gel also modifies viscosity, elasticity, and overall gel strength [82]. For example,

Dai et al. [85] evaluated the polymeric gels containing SiO_2 NPs, which exhibited high gel strength and reduced gelation time. However, it is essential to highlight that the enhanced performance of the gel system is mainly contingent on factors such as concentration, size, and types of NPs [86,87]. Due to their small size and high surface area, nanocarriers can influence the rheological behaviour of the gel.

Inhibition of polymeric gel degradation: Nanocarriers can serve as a protective barrier around the encapsulated drug and the polymer matrix of the gel. This shielding effect helps prevent direct contact between the drug, polymer, and external factors such as light, moisture, and temperature fluctuations, all of which can contribute to drug degradation over time. Nanocarriers adsorb onto the polymer chains and interact with the active groups of the polymers, impeding the degradation of the polymer [82]. Thus, gel-based nanocarriers provide a platform for achieving the sustained release of therapeutic drugs directly at the targeted site.

5.1.3. *Potential benefits*

In the case of arthritis, topical/transdermal gel-based nanocarriers have been used to deliver anti-inflammatory drugs/corticosteroids/NSAIDS/DMARDs directly to the affected joint through percutaneous absorption. This improves the therapeutic efficacy while reducing adverse effects associated with systemic or oral drug delivery. Gel-based nanocarriers are advantageous for prolonged therapy of both RA and OA because they offer a practical approach for localized drug delivery and significantly lengthen the drug's retention time on the skin [88]. The higher drug accumulation in the arthritic cavity of RA patients is made possible by the nanocarrier's ability to permeate into the deeper skin layers [88]. The accumulated nanocarriers in the inflamed joints can quickly/slowly release the drug based on the composition and properties of the nanocarrier. The faster or slower drug release also depends on the ability of quicker/slower degradation of nanocarriers, respectively. The choice of the polymeric composition of a nanocarrier can influence the degradation rate and, consequently, the drug release. For example, poly-lactide-co glycolic acid (PLGA) polymers were available in different grades with changes in the ratio of lactic acid and glycolic acid in their composition. PLGA polymer grades with a high proportion of hydrophilic glycolic acid exhibit a faster degradation rate, while PLGA polymer grades with a high proportion of lactic acid exhibit a slower degradation rate [89]. Hence, nanocarriers prepared with hydrophilic polymers may allow faster drug release, whereas nanocarriers formulated with hydrophobic polymers can provide a more sustained release. Fabricating core-shell NPs with hydrophilic inner core results in more rapid drug release [90]. Stimuli-responsive nanocarriers refer to the ability of the nanocarriers to control drug release in response to triggers by external stimuli such as ultrasound, heat, magnetism, light, pH, and ionic strength [91].

Localized delivery of gel-based nanoengineered therapy in arthritis offers several advantages for targeted and sustained delivery. Gel-based nanocarriers can provide sustained drug release for a longer time, reducing drug dosing frequency and improving patient compliance. Nanocarriers improve the drug's pharmacokinetic properties when loaded into the gel. They exhibit extended or sustained release, which maintains a consistent level of drug at the site of inflammation. This can result in better pain relief and reduced inflammation in the long-term management of arthritis. The poor solubility and low dissolution rate of poorly water-soluble drugs often cause insufficient bioavailability [92,93]. Gel-based nanocarriers enhance bioavailability (nanocarriers will enhance the drug's bioavailability by improving their solubility). Hence, gel-based nanocarriers have several significant advantages over traditional formulations, including bioavailability, localized action, targeted delivery, enhanced therapeutic efficacy, lower side effects, dose reduction, controlled release, the improved shelf life of drug-loaded nanocarriers, and enhanced stability [88].

5.2. *Intra-articular delivery*

Local delivery methods such as intra-articular injection are commonly employed to target avascular tissues, including tendons, ligaments, and cartilages. There are two significant biological barriers to effective drug delivery to chondrocytes. One is the rapid elimination of drugs from the joint space after direct injection into the affected joint, and the other is the dense avascular nature of cartilage tissue [94].

5.2.1. *Challenges associated with drug delivery to joints*

One of the main challenges in drug delivery for OA and RA is the unfavourable pharmacokinetics within the joint [95]. Upon injection into the synovial joint cavity, a drug enters the synovial fluid; however, it remains in the cavity for a short time due to its short half-life of 2 to 4 h [96,97]. The drug available in the synovial fluid quickly drains through the venules (in the case of small molecules) and lymphatic vessels (in the case of large molecules) found in the synovial membrane. As a result, a significant portion of the drug is lost to the systemic circulation and does not remain within the joint for an extended time.

The articular cartilage, which is often the target of many DMARDS, also acts as a formidable biological barrier to drug penetration. Its avascular nature (devoid of blood vessels) and lacking lymphatics and nerves create a harsh biomechanical environment. Avascular tissues have limited blood supply, so drugs cannot be efficiently delivered through the bloodstream to the target cells within these tissues. In cartilage and similar avascular tissues, the limited interstitial fluid flow further complicates the transport of nutrients and waste products within the tissue. The absence of an efficient fluid flow system also hampers drug transport into and within the cartilage matrix. Therefore, drugs can only reach the resident chondrocyte cells within the cartilage through a diffusion mechanism. The high collagen content and the intricate arrangement of collagen fibres create a physical barrier that restricts the diffusion of drugs. However, three factors impede the diffusive transport of molecules (including drugs) through cartilage. These include its highly dense network of collagen fibrils, highly anionic ECM, and small pore size of less than 15 nm [98]. The diffusion rate of drugs through the cartilaginous matrix is slower than the clearance rate of the drugs in the joint. As a result, drugs within the joint space are usually cleared off before achieving

the therapeutic concentrations within the deeper layers of cartilage [95].

Therefore, the traditional drugs delivered intra-articularly exhibit low retention in the cartilage of joints, leading to sub-optimal therapeutic efficacy. Hence, there is an urge to develop efficient drug delivery strategies. One of the best approaches to prevent rapid clearance is the encapsulation of drugs in nanocarriers.

5.2.2. *Potential benefits*

The gel-based nanocarriers' improve drug retention for a longer time in the joint when given intra-articularly. This can function as a depot for controlled drug release over a significantly extended period when compared to administering a free drug by injection. This is because gel-based nanocarriers often possess viscoelastic properties similar to the synovial fluid in joints, aiding in its distribution and retention within the joint space. This increased viscosity forms a gel-like structure, which adheres to the joint surfaces and helps maintain a localized drug concentration for an extended period. Compared to neutral and negatively charged nanocarriers, positively charged nanocarriers may interact more favourably with negatively charged cell membranes, facilitating cellular uptake. The retention ability of positively charged nanocarriers is attributed to the electrostatic interactions that exist between their positive charge and the negatively charged ECM of cartilage. Therefore, most of the positively charged nanocarriers can penetrate through the full thickness of cartilage under the charge guidance and retain inside the tissue [99].

The gel matrix of nanocarriers can provide a physical barrier that hinders the rapid clearance of drugs from the joint space. This extended residence time allows for a more gradual release of the drug, maintaining therapeutic concentrations within the joint. Therapeutic drugs encapsulated in nanocarrier-based drug delivery systems have less drug efflux at the intra-articular cartilage of the joint. Additionally, when drugs are loaded in nanocarriers, they are protected from cellular and enzymatic clearance that occurs quickly after intra-articular injection [70]. For instance, to manage RA, Turker et al. [100] developed lipogelosomes, *i.e.*, diclofenac-loaded liposomes, and incorporated them in the carbopol gel. The lipogelosomes of diclofenac labelled with 99mTc were injected intra-articularly in an antigen-induced arthritic rabbit model. Then, scintigraphic imaging studies were performed on the rabbits' arthritic knees using a gamma camera. The results showed that longer retention times of diclofenac lipogelosomes were observed in the arthritic knee joint of the rabbits. The results align with their next research work carried out by the same research group [101], where the lipogelosomes of diclofenac exhibited better anti-inflammatory efficacy with reduced joint swelling when compared to the application of topical marketed product VE-CP and solution of diclofenac sodium. This proved that better efficacious treatment is due to the retention of diclofenac drug from the lipogelosomes drug delivery.

NPs can play a supportive role in enhancing the stability of hydrogels. One example is using laponite NPs as an injectable, which can create an interpenetrating network within the HPMC-hydrogel structure for cartilage repair. This incorporation of NPs contributes to improved mechanical properties of the hydrogel, enhancing its overall stability [102]. Hence, the above advantages make the gel-based nanocarriers via intra-articular delivery finally enhance the effectiveness of therapy. Drug-loaded nanocarriers also favour sustained drug release behaviour; thereby, the dose of the drug and frequency of dosing through intra-articular delivery is also decreased, making patients compliant. For example, Chang et al. [103] developed HA-based hydrogels containing NLCs coloaded with diclofenac and dexamethasone (DEX) to manage OA and control joint pain. The study results revealed that the formulation exhibited an effective dose within 4 h of intra-articular injection and localized and sustained drug release for up to 168 h. A similar type of sustained release drug behaviour was observed with HA-based hydrogels containing liposomes of celecoxib developed by Dong et al. [104] when given intra-articularly in an OA-induced rabbit model.

The challenges associated with intra-articular drug delivery are aligned with the potential benefits of gel-based nanosystems, which can overcome physical barriers, provide sustained drug release, protect drug molecules, and enable targeted delivery. These attributes make gel-based nanocarriers a promising approach to improve the effectiveness and safety of drug treatments for joint-related conditions.

5.3. *The significance of hydrogels in arthritis treatment*

Hydrogels, composed of cross-linked hydrophilic polymers, can retain water and mimic the cartilage ECM's three-dimensional (3D) structure. This property makes hydrogels suitable for improving lubrication in various applications. Hydrogels exhibit excellent biocompatibility and high permeability for nutrients, effectively supporting cell growth and tissue regeneration. Additionally, their unique properties enable minimally invasive filling of cartilage defects, regardless of size. These features make the hydrogels a promising approach for cartilage repair and regeneration.

Free drugs in the articular joints are rapidly expelled into the synovium's venules and lymphatic channels. Hence, hydrogels act as drug reservoirs, as they are relatively large, and their structure can offer resistance to easy clearance from the joint cavity. This characteristic feature ensures that the hydrogel, along with the entrapped drug, remains in the joint space for a more prolonged period. Additionally, the porosity inherent in hydrogels facilitates the encapsulation of drugs within the gel matrix. As the hydrogel retains water, it swells and gradually releases the drug into the surrounding joint tissues, providing a continuous and steady drug supply. This controlled drug release occurs at a rate dictated by the drug molecule's diffusion coefficient through the hydrogel network. Thus, the porous structure of the hydrogel serves as a reservoir and exhibits a diffusion-dependent mechanism. This mechanism permits the drug to diffuse through the gel matrix in a controlled manner, thereby prolonging the duration of therapy in arthritis management [105,106]. The sustained release from hydrogels can lead to a reduction in the frequency of drug administration. This is advantageous in arthritis management, where minimizing the number of injections or doses can improve patient compliance and

convenience. In the case of gel-based nanosystems, the nanocarriers are entangled within a gel matrix and are released gradually over time. Once the gel matrix breaks down, the NPs are released and can deliver the drug to the inflamed joint.

Hyaluronic acid (HA) is the main constituent in the synovial fluid of joints and improves joint functions. It also acts as a lubricant, thereby imparting lubrication, which helps improve joint mobility. Therefore, HA-based hydrogels were more useful in treating arthritis. The low viscous HA-based hydrogels can afford syringeability for intra-articular administration. Additionally, HA-based hydrogels provide restoration/improvement of the viscoelastic properties of the damaged synovium, finally leading to pain reduction in arthritis patients. In general, polymeric networks of hydrogels can hold nanocarriers effectively and help improve their retention in the joint space. They also protect the embedded nanocarriers from phagocytosis of synovial cells in the joint. As a result of the progressive enzymatic hydrogel degradation in the synovial joint, a drug from the encapsulated nanocarriers is released over time and enables sustained release. Therefore, hydrogels afford a superior mode of sustained drug delivery in treating arthritis.

HA hydrogels can relieve the pain and stiffness caused by joint diseases, in which HA concentration and distribution were altered and significantly reduced [107]. The primary limitations of HA include its quick elimination from the synovial fluid due to its enzymatic destruction *in vivo* by hyaluronidase (HAse). This feature restricts the widespread usage of HA in many biomedical applications, particularly for the treatment of OA. Due to its quick elimination, HA as a visco-supplement in the treatment of OA does not offer long-term therapeutic efficacy and requires regular injections. Developing HA hydrogel systems is an interesting approach to extending HA's half-life and lowering the infection risk [108]. The clinical use of HA hydrogels can delay the synovium's fast elimination of HA and prevent their rapid clearance from synovial fluid of the joint [109]. The hydrogel matrix can act as a reservoir, gradually releasing HA and maintaining its presence in the joint longer than in a situation without a hydrogel. The hydrogel's 3D network can trap and hold HA molecules, preventing their rapid clearance from the synovial fluid. Hydrogels' porous and water-absorbing nature contributes to HA retention within the joint space. Hydrogels, by retaining water and contributing to the overall viscosity of the synovial fluid, may indirectly influence the rheological properties of HA. Maintaining optimal viscosity is crucial for the effective functioning of HA in lubricating joint movements [108]. As a result, hydrogels containing HA hold considerable significance in conditions related to joints, such as OA and RA. These hydrogels become particularly valuable as they address the decreased levels of HA observed in patients affected by these joint-related conditions.

Some gels are stimulus-responsive, such as thermal-responsive gels, which are in sol form and are, therefore, simple to inject but turn into gel at body temperatures to prevent drug efflux [70]. Injectable gel systems, such as thermo-responsive or in-situ forming hydrogels, can be loaded with nanoengineered carriers for local delivery in arthritis. These gels can be injected into the joint space or periarticular tissues, where they undergo a sol-to-gel transition, forming a depot for sustained drug release. The nanocarriers embedded within the gel matrix enable targeted delivery of therapeutic agents to the inflamed joint, providing localized treatment. For example, the thermosensitive hydrogel is embedded with NPs of indomethacin (INDM) and DEX. This hydrogel demonstrates a liquid (sol) state at room temperature. Upon injection into the articular cavity of CFA-induced RA rats, a rapid transformation into a gel occurs from the sol state. The gel state results from the hydrogel's response to the physiological conditions within the joint. This hydrogel formulation allows sustained and stable release of drugs over an extended period of more than 72 h.

To overcome the inconvenience of repeated injections and the rapid degradation of exogenous HA treatments, Maudens et al. [110] developed the HA conjugates with a thermosensitive polymer, enabling the spontaneous formation of NPs after injection at body temperature, which is referred to as HA Nano. Until the temperature attains 37 °C, the HA nano is just an HA-based hydrogel (at 20 °C) but immediately forms NPs at 37 °C. In this study, the murine OA model was developed to test the formulation's efficacy. HA Nano was loaded with DEX and delivered via intra-articular injections. The results showed that NPs are biocompatible and exhibited retention for 21 d, explicating the efficacy of NPs in revealing longer residence time. The presence of HA nano in joints was detected for two months after the first injection. The study also found that HA nano is less sensitive to degradation than HA. Moreover, it demonstrated the ability to protect the cartilage, lowering the cytokine levels and preserving the thickness of the epiphysis. This HA nano conjugation strategy aims to restore HA's unique biochemical and biomechanical properties, ensuring prolonged lubrication and cushioning effects without the need for repetitive injections. As a result, the administration of HA-based hydrogels leads to significant improvement in joint swelling, reduction in the expression of pro-inflammatory cytokines in the synovial cavity, and mitigation of bone erosion [70]. HA in gel dosage form has also demonstrated significant efficacy in treating arthritic conditions independently and in combination with kartogenin, celecoxib, and pirfenidone, showcasing remarkable therapeutic effects [111].

Injectable hydrogels of natural biopolymeric substances other than HA, such as chitosan (CS) and gelatin, are utilized to manage OA. CS-glycerine borax was employed to create thermo-sensitive hydrogels for encapsulating DEX, which reduced pain and inflammation in mouse models [112]. Therefore, considering all the advantages above, injectable hydrogels hold great potential as a drug delivery system in managing arthritis.

6. Nanocarriers and their significance in OA and RA

The ultimate goal of any formulation strategy is to enhance safety, maximize therapeutic efficacy through controlled and targeted release, and minimize adverse effects, which can be achieved by using nanocarriers that are believed to address

the challenges associated with current drug delivery systems [113].

Liposomes and NPs are two nanocarrier types commonly used in drug delivery systems. Hence, these nanocarriers have been developed to enhance the efficiency of arthritis management. They can be designed to deliver anti-inflammatory drugs such as corticosteroids, NSAIDs, and DMARDs to target the site of inflammation and treat arthritis, reducing the risk of their systemic side effects. Additionally, this nanoscale technique protects the drugs from degradation. Nanocarriers encapsulate drugs within their structure, forming a protective barrier around the drug molecules. This encapsulation shields the drug from external factors such as enzymes, pH variations, or other environmental stressors that could lead to degradation [114]. The physical structure of nanocarriers provides a shield against degradation by preventing direct contact between the drug and potentially harmful elements. This physical protection helps maintain the stability of the drug at the nanoscale. Nanocarriers can limit the exposure of drugs to the external environment by creating a controlled microenvironment. Nanotechnology is undoubtedly a growing area of interest and a promising new technique in treating inflammatory diseases. For example, the HA-coated solid lipid NPs (SLNs) of prednisolone (PD), when given intra-articularly, accumulated in inflamed synovial diseases, reduced the pro-inflammatory cytokines significantly and exhibited good therapeutic efficacy in managing arthritis [115]. A preferential accumulation at the target areas is made possible by nanocarrier, increasing drug bioavailability and therapeutic effectiveness. Nanotechnology is highly beneficial because it enhances the therapeutic efficacy of nanocarriers, as it exhibits localized and targeting properties and aids in dose-reduction, thereby reducing drug-related toxicities [116,117]. Such treatment with nanocarriers even reduces the drug dosing frequency due to sustained drug release behaviour, making patients compliant [118,119].

6.1. *Enhancement of skin permeation*

The therapeutic agents can be made more useful if the synthesis of nanoformulations is controlled to encapsulate a drug, stabilize it, and target it to the epidermis or dermis of the skin. Nanotechnology-based preparations offer a potential solution to minimize adverse effects by requiring only a minimal dose [120]. This is made possible through the tunable properties of nanocarriers, ultimately enhancing the therapeutic efficacy of the formulation. The function of the skin barrier SC makes it difficult for most drug molecules to penetrate and be absorbed through the skin, making topical drug delivery challenging [121]. As nanocarriers are of the nanoscale range, they considerably enhance the penetration rate. This is because of the reason that they might quickly penetrate the SC and transport drugs across the skin barrier. Vesicular-based nanoformulations are mostly preferred for local inflammatory diseases via the skin, as they mimic the composition of skin layers. The permeation of drug-loaded vesicular systems via the skin is crucial for evaluating the degree of drug penetration from the vesicles to the skin. Percutaneous absorption is a very appealing and unique way of drug delivery to local inflammatory areas. Substances are passively absorbed via the skin during percutaneous absorption. The penetration process may occur via diffusion through shunts, particularly those offered by the relatively widely dispersed hair follicles and endocrine glands. Alternatively, it can also happen by passing through the epidermis itself. Compared to oral and intravenous administration, drug delivery through the skin has huge benefits, including patient convenience, avoiding first-pass metabolism and GIT irritants, maintaining a constant drug release at the targeted area, decreasing the drug dosing frequency, and avoiding systemic side effects. When administered through the skin, because of percutaneous absorption, nanomaterials embedded in the gel base reach the target area of inflammation where nanocarriers interact with the tissue-resident macrophages and help deliver drugs to treat OA or RA. Nanocarriers can be engineered to be readily phagocytosed by activated macrophages of the synovium. This interaction enables the internalization of the nanocarrier and the subsequent release of therapeutic drugs within the macrophages, modulating their activity [122].

6.2. *Pharmacokinetics of nanocarriers in the joint cavity*

The physical properties of nanocarriers, their interactions with biological barriers, distribution to the inflamed joints, metabolic transformations, elimination routes, and clearance mechanisms influence their pharmacokinetics. To ensure effective interaction between NPs and various components in the joint, it is crucial to achieve proper space-time retention within the synovial cavity. Hence, monitoring the behaviour of nanocarriers in real time yields valuable insights into their interactions with biological systems, assisting researchers in comprehending and optimizing their therapeutic impact [123,124]. The pharmacokinetics of nanocarriers in arthritis treatment vary depending on the chemical composition, *i.e.*, the type of carrier, such as lipidic nanocarrier, polymeric nanocarrier, or inorganic nanocarrier, as well as the specific drug payload and the type of formulation chosen. Therefore, studies in this field aim to optimize the design and formulation of nanocarriers to improve drug delivery efficiency and enhance therapeutic efficacy. The longevity and efficiency of nanocarrier retention depend on trade-offs between cartilage targeting, tissue penetration, and joint clearance of the delivery system.

6.2.1. *Retention of nanocarriers in the joint*

The effective retention of drug carriers in cartilage relies on two factors: the net flux of drug penetration from synovial fluid into cartilage and the rate at which they get cleared off. For successful drug delivery, the net influx of drugs penetrating cartilage from synovial fluid must reach therapeutic levels before clearance occurs. This ensures sufficient drug concentrations are achieved and maintained within the cartilage for effective therapeutic outcomes. When the concentration of NPs in the synovial fluid exceeds that in the cartilage, the NPs can penetrate the cartilage matrix. As the concentration of NPs in the synovial fluid decreases due to clearance mechanisms involving lymphatic and blood vessels, the NPs diffuse outward from the cartilage back into the synovial fluid. Concentration gradients drive this

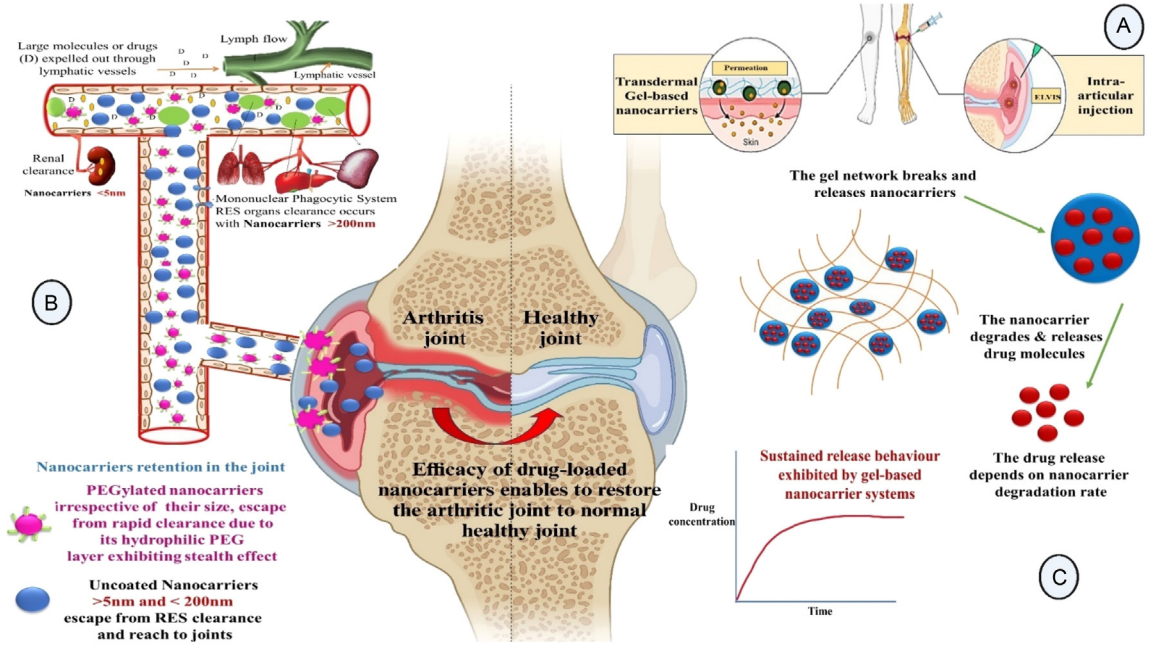

Fig. 3 – Nanocarriers escape from rapid clearance, accumulate in joints, and favour the controlled release of drugs. (A) Gel-based nanocarriers administered through transdermal route and intra-articular drug delivery favours localized drug delivery. (B) Elimination of rapid clearance by nanocarriers is dependent on their size. The nanocarriers' size of a particular range escapes from RES organ clearance, followed by the accumulation of nanocarriers in the joint tissue. (C) Mechanism of gel-based nanocarriers contributing to the release of payloads in a controlled manner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dynamic process of NP movement and play a crucial role in regulating the distribution and retention of NPs within the joint environment [123].

Nanocarrier entry into the synovial fluid occurs through a size-dependent cell uptake process. The cell uptake of nanocarriers is a plausible scenario mediated by synovial macrophages and fibroblasts in the inflamed joints [125]. The effectiveness of drug delivery depends not only on nanocarrier entry into the synovial fluid but also on their ability to persist within the joint. Monitoring clearance helps ensure that nanocarriers remain in the synovial fluid for an adequate duration, allowing the drug to reach higher concentrations at the target site and exert its therapeutic effects. The clearance pathways for nanocarriers in the joint depend on their size. Because smaller nanocarriers are more likely to exit the joint's synovial fluid through small blood venules, whereas the larger nanocarriers and their degradation products will be cleared through the lymphatic system regardless of size [126,127]. It is noted that synovial lymph flow is enhanced by two factors, one with the systemic inflammation process that occurs in RA and the other with the dysfunction of the autoimmune system in RA [127]. This leads to increased clearance of large nanocarriers or particles [128]. This is how the pathogenesis of OA and RA impacts the elimination of injected biomaterials from the joint. Fig. 3 explains the nanocarrier's role in preventing rapid clearance, followed by the accumulation of nanocarriers in the target tissue and finally contributing to the release of payloads in a controlled manner.

Small nanocarriers (<5 nm) exit the joint through synovial blood capillaries. When these small nanocarriers enter the blood circulation, they are eliminated by the renal clearance mechanism through the kidneys. Whereas the nanocarriers (>200 nm), when they enter the blood circulation, are rapidly eliminated by the mononuclear phagocytic system of reticuloendothelial system (RES) organs like the spleen, liver, and lungs [129]. In general, the nanocarriers ranging from 20 to 200 nm are well suited for accumulation in the joints or cancerous tissues through passive targeting. This happens because, in both conditions, the vasculature surrounding them is leaky, which helps the nanocarriers pass through them. The half-life and retention of nanocarriers also vary depending on their size, shape, surface charge, and other physical properties.

6.2.2. *Role of physical properties of nanocarriers in managing OA and RA*

When injected into the joints, NPs have the potential to interact with different cell types, including immune cells, synoviocytes and chondrocytes. These interactions can occur by entering the cells or releasing the therapeutic drugs. The nature of these interactions is governed by the physical properties of nanocarriers, such as size, shape, elasticity, surface charge and surface coating with targeting ligands [128].

Size: Tailoring the size of nanocarriers is crucial for effective treatment at specific target sites in the synovial joint. Large and non-penetrating drug carriers prevent clearance by

blood venules and lymphatics for inflamed synovial fluid or synovial membrane targets. For superficial cartilage zones, nanocarriers should be smaller than the collagen type II fibrillar network pores (50–60 nm) to bind to the cartilage surface and release drugs at deeper sites. Full-thickness cartilage targets require even smaller nanocarriers (20 nm) to navigate the proteoglycan network pores effectively [130]. Nanocarriers were engineered with sizes ranging between 5 and 300 nm and have been designed to transfer between synovial membrane and fluid [131]. Nanocarriers in this size range benefit from enhanced cell uptake by synoviocytes and macrophages of the synovial membrane. For example, magnetic iron oxide (Fe_3O_4) NPs with well-defined sizes (70–350 nm) were synthesized for treating RA. Size-dependent cell uptake was observed when incubated with macrophages under *in vitro* conditions [132]. Large NPs (>250 nm) tend to passively accumulate naturally in the synovium due to microvascular endothelium and interstitial spaces. This finally leads to prolonged retention of drugs in the synovium [128]. Some studies proved that larger-sized NPs exhibit prolonged retention times, offering potential benefits in improving the efficacy of arthritis treatments. For example, a study conducted by Singh et al. [133] found that 900 nm NPs had a half-life of 2.5 d, which was longer than the 1.9-d half-life observed for 500 nm NPs. Significantly, they also demonstrated the sustained retention of 900 nm particles in the joint space, with ~30% still present at 14 d, surpassing the retention observed with smaller NPs. Therefore, the selected size range of nanocarrier allows for prolonged residence time within the joint, ensuring a sustained release of drugs, which is beneficial in chronic conditions like OA and RA.

Shape: Generally, the shape of the nanocarriers influences their uptake, ability to marginate and escape the blood flow, and binding affinity to the receptors they target [134]. In terms of cell uptake, macrophages are key targets in the arthritic synovium, and the shape of nanocarriers plays a role in the rate of macrophage uptake. For a non-spherical nanocarrier, the rate of macrophage uptake is influenced by its angular orientation concerning the cell membrane. Additionally, hydrodynamic forces affect the rate of a nanocarrier's uptake [134]. On the other hand, spherical nanocarriers typically stay centred within the flow of blood, but the non-spherical particles have demonstrated the ability to undergo margination and escape from blood flow more readily [134]. This is because variable forces and torques acting on non-spherical (disc-shaped or rod-shaped) nanocarriers in blood flow enable them to marginate and move toward the blood vessel wall [135]. Once they reach the wall, these rod-shaped nanocarriers can bind to wall receptors or undergo extravasation through gaps between endothelial cells. A study reported that fusiform nanocarriers facilitate better skin tissue penetration than spherical nanocarriers [88]. Another study reported that rod-like mesoporous silica NPs (MSNPs) with a higher aspect ratio (length-to-width ratio) demonstrated improved diffusion into the mucus and prolonged residence compared to their spherical and shorter counterparts. A higher aspect ratio of rod-shaped nanocarriers was attributed to the longer channels [136]. These rod-like MSNPs offer advantages for the enhanced permeability and retention (EPR) effect in mucus, resulting in delayed drug release.

Elasticity: When nanocarriers are chemically modified into flexible nanocarriers, the circulation time and targetability properties get altered. For example, Anselmo et al. [137] synthesized polyethylene glycol (PEG)-based hydrogel NPs of uniform size (200 nm) with elastic moduli ranging from 0.255 to 3,000 kPa. The results revealed that softer NPs of 10 kPa offer enhanced circulation and subsequently enhanced targeting compared to harder NPs of 3,000 kPa *in vivo*.

Coating or surface chemistry: Surface chemistry is another essential property that impacts passive targeting in the synovium. The PEG-coated nanocarriers have been shown to accumulate more in the inflamed synovium and are removed to a lower level in the spleen and liver [138]. When injected systemically, nanocarriers face rapid elimination by monocytes or macrophages of RES organs. The hydrophobic surface of nanocarriers tends to undergo an opsonization process. This process involves the aggregation of opsonin protein surrounding the surface of nanocarriers. The opsonin aggregates make nanocarriers attractive for RES macrophages, allowing them to undergo phagocytosis. This process diminishes the availability of drug-loaded nanocarriers at RA-affected joints. Therefore, altering nanocarriers is required to prolong their circulation time and evade RES interaction [112]. The attachment of hydrophilic PEG chains to the hydrophobic surface of nanocarriers exhibits a stealth effect (offers protection from recognition and elimination by RES organs) [112]. PEGylation increases the circulation time of nanocarriers in the bloodstream, allowing them to take more time to reach the inflamed synovium and providing the possibility of enrichment at sites of inflammation [122]. For example, Certolizumab pegol encapsulated in PEGylated nanocarriers augments the time required to reach half of its concentration to 14 d, and it also depicts encouraging outcomes in RA patients [112].

Pegylated nanocarriers passively accumulate in the inflamed synovium due to the leaky permeability nature of the blood vessels surrounding the synovium. Moreover, the PEG coating can provide stability to the nanocarrier, preventing aggregation of nanocarriers or degradation of drugs during circulation. This ensures that the nanocarriers maintain integrity until they reach the inflamed synovium. For example, Lorscheider et al. [138] recently prepared PEGylated DEX palmitate NPs (PEG-DEXP-NPs) to treat damaged synovium of RA. These NPs prevented the crystallization of drug DEX, ensuring high drug loading and providing a stable suspension. They circulated for a longer time in blood vessels and finally improved their anti-inflammatory effect compared to free DEX. Due to the high vascular permeability of inflammatory joints, the fluorescent PEG-DEXP-NPs might be passively diffused and exhibit higher accumulation in the joint, which is demonstrated by *in vivo* near-infrared (NIR)-fluorescence imaging studies. Due to the stealth effect, PEG-DEXP-NPs also exhibited lower uptake by the liver (RES organ) than the free drug. PEG-coated nanocarriers can be customized to precisely target inflamed tissues, including the synovial membrane in arthritic joints. This customization involves integrating ligands onto the PEG surface that selectively interact with receptors overexpressed in inflamed

tissues. For example, Yang et al. [139] developed PEGylated silver NPs decorated with folic acid ligands to target the inflamed synovial membrane of RA. The folic acid ligand specifically targets the folate receptor, which is overexpressed on M1 macrophages within the inflamed synovial joint.

The concentration of PEGylation affects the drug release from nanocarriers in the synovial joint. For example, Ren et al. [125] conducted a study in mice regarding the effect of PEGylation on liposomes. The study results found that liposomes containing 10% or 20% PEG had similar fates *in vivo* and similar RA targeting distribution. Considering that increasing PEG content may hinder drug release and interactions of liposomes with target cells and ligands, 10% was chosen as optimal PEG content. The same research study revealed that PEG chain length impacts the biodistribution of nanocarriers in the inflamed synovial joint [125]. The study results proved that as the PEG chain lengths increase, the longer the half-life of nanocarriers and the higher the accumulation of nanocarriers in the joint cavity. Liposomes with 5 kD PEG yield optimal long-circulation times and inflamed joint targeting [125]. PEGylation reduces the immunogenicity of nanocarriers, making them less likely to provoke an immune response. This is important in chronic conditions like arthritis, where sustained treatment may be necessary. Thus, the surface chemistry of nanocarriers is essential in achieving their enhanced accumulation in the inflamed synovium for better improved therapeutic outcomes

Surface charge: The presence of glycosaminoglycans content in the ECM of cartilage is responsible for the anionic charge. As the ECM of articular cartilage is inherently anionic, the cationic nanocarrier uptake through passive targeting will be apt [94]. This is possible through the electrostatic interaction between the anionic ECM of cartilage and cationic nanocarriers. As a result, the cationic nanocarriers enhance their transport, uptake, and intra-tissue distribution, finally shortening the intra-cartilage drug's time to reach therapeutic concentration and extending the half-life *in vivo* [140]. For example, cationic surfactants like didodecyldimethylammonium bromide (DMAB) enhance the passive targeting of NPs, improving their retention in cartilage. DMAB-coated PLGA NPs exhibit four-fold higher retention than negatively charged NPs in the presence of synovial fluid [141]. Another example includes the triblock polymeric cationic charged micelles developed by Zhu et al. [99] for targeting OA and comparing them with neutrally charged micelles. The study results revealed that porcine cartilage explants took up to 87% of the cationic micelles, and 71% of the absorbed micelles were retained in the tissue for at least 4 d In contrast, the neutral micelles showed lower uptake (44%) and retention (44%) rates. This observation implied that the surface charge of micelles could play an essential role in efficient intra-cartilage drug delivery. A similar scenario was observed with nanocarriers coated with positively charged avidin, where the cell uptake was 400 times greater than neutral avidin-coated nanocarriers. The study showed that >90% of the absorbed Avidin remained within cartilage explants for at least 15 d [142]. Some positively charged cationic materials used to prepare or fabricate nanocarriers for treating arthritis include CS, dendrimers, avidin-based carriers, etc. [99]. Therefore, coating the drug-loaded nanocarriers with positively charged ligands via active targeting for anionic cartilage will be best suited for improved targetability into the joint cavity for managing arthritis [123]. Hence, by engineering NPs with suitable physicochemical properties and incorporating specific ligands, the targeting and uptake properties can be enhanced, opening up new possibilities for targeted therapies in conditions such as OA and RA. The role of nanocarrier interaction with these activated macrophages or other immune cells in the inflamed joint can be better explained with the approach mentioned below.

7. ELVIS effect of nanocarriers

The Extravasation through Leaky Vasculature and subsequent Inflammatory cell-mediated Sequestration (ELVIS) effect is observed in arthritic conditions such as OA and RA, which is analogous to the EPR effect, as found in many tumours [143]. This is because both the EPR and ELVIS effects are related to the accumulation of drugs in specific tissues. However, they are distinct in their specificity (targets) and underlying mechanisms. Because the ELVIS effect is specific to inflamed joints, while the EPR effect is specific to tumours. The ELVIS effect is a phenomenon where NPs accumulate in inflamed joints. Nanocarriers have a higher permeability and retention rate in inflamed joints compared to healthy joints. This ELVIS effect makes the nanocarriers aggregate in arthritic joints [112]. This ensures the passive targeted delivery of drugs to the arthritic inflammatory microenvironment. The EPR effect is a property where nanocarriers accumulate more in tumours than in normal tissues. It is mainly due to the larger pore size of neovasculatures and poor lymphatic clearance of tumours [144].

7.1. *Series of events that occur in arthritic synovium favouring nanocarriers accumulation through elvis effect*

Neoangiogenesis: Severe stages of OA and RA are characterized by increased neoangiogenesis (formation of new blood vessels), similar to tumour angiogenesis in cancer pathogenesis. Abnormal proliferation of synovial cells disrupts the synovial joint lining, creating hypoxic and nutrient-deficient microenvironments that promote neoangiogenesis [145]. Newly formed blood vessels supply oxygen and nutrients to the inflamed synovium, contributing to the perpetuation of inflammation.

Enhanced permeability: The persistent chronic inflammation in the arthritic joint leads to augmented vascular permeability within the synovium. This allows substances to pass through it more easily. Arthritic inflammation induces about a 6 to 40-fold increase in blood joint-barrier permeability [146,147].

Leaky vasculature: The width of the synovial membrane increased from 2 to 3 cell layers to multiple cell layers, called synovial hyperplasia. A gap as wide as 700 nm is also produced between neovascular endothelial cells to cause increased permeability in diseased joints. Consequently, the resulting vasculature becomes leaky with the larger fenestrations of around 600 nm [148]. These leaky blood vessels allow

macromolecules to diffuse into the inflamed joint tissues, supporting the delivery of nanocarriers. Hence, nanocarriers can be designed with specific properties to pass through the leaky vasculature of inflamed tissues.

Inflammatory cascade in arthritic synovium: The increased vascular permeability and leaky vasculature allow inflammatory cells, like macrophages, lymphocytes, and neutrophils, to extravasate (escape out) from the bloodstream and enter the joint space, leading to an accumulation of immune cells in the synovium [122,149]. Dendritic cells activate T-cells, which initiate immune responses and produce pro-inflammatory cytokines. Dendritic cells produce signalling molecules called chemokines, which attract leukocytes to the site of inflammation. Hence, the dendritic cells trigger the movement of leukocyte infiltration into the arthritic joint [145]. The extravasated inflammatory cells play a crucial role in amplifying the local inflammatory response within the joint. These inflammatory cells release pro-inflammatory mediators, cytokines, and enzymes in the joint tissue that contribute to tissue damage, joint destruction, and the perpetuation of inflammation in arthritis.

ELVIS effect: As nanocarriers extravasate from the highly permeable leaky vasculature of RA-affected regions, they are further sequestered by inflammatory cells in the inflames synovium. Hence, the phenomenon of the ELVIS effect is named so, which holds significance in arthritis management [119,146,150,151]. In this manner, nanocarriers accumulate well in the inflamed joint.

7.2. *Mechanism and significance of elvis effect*

An ideal drug delivery system for RA should be able to deliver the optimal concentration of drug to the affected synovial joints, which is not feasible with conventional oral and parenteral delivery of drugs as the former drug delivery lacks target-specificity and the latter results in rapid clearance of the drug. However, it is possible with the help of the ELVIS effect by which nanocarriers accumulate in the inflamed joints due to the increased permeability and leaky vasculature effects associated with arthritis disease as mentioned above; the ELVIS effect is facilitated by designing nanocarriers' size, surface charge and other characteristics that allow them to navigate through the endothelial gaps present in the blood vessels. Once entered into the inflamed tissue, nanocarriers may be sequestered by inflammatory cells, such as macrophages or neutrophils, through various mechanisms, either phagocytosis or endocytosis [151,152]. Within the inflammatory cells, the nanocarriers can release their cargo, such as anti-inflammatory drugs, targeting the site of inflammation. Harnessing the ELVIS effect for targeted therapy could involve designing nanocarriers with specific surface properties or ligands that facilitate interactions with inflammatory cells, optimizing drug delivery to the site of action. Taking advantage of this phenomenon, nanomedicine can be precisely delivered to the inflamed synovium, allowing for localized therapy. This targeted and localized approach enhances treatment efficacy while minimizing systemic and off-target side effects. Understanding the ELVIS effect might be valuable in developing therapeutic strategies to reduce inflammatory cell infiltration and subsequent joint inflammation in arthritis.

8. Therapeutic manipulation of macrophages mediated by nanocarriers

8.1. *Internalization of nanocarriers by uptake of macrophages*

A large number of activated macrophages reside in the synovial membrane of knee joints of arthritis patients when compared to healthy joints. In the inflamed joint, these synovial macrophages undergo activation and constitute approximately 30%–40% of the cellular composition. They play a crucial role in regulating the secretion of pro-inflammatory cytokines and enzymes that drive the inflammatory response and joint destruction [153]. In the therapeutic manipulation of macrophages using nanotechnology, researchers have focused on harnessing the inherent ability of synovial macrophages to recognize and engulf foreign or potentially harmful pathogens. The mechanism of uptake of nanocarriers may be phagocytosis, micropinocytosis, or endocytosis [154,155]. Thus, nanocarriers may be successfully absorbed and phagocytosed by macrophages without any ligand or surface modifications, facilitating passive targeting. Therefore, targeting immune cells like macrophages using a nanocarrier system was a way that was examined on priority. Hence, nanocarriers can be engineered for the passive-targeting approach with specific physicochemical properties, such as mean particle size (MPS), shape, charge, and surface chemistry. The surface functionalization of nanocarriers can be done with coating ligands to facilitate the active targeting by specific cells in the inflamed synovium.

The uptake of nanocarriers by macrophages can be done either by using non-specific mechanisms or specific receptor-mediated pathways, such as clathrin-mediated and scavenger receptor-dependent endocytic pathways. In the process of endocytosis, the cell membrane undergoes invagination and forms a vesicle that encapsulates the nanocarriers. Subsequently, this vesicle merges with the cell organelle known as the lysosome, which contains enzymes that help degrade the vesicle's contents, including the nanocarriers. As a result, drugs get released from the nanocarriers into the cytosol and are available at the targeted site of inflammation [112]. The covalent bond strength between NPs and drugs makes them highly stable and, therefore, most likely to be disrupted only under harsh environments such as inside lysosomes [156]. In this manner, after being recognized and internalized by macrophages, nanocarriers are typically disassembled within the lysosomes or cytosol of the cells, leading to the release of the encapsulated drugs, which will aid in the improved efficacy of treatment [157]. For example, to treat RA, Qindeel et al. [158] have developed transdermal PCL-PEG-PCL loaded MT micelles, incorporated them into the solution of Carbopol 934 gelling agent, and eucalyptus oil was used as a penetration enhancer to form a hydrogel. An *in vitro* study revealed that the formulation has shown a high uptake of nano micelles by activated macrophages through clathrin-

mediated and scavenger receptor-dependent endocytic pathways. MT micelles exhibited higher accumulation, which resulted in longer retention of the MT drug in the diseased arthritic joint of mice.

However, alternate strategies have been explored to modulate the recognition and internalization of nanocarriers by macrophages. One of these includes the use of protective coatings, aiming to achieve sustained drug delivery. This approach involves designing drug-delivery systems with non-spherical sizes or enveloping nanocarriers in protective coatings, such as PEG or erythrocyte membranes. These modifications aim to prevent or delay macrophage recognition, allowing the nanocarriers to remain in the joint for an extended period [157]. This strategy has been mainly employed to achieve sustained drug release from the nanocarriers for prolonged therapeutic benefit, as the nanocarriers are not rapidly taken up by macrophages. One such approach is the "inverse-targeting approach", which involves a strategic design of nanocarriers to circumvent specific clearance mechanisms, allowing the therapeutic agent to reach its intended target more effectively. Simply, it is the concealment or camouflaging of nanocarriers through hydrophilic coatings like PEG polymers that prevent recognition and clearance by the immune system. Hence, this approach helps escape the nanocarriers by preventing their passive uptake by the RES, thereby facilitating the nanocarriers to have biocompatibility, long half-lives, and transport the drugs directly to the targeted area [159].

8.2. *Enhancement of macrophage targeting*

Targeting macrophages is crucial for optimizing drug delivery in arthritis, as macrophages play a central role in the inflammatory response within the affected joints. Nanocarriers can be decorated with ligands such as sugars, lipids, peptides, or antibodies specific to macrophage receptors, facilitating macrophage uptake by macrophages. These macrophage-targeting ligands (like CS) have also been extensively studied in cancer, showing improved macrophage-targeting capabilities [160]. Although the details of these ligand-nanocarrier interactions are beyond the scope of this review, insights gained from these studies can provide valuable information for designing NP-based targeting strategies for macrophages in the context of arthritis.

The specific ligand-receptor interactions improve the targetability in the case of arthritis management. Macrophages in the inflamed joints often overexpress particular surface receptors, such as folate receptors, mannose receptors, galactose receptors, scavenger receptors-A (SR-A) and others [161]. These receptors become targets for ligand-based drug delivery. The common ligands for macrophage targeting include folic acid, mannose, CS, dextrin, HA, or antibodies targeting specific macrophage antigens. This ligand-receptor interaction is based on the affinities between them, *i.e.*, through the interaction of chemical functional groups. Hence, ligands are specific and chosen based on their high affinity for the identified macrophage surface receptors. Thus, the specific ligand-receptor interaction is highly selective, like folic acid ligand interaction with folic acid receptors, HA ligand interaction with cluster determinant 44 (CD44) receptors, and galactose ligand interaction with galactose receptors [162]. This specific ligand-receptor interaction facilitates the binding and delivery of nanocarriers to macrophages, minimizing off-target effects on other cell types and tissues. The delivered therapeutic agents within macrophages can modulate their activity, influencing the inflammatory response. In this manner, this targeted and localized approach contributes to the management of arthritis by addressing the central role of macrophages in inflammation. The receptor-ligand interactions regulate multiple aspects of macrophage polarization and function, including aggregation, phagocytosis, and macrophage-derived products [163]. Some of the examples regarding ligand-receptor interactions used in managing arthritis are mentioned below.

Targeting the folate receptors on activated macrophages, folic acid can be used as a ligand to fabricate nanocarriers [164]. Yang et al. [139] prepared PEGylated silver NPs decorated with folic acid that can target the activated macrophages of the RA-inflamed synovial membrane. Once entered into the macrophages, the folic acid coated-AgNPs dissolved, releasing silver ions (Ag^{+}) in response to intracellular glutathione (GSH). This triggered a cascade of events wherein the M1 macrophages underwent apoptosis, contributing to their depletion. Simultaneously, the released Ag+ ions facilitated the phenotypic transition of M1 macrophages into the M2 phenotype, known for its anti-inflammatory properties, which are beneficial in treating RA.

To target the SR-A receptors overexpressed on macrophages, Ting Gong et al. [165] synthesized palmitic acid (ligand) coated bovine serum albumin NPs (PA-BSA NPs) and loaded celastrol. They evaluated the targeting effect of PA-BSA NPs, both *in vitro* and *in vivo*. The results showed the remarkable targeting ability of SR-A, leading to enhanced uptake by activated macrophages with a more pronounced targeting effect (~9 times when compared to BSA NPs) and improved delivery of anti-inflammatory drugs (celastrol) to inflamed tissues. These findings hold promise for developing targeted therapies for inflammatory conditions, potentially improving treatment efficacy in RA.

The over-expression of CD44 receptors on macrophages and articular chondrocytes can be better targeted by using HA as a ligand on the surface of nanocarriers to manage arthritis [166,167]. Chen et al. [168] synthesized HA-PLGA-NPs to treat OA. The study results demonstrated that the HA-PLGA-NPs have a higher tendency to localize in the innermost layer of the synovial membrane. This is due to the less dense ECM of cartilage in case of degenerative OA lesions. Cell internalization of HA-PLGA-NPs was higher in OA-damaged cartilage, whereas internalization within the healthy cartilage rats was relatively weaker. This could be attributed to the dense ECM of the cartilage in healthy rats. This change in matrix density in OA may facilitate the accessibility of NPs to chondrocytes in damaged areas of the cartilage [168,169]. Similarly, for RA-targeted delivery, polymeric NPs of MT coated with HA exhibited more cell uptake by activated macrophages through CD44 receptor-mediated endocytosis [170].

The over-expression of dextran-binding C-type lectins and SR-A can be better targeted using dextran sulfate as a macrophage-targeting ligand. For example, Yang

et al. [171] synthesized dextran sulfate grafted (coated) MT conjugate (DS-g-MT) macrophage-targeted micelles to study macrophage-targeted drug delivery systems and also synthesized untargeted micelles of MT for comparison. The targeted micelles demonstrated effective localization in the inflamed joints via the EPR effect instead of being rapidly eliminated by RES. The remarkable targetability of DS-g-MT was validated through fluorescence imaging in *ex vivo* biodistribution studies. Compared to free MT, higher accumulation of DS-g-MT is due to the specific bond between DS and SR-A overexpressed on the activated macrophages.

Overall, coating with specific macrophage-targeting ligands on nanocarriers in arthritis management improves precision, efficiency, and the therapeutic effectiveness of drug delivery. This approach provides a targeted strategy for treating inflamed joints while concurrently minimizing systemic side effects.

8.3. *Macrophages polarization and depletion in arthritis exhibited by nanocarriers*

Macrophages play a critical role in the pathogenesis of arthritis, and their polarization state imbalance significantly impacts the progression and resolution of the disease [172]. Macrophage polarization refers to the functional and phenotypic changes that macrophages undergo in response to different microenvironmental signals. In arthritis, macrophages can adopt distinct polarization states, primarily characterized as either pro-inflammatory (M1) or anti-inflammatory (M2) phenotypes [172]. In arthritis, an abundance of M1 macrophages is more when compared to M2 macrophages [172–174]. The M1 macrophage phenotype will be dominant in the joints of arthritic patients. They trigger the release of pro-inflammatory cytokines, leading to joint inflammation and damage, which harm arthritis patients. Apart from the pro-inflammatory triggering nature exhibited by M1 macrophages, they also secrete MMPs [175], reactive oxygen species (ROS) [176], and nitric oxide (NO) [177]. MMPs are the enzymes that degrade the components of ECM in the joint. This matrix degradation contributes to tissue destruction and joint damage seen in arthritis. M1 macrophages produce ROS and NO. This is possible for macrophages by activating enzymes called inducible nitric oxide synthase (iNOS) and NADPH oxidase [177]. These reactive molecules like ROS and NO can cause oxidative stress, leading to tissue damage, and promote the recruitment and activation of immune cells. In arthritic conditions, the detrimental effects of M1 macrophages highlight the imperative to eliminate or reduce their presence. One such approach to reduce the M1 macrophages is macrophage depletion to reduce the inflammation cascade.

M1 macrophage depletion: Functionalized NPs can be engineered to carry drugs or molecules that specifically induce macrophage apoptosis or facilitate their phagocytosis by other immune cells, thereby achieving macrophage depletion. For example, a study demonstrated the potential of ligand-receptor active targeting to treat RA. Folic acid receptor β-specific monoclonal antibody (FRβ-mAb) is used as a coating ligand. FRβ-mAb targets the folic acid receptor β, which is present on activated M1 macrophages only but not on resting macrophages. Study results revealed that FRβ-mAb caused the depletion of activated M1 macrophages in the *in vivo* studies of arthritic rats [178]. Macrophage repolarization: Macrophage repolarization involves shifting macrophage phenotypes from the inflammatory M1 state to the anti-inflammatory M2 state. When M1 macrophage transitions to the M2 phenotype, they demonstrate anti-inflammatory effects, contributing to the repair of cartilage and joint tissues [172,179].

Utilizing either passive or active targeting approaches, the selective delivery of drugs, genes, anti-inflammatory interleukins, or plasmids that target the macrophages is possible. This targeted delivery aims to promote the transition of macrophages toward the M2 phenotype. For example, a study conducted by Kim et al. [180] demonstrated the potential of manganese ferrite and ceria-anchored MSNPs to alleviate inflammation in arthritis. The NPs exhibited a synergistic ability to scavenge ROS and generate oxygen, leading to a favourable therapeutic outcome. Moreover, their administration resulted in the desirable phenotypic conversion of macrophages from M1 to M2, indicating a potential strategy for modulating macrophage polarization in inflammatory conditions. In another study, Paoletti et al. [181] evaluated the therapeutic potential of antagomiR-155–5p (micro-RNA) entrapped within PEG-liposomes to treat RA. The study revealed that PEG-liposomes facilitated micro-RNA delivery to monocytes and M1 macrophages and impaired their functioning. The study results also showed that micro-RNA is also responsible for promoting the transition of M1 macrophages to M2 macrophages and reducing joint inflammation in murine models of RA.

Overall, nanocarriers offer a sophisticated and targeted approach to modulating macrophage behaviour in arthritis. This enhances the precision and effectiveness of therapeutic interventions, potentially leading to improved outcomes in managing arthritis.

8.4. *Cell membrane-camouflaged NPs*

Cell membrane-camouflaged NPs (CMCNPs) feature a “core-shell” structure with a synthetic nanocarrier core enveloped by a thin layer of the natural cell membrane [182] They are created through the fusion of cell membranes with NPs and offer promising advantages such as prolonged circulation time, evasion of immune responses, targeted delivery to specific tissues or cells, and sustained drug release behaviour [183,184]. The body treats nanocarriers prepared by synthetic polymers or substances as foreign particles and triggers immune responses. But, when the natural cell membrane coating is used, it mimics the natural cells in the body and enhances biocompatibility. In general, the membranes obtained from blood cells have the innate property of immune escape. Hence, this natural property of biomimetic cell membrane-coated nanocarriers diminishes the risk of immune recognition. The cell membrane coating provides a stealth effect, allowing the NPs to evade the immune system and circulate in the bloodstream for extended periods. For instance, Rao et al. [183] prepared biomimetic magnetic NPs coated with RBC membrane. This nanosystem utilizes the “do not eat me” marker CD47 on RBCs to evade immune clearance

through interactions with the signal regulatory protein-alpha (SIRP-α) receptor. The *in vivo* study results revealed that prolonged circulation time was observed without inducing immune responses at both cellular and humoral levels.

The natural cell membrane's surface proteins and receptors of CMCNPs allow targeted delivery, enhancing precision in drug delivery to specific tissues or cells. For example, Li et al. [185] prepared macrophage-derived microvesicle (MMV)-coated NPs containing tacrolimus drug that mimic macrophages for targeting RA. The MMV membrane proteins were similar to those of RA-targeting macrophage macrophages and exhibited bioactivity in mice. These MMV-coated NPs efficiently targeted M1 macrophages, facilitating efficient drug delivery to the desired sites of the inflamed joints. Another study conducted by Wang et al. [184] developed MMVs with ZIF-8 NPs containing DEX drug to treat arthritis. *in vitro* and *in vivo* experiments showed that this nanosystem had a prolonged circulation time, which permitted sustained drug release in inflamed joint tissues.

Overall, the above strategies demonstrate the potential of the nanocarriers to manipulate macrophages to enable efficient drug delivery in arthritis management.

9. Types of nanocarriers and the significance of their physicochemical characterization

Nanocarriers, miniature structures on the nanoscale, have revolutionized biomedical applications by offering innovative solutions for drug delivery. A nanocarrier is a nanomaterial used as a transport module for another substance, such as a drug, gene, or other bioactive agent. Their small size allows for precise targeting at the cellular or molecular level, while their versatile nature enables customization for diverse therapeutic payloads. Additionally, nanocarriers can improve the pharmacokinetics of drugs, providing sustained release profiles and minimizing toxicity. This discussion explores the classification of nanocarriers, shedding light on their diverse types and functionalities.

9.1. *Classification of various nanocarriers*

Different nanocarriers are used in biomedical applications, which has revolutionized the improvement of therapies in the medical field. Fig. 4 displays the classification of several kinds of nanocarriers that are widely used to improve drug delivery. Nanotechnology primarily provides two types of nanocarriers, namely nanomaterials and nanodevices, which significantly impact the pharmaceutical industry and other related fields. Nanomaterials focus more on material properties, whereas nanodevices focus more on device functionalities.

9.1.1. *Nanodevices*

Nanodevices are tiny functional devices designed and engineered at the nanoscale range. Nanodevices include microfluidics, microarrays, nano, and micro-electromechanical systems (NEMS/MEMS) [186]. Microfluidics deal with the manipulation of fluids in the microlitre or nanolitre scale). Microarrays deal with the conduction of diverse biological tests like DNA, protein, cell, and antibody analysis). NEMS/MEMS have one common characteristic, i.e., they have moving elements whose motion is managed by external electrical connections, providing them with mechanical functionalities [187].

9.1.2. *Nanomaterials*

Nanomaterials are materials that possess a nanoscale size of 1 to 100 nm or below 100 nm in at least one dimension that are prepared by nanotechnology processes [188]. Nanocrystalline and nanostructured materials are subcategories of nanomaterials [189]. Nanocrystalline materials are polycrystalline substances with a few nanometer-sized crystallites (grains). Nanostructured materials are nanomaterials that have been processed to create unique shapes and characteristics, which can be generally categorized as organic, inorganic or hybrid-a blend of the two.

9.1.2.1. Organic nanostructured carriers Organic nanostructured carriers are typically made of biocompatible and biodegradable materials such as biopolymers and lipids designed to encapsulate the drug. Lipidic nanocarriers and polymeric nanocarriers are the sub-categories of organic nanostructured carriers that are entirely different from inorganic nanocarriers, as shown in Fig. 4.

Lipidic nanostructured carriers: Lipidic nanostructured carriers are the nanocarriers where the lipidic components are used for their formation. Based on their chemical composition and properties, lipidic nanocarriers may have micellar, particulate, and vesicular types. Fig. 5 displays the overview of lipidic nanostructured carriers. Micellar, particulate, and vesicular types are colloidal systems with dispersed phases available as micelles, particles, and vesicles, respectively. Micellar type of lipidic nanocarriers include emulsomes, nanoemulsions (NEs) and lipidic micelles. Particulate types of lipidic nanocarriers include SLNs, NLCs, lipid-drug conjugates, and lipospheres. Vesicular types of lipidic nanocarriers include liposomes, ethosomes, proliposomes (PLs), transferosomes (TRSs), transethosomes, cubosomes (CBSs), and hyalurosomes [123].

Polymeric nanostructured carriers: Polymeric nanocarriers include nanocarriers made up of polymers that may be natural or synthetic in origin and biodegradable or non-biodegradable [190,191]. Polymeric nanocarriers include polymeric NPs, nanogels (NGs), polymeric micelles, dendrimers, polymersomes, nanocapsules (NCs), nanospheres, polymeric-drug conjugates, hydrogel NPs, polymerized cyclodextrins and nanosponges (NSPs) [192]. Fig. 6 displays the overview of polymeric nanostructured carriers. Natural polymers include dextran, HA, gelatin, alginate, CS, elastin, silk fibroin, alginate, and cellulose derivatives. Synthetic polymers include PLGA, PCL (poly ε-caprolactone), PLA (polylactic acid), PGA (polyglycolic acid), PE, HPMA (N-(2-hydroxypropyl) methacrylamide co-polymers), PHEMA (N-(2-hydroxyethyl) methacrylamide polymers), PVP (poly vinylpyrrolidone), poly(ethyleneimine), PAA (poly amidoamines), PDMAEMA (poly [2-(N, N-dimethylamino)ethyl methacrylate]), PAsp (poly aspartic acid), poly organophosphazene), PPS (Poly(propylene sulfide)), polyurethanes, PNIPAM (poly N-isopropylacrylamide), PVCL

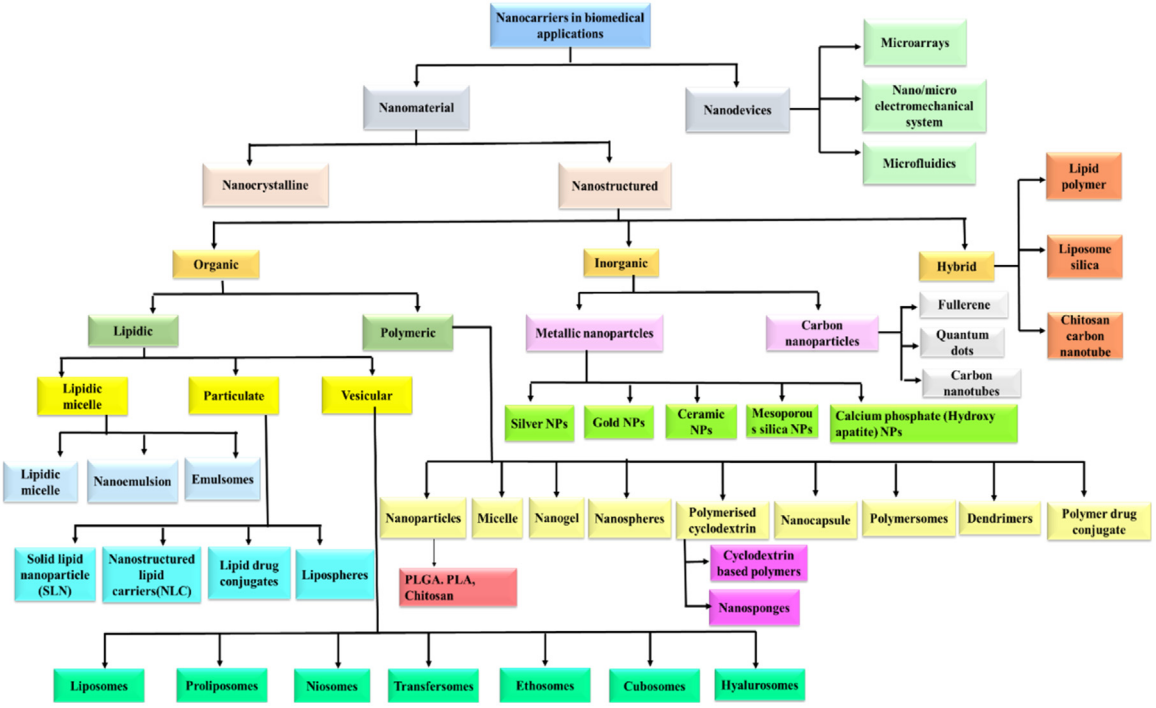

Fig. 4 – Classification of types of nanocarriers used in various biomedical applications.

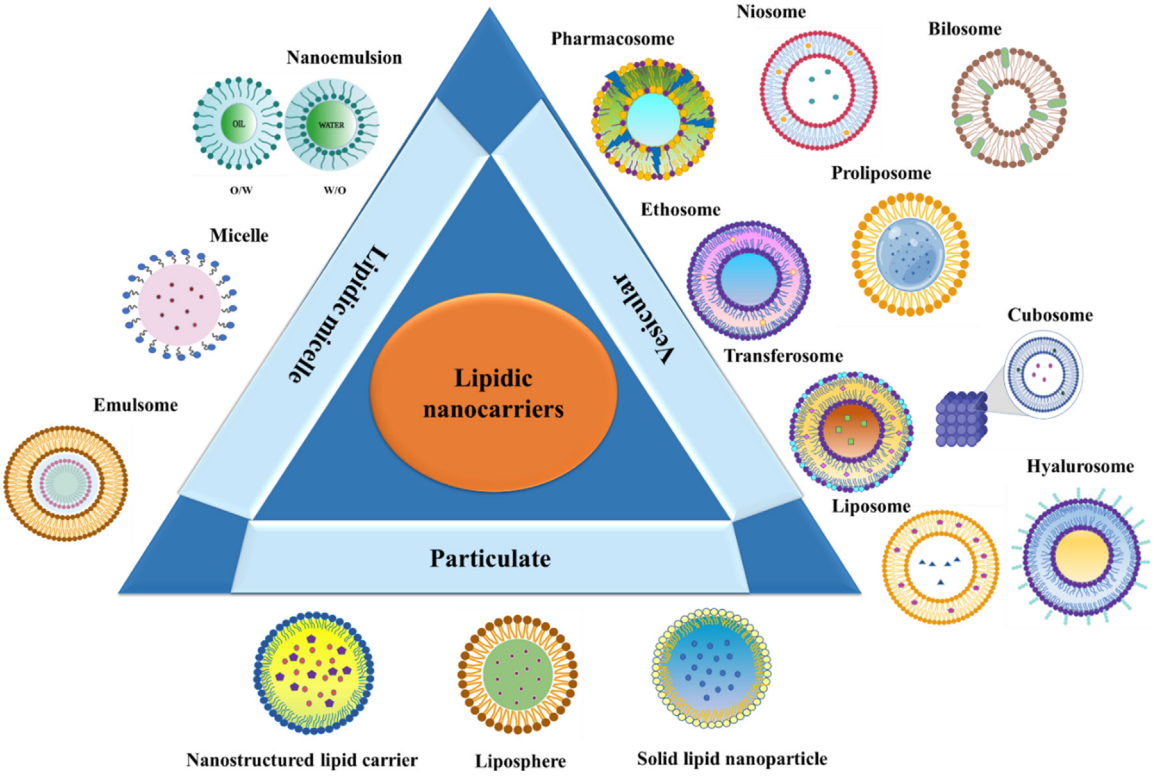

Fig. 5 – Overview of lipidic nanostructured carriers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

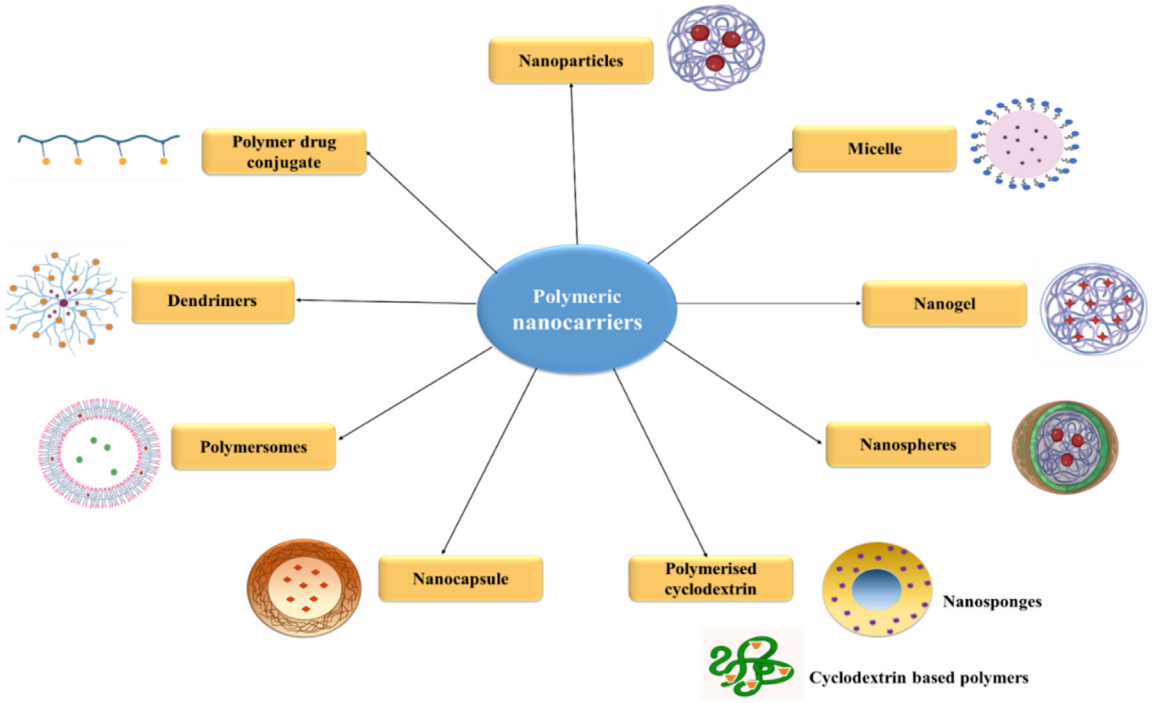

Fig. 6 – Overview of polymeric nanostructured carriers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

(poly N-vinyl caprolactam) and terpolymer [193]. Widely used biodegradable polymeric NPs include PLGA NPs, PLA NPs, PGA NPs, CS NPs and gelatin NPs, and PNIPAM and PVCL are widely used nonbiodegradable synthetic polymers [194]

9.1.2.2. *Inorganic nanostructured carriers* Metallic nanocarriers and carbon-based nanocarriers are the sub-categories of inorganic nanostructured carriers. Inorganic nanocarriers comprise metallic nanocarriers like gold NPs, silver NPs, copper NPs, magnetic NPs, etc., and their metal-oxide NPs like iron-oxide NPs, copper-oxide, and zinc-oxide NPs, etc. Inorganic nanocarriers also include MSNPs (silica NPs with a mesoporous structure, *i.e.*, voids or cylindrical channels with pore size ranging from 2 to 50 nm), metal sulfide NPs, ceramic NPs, calcium-phosphate (hydroxy–apatite) NPs, carbon-based nanocarriers like carbon nanotubes, fullerenes and quantum dots (QD) [195] which are shown in Fig. 7.

9.1.2.3. *Hybrid nanostructured carriers* Hybrid-type nanocarriers may include organic-organic, inorganic, or organic-inorganic types. They include lipid-polymer hybrid NPs (LPHNPs), CS carbon nanotubes, and liposome-silica nanomaterials. Examples of LPHNPs used in the treatment of RA are MT-loaded LPHNPs coated with folic acid ligand [196] and dual loading of tripterine and all-trans retinoic acid in LPHNPs for synergistic therapy [197]. An example of CS carbon nanotubes used to treat OA is carbon nanotubes loaded with keratin/CS/chondroitin sulfate (CDS) composite [198]. Another example of a hybrid nanostructured carrier to treat RA is the development of a liposome/gold hybrid nanocarrier [199].

9.2. *Significance of physicochemical properties and their implications in drug delivery*

Due to their nano size and high specific surface area, NPs exhibit unique structural, physicochemical, and biological properties [149]. The MPS, PDI (polydispersity index), ZP (zeta potential), and EE are the critical physicochemical parameters for the evaluation of any nanocarrier. MPS plays a crucial role in drug delivery systems as it influences the rate of drug release and bioavailability. PDI serves as a metric for assessing the distribution of PS within a sample. A low PDI signifies a narrow size distribution, which is desirable in drug delivery systems as it ensures homogeneity and uniform drug release, while a high PDI indicates a broader size distribution. ZP represents the potential difference between a particle's surface and the surrounding fluid. It is the best predictor of dispersion stability since it estimates the electrostatic repulsion or attraction between particles. EE is the ratio of the drug entrapped into the carrier to the total amount of drug contained in the dispersion.

The importance and implications of these parameters vary based on the specific application and the type of nanocarrier used. In drug delivery, these parameters can affect the drug's pharmacokinetics, pharmacodynamics, toxicity, and immunogenicity.

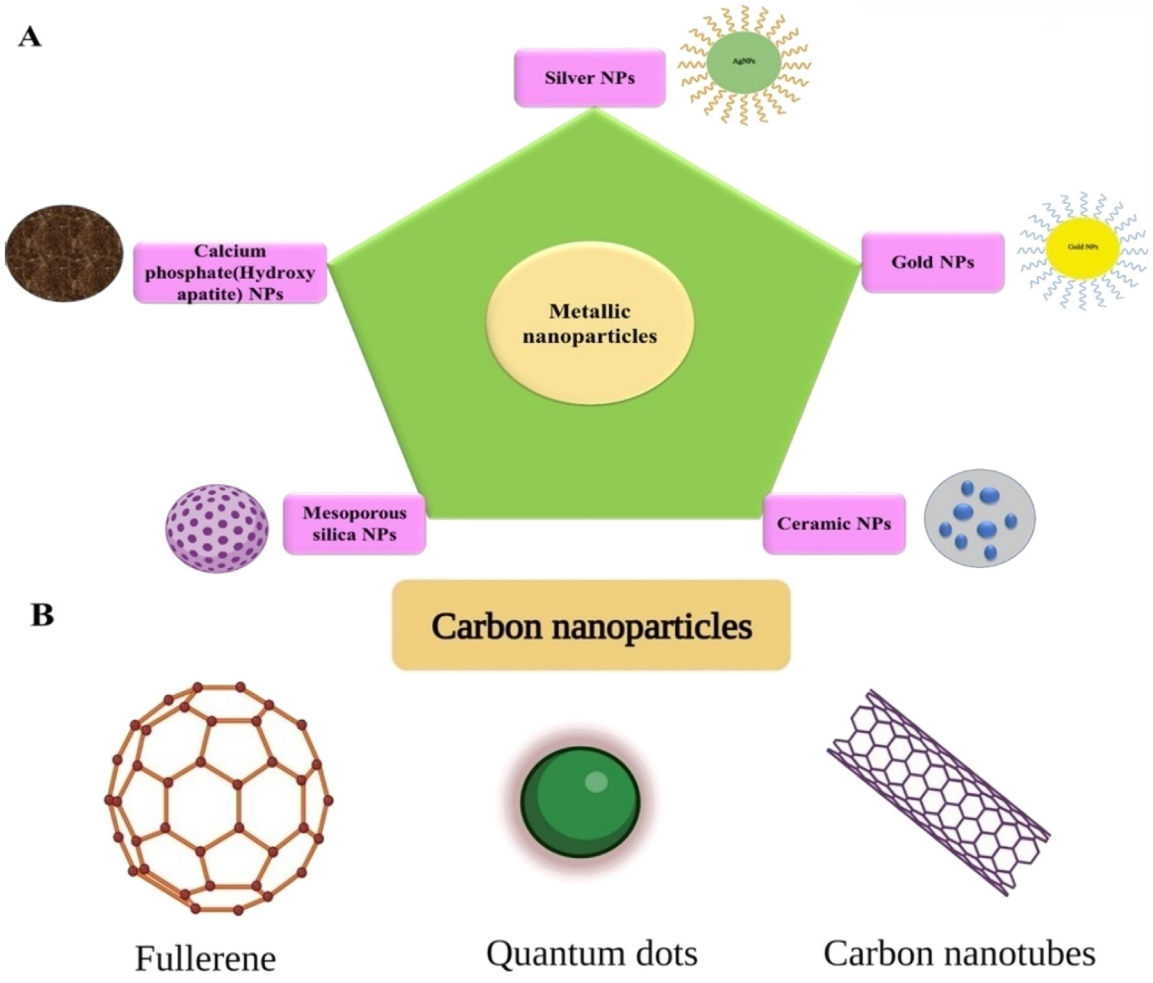

Fig. 7 – Overview of inorganic structured nanocarriers. (A) Metallic nanoparticles and (B) Carbon nanoparticles.

10. Applications of gel-based nanocarriers in the management of OA and RA

The application of various gel-based nanocarrier systems was explained in terms of formulation aspects and anti-inflammatory activity below.

10.1. *Micellar type*

NEs come under micellar type of lipidic nanocarriers. They are transparent colloidal dispersions of the two immiscible liquids, the oil phase (o) and aqueous phases (w), in which one is dispersed in the other with the help of a stabilizer, *i.e.*, emulgent. This emulgent may be surfactants or co-surfactants used to form a stable homogenous dispersion [200]. The "o" acts as a dispersed phase (in the form of nano-sized droplets) and disperses in the dispersion medium "w" to favour o/w NE (Fig. 8). It is vice-versa for w/o NE (Fig. 8). They serve as the best method by which hydrophobic drug solubility enhancement is possible and enhances bioavailability. Despite their many benefits, NEs have lower viscosity, leading to lower skin retention time, poor spreadability, and faster drug release, making transdermal application challenging. To address this issue of NE's low viscosity, it is incorporated into various appropriate gelling agents, such as polymers and copolymers [201]. The o/w or w/o NEs are combined with the gelling agent to form emulgels, which have a high level of patient acceptance as they have the combined benefits of emulsion and gels [202].

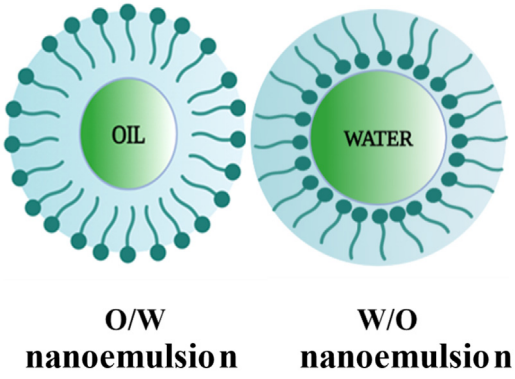

Fig. 8 – Diagrammatic structure of types of NE.

10.1.1. MT-Mgo transdermal nanoemulgel (NEG)

MT is a widely used DMARD for the management of arthritis, but its oral use can lead to GIT side effects and systemic toxicity. Hence, transdermal/topical administration of MT has been explored as an alternative strategy to treat arthritis, but its poor skin permeation and low bioavailability have limited its clinical use. To overcome these drawbacks, Yang et al. [203] developed magnesium oil (Mgo) loaded transdermal NEG of MT for improved skin penetration, improved arthritic joint mobility, repair, and reduced inflammation. In this study, Mgo enhanced joint mobility and repair. The MT (0.2%, w/v) and Mgo (2%, v/v) were combined to produce the organic phase. The aqueous and organic phases were homogenized quickly to create MT-Mgo NE. MPS and PDI were 175 ± 35.4 nm and 0.146 ± 0.034. The ZP of MT-Mgo NE was found to be −19.1 ± 2.3 mV. Carbopol 940 as a gelling agent and triethanolamine as an alkalizer were used for MT-Mgo NEG preparation. A plethysmometer was used to measure the increase in paw volume. In *ex vivo* studies, MT-Mgo NEG demonstrated nearly 100% penetration in 24 h and roughly 89.3% permeation in 12 h, indicating that MT NE considerably enhanced the skin permeation rate. MT and Mgo solution in PEG-200 demonstrated very little permeability (only 11.6%) in 24 h. When evaluated regarding functional recovery and increased *in vivo* efficacy, Mgo helped reduce pain at the inflammation site and improved joint healing and mobility. Hence, developing transdermal MT-Mgo NEG could be a better option for treating arthritis.

10.1.2. Valdecoxib NEG

Mishra et al. [204] formulated the NEG of valdecoxib to manage arthritis. In this study, Tween 80 and ethanol were used as surfactant and co-surfactant for preparing the valdecoxib-NE. The MPS and ZP of valdecoxib-NE were reported as 28.6 ± 9.0 and 9.22 to −0.044 mV. A gelling solution of carbopol is used to make a valdecoxib NEG. *In vitro*, drug release of valdecoxib-NEG exhibited 76% in 24 h, explicating NEG's sustained release behaviour. *in vivo*, NEG of valdecoxib has shown 72% inhibition of oedema, and valdecoxib plain gel has shown only 38%. Hence, developed valdecoxib NEG could be a better option when compared to a plain drug.

10.1.3. MT topical NEG

Das et al. [205] developed and evaluated topical MT-NEG formulation to treat RA. Optimized MT-NE preparation includes the oil phase (peanut oil), surfactant (Tween 20), and co-surfactant (PEG 400), where the preparation is done through an emulsification process. The optimized MT-NE was translucent, where the average droplet size and ZP were reported to be 195.1 nm and −0.278 mV, respectively. Badam gum was employed as a gelling matrix to form MT-NEG. The drug content of MT NEG was found to be 98.11% ± 0.34%. The drug release study for the MT topical NEG was 95.11% ± 0.02% release of MT in 12 h. The pH range, viscosity values, and spreadability values were in optimal range. The developed MT NEG was stable at temperatures range of −25 to +45 °C. Therefore, developed MT NEG could be a better option when compared to plain drugs.

10.1.4. Diflunisal topical NEG

Bashir et al. [206] designed and evaluated the topical diflunisal (DIF) NEG as well as DIF-IC [solubility-enhanced DIF inclusion complexes (IC) made with hydroxy propyl beta cyclodextrin (HPβCD) and poloxamers-188] NEG to treat inflammation. Upon finding satisfactory results in the case of optimal release profiles, DIF and DIF-IC were prepared as NEG formulations with suitable gelling agents such as carboxymethyl cellulose sodium, sodium alginate and xanthan gum (XG) to prepare optimized respective NEGs. Subsequently, these NEGs were used to test three *in vivo* anti-inflammatory models: the carrageenan-induced, histamine-induced and formalin-induced paw oedema model. Comparisons of the *in vitro* skin permeation of DIF-IC–NEG and DIF-NEG revealed a significant boost when using the former. The more skin permeation of DIF-IC–NEG might be due to cyclodextrin liberating DF molecules from the IC, thereby maintaining a higher proportion of DIF-free drugs and leading to higher flux values. Moreover, the anti-inflammatory activity was improved when XG was added to the NEG formulation containing DIF-IC. Thus, DIF-IC–NEG formulation prepared with XG could be a better option for treating inflammatory conditions topically.

10.1.5. Tofacitinib topical NEG

Nishal et al. [207] prepared topical tofacitinib (TF)-NEG to manage RA. A high-energy ultrasonication method was used to prepare the TF-NE. The MPS of TF-NE was found to be 106.3 ± 2.8 nm, and loading efficiency was found to be 19.3% ± 1.8%. To formulate TF-NEG, the gelling solution of carbopol 934 was used. *In vitro* drug release experiments of TF-NEG showed a cumulative release of 89.64% ± 0.97% over 24 h. This designed formulation of TF-NEG could be a suitable option for delivery mechanism via topical route for the management of RA.

10.1.6. Dasatinib-loaded topical NEG

Donthi et al. [208] developed topical dasatinib (DST) NEG for RA treatment. DST-NEG was optimized using a central composite design and the quality-by-design (QbD) methodology. The DST-NE was prepared by utilizing a hot emulsification approach, and then the homogenization procedure was used to minimize the MPS. The obtained MPS and EE were 172.53 ± 3.33 nm with 0.160 ± 0.014 PDI and 95.11% ± 0.16%, respectively. Sustained drug release of DST from the DST-NE was found to be 89.90 ± 6.25 in 12 h. *Ex vivo* skin permeability of DST-NEG revealed greater permeation than that of the DST-gel. For DST-NEG, the transdermal flux was found to be 2.11 ± 0.25 μg/cm^2/h, while the transdermal flu for formulations with the free drug was found to be 0.6 ± 0.19 μg/cm^2/h. Compared to adjuvant-induced arthritis (AIA), paw swelling was reduced in the FCA-induced arthritis model. This designed formulation of DST-NEG could be a better option for RA treatment

10.2. Particulate type of lipidic nanocarriers

It includes lipids NPs like SLNs and NLCs. Fig. 9 depicts the types of particulate lipidic nanocarriers along with their compositions.

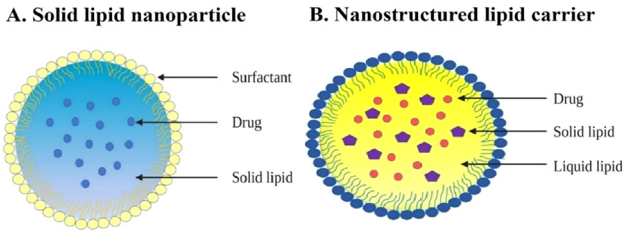

Fig. 9 – Types of particulate lipidic nanocarriers and their compositions. (A) SLN and (B) NLC.

10.2.1. SLNs and applications of gel-based SLNs

The newest generation of nanoparticulate drug carriers is SLNs, for which much attention was received as a novel topical colloidal drug carrier system. The SLNs have a diameter of 50–1000 nm and are spherical, including phospholipid components. They promote the absorption of lipophilic and hydrophilic drugs via the skin because of their amphiphilic nature. They comprise solid lipids and surfactant molecules, as shown in Fig. 9. The biocompatible and biodegradable physiological lipids used to prepare SLNs have a GRAS (generally recognized as a safe) rating. GRAS rating refers to a designation given by the U.S. Food and Drug Administration (FDA) regulatory for substances or chemicals considered safe for human consumption. Thus, using GRAS materials in SLNs makes them safer nanocarriers for drug delivery systems. These SLN carriers can promote controlled drug release, targeted drug delivery, improved physical stability, and tolerability [209]. They combine the benefits of polymeric NPs, fat emulsions, and liposomes while avoiding their drawbacks [210]. Unlike liposomal delivery systems, SLNs can maintain stable nano-suspensions for extended durations [211]. SLNs do not exhibit drawbacks such as unexpected expulsion or leakage of drugs from the lipid core, which is commonly observed in liposomes [211]. Therefore, SLNs impose higher drug EE and impart higher stability to the drug due to the presence of the rigid core lipid matrix [212].

Kesharwani et al. [213] prepared topical gel-based SLNs of etoricoxib (ETC) to treat arthritis. Stearic acid (as solid lipid) and Tween 80 were used to produce optimized SLNs through melt emulsification and solidification methods at low temperatures. MPS, ZP and EE of the ETC-SLNs were found to be 334 nm, −25.6 mV, and 70.76%, respectively. ThePS of the ETC-SLNs formulation was reduced as concentrations of Tween 80 were increased in the formulation. The higher negative ZP value indicates that the formulation might have good stability. Higher EE of the formulation was attributed to higher concentrations of stearic acid used. This study mainly evaluates the effect of a gelling agent on skin permeability. Therefore, two gelling bases, carbopol 934 and HPMC, were selected to prepare ETC-SLNs-carbopol gel and ETC-SLNs-HPMC gel. Compared to the ETC-SLNs-HPMC gel formulation, the ETC-SLNs-carbopol gel exhibited controlled release behaviour. Steady-state flux (Jss) is the rate of substance transport across a membrane or through a channel where the concentration gradient remains constant. Jss of ETC-SLNs-HPMC gel was found to be 19.892 ± 1.934 μg/cm^2/h, and Jss of ETC-SLNs-carbopol gel was found to be 21.968 ± 0.862 μg/cm^2/h. These results state that Jss was higher in the ETC-SLNs-carbopol gel formulation. Lesser Jss of ETC-SLNs-HPMC gel was due to the gummy nature of HPMC when compared to carbopol. Thus, ETC-SLNs-carbopol gel might be effective for topical administration as it enhances skin permeability.

Bhalekar et al. [214] formulated chloroquine (CQ)-SLNs gel to treat RA. The probe sonication method was used to prepare CQ SLNs. Probe sonication is a process in which sound waves are generated to agitate particles in a solution. As a result of the agitation, the particles are broken down into smaller ones, favouring further size reduction. CQ-SLNs have displayed a MPS of 113.75 nm, and the EE of CQ-SLNs was 97.23%. Both PS and drug EE are in agreement with the good physicochemical characteristics of a nanocarrier. To formulate CQ-SLNs gel, the optimized CQ-SLNs should be loaded into the 5% gelling solution of sodium carboxy methyl cellulose (SCMC). CQ-SLN gel exhibited the highest drug retention on the skin compared to CQ gel, indicating that SLNs are good nanocarriers which mimic the lipidic components of the SC layer of skin, thereby enhancing skin followed by retention on the skin. The CFA-induced arthritis test model was used to test the efficacy of CQL-SLNs gel. In the histopathology study, the degree of erosion of joints for CQ SLNs gel was 50% and 75% for the CQ gel group. These results indicate that the CQ-SLNsgel formulation effectively decreased bone erosion compared to other group rats administering CQ gel.

10.2.2. NLCs and applications of gel-based NLCs

NLCs are one of the new-generation lipid-based drug delivery systems [215]. Their emergence as a unique delivery system can be attributed to simple preparation techniques conducive to large-scale production, comparatively low toxicity, and a substantial drug-loading capacity [216]. NLCs were developed as an improvement over SLNs, which have limited drug-loading capacity due to their highly ordered lipid matrix. NLCs are the second generation of lipid NPs comprising a combination of solid lipid matrix and liquid lipids, as shown in Fig. 9. The solid and liquid lipid matrix provides increased drug loading, sustained release profiles, and improved stability. NLCs are usually found in a size range between 200 and 400 nm [217]. NLCs are impulsive colloidal nanocarriers for efficient transdermal drug delivery. They also have an advantage over alternative delivery technologies for local topical applications. NLCs have an occlusive action, which increases hydration and improves the skin's absorption of active substances. Increased biodistribution and bioavailability confer greater physical stability of topical preparations [218]. NLCs are linked to major quality problems such as the presence of various colloidal species, sterilization stability, presence of supercooled melts, gelation, polymorphic changes in lipids, etc. [217,219]. The supercooled melts refer to the situation wherein a sample may be stored below the lipid's melting point without undergoing lipid crystallization [219]. Otherwise, the lipid crystallization affects the drug release and drug stability in NLCs. By incorporating NLCs into hydrogels, the difficulties and disadvantages of using them in drug delivery could be solved and also maximize the prolonged drug release [217]. Hydrogels, being semi-solid systems, serve as effective carriers to impart the desired

consistency for applying NLC formulations onto the skin. Integrating NLCs and hydrogels not only strengthens the mechanical properties of the hydrogel but also reduces the NLC aggregation [217].

Shinde et al. [220] formulated intra-articular delivery of MT-NLCs gel to treat RA. The chemical ingredients used to prepare NLC were Capmul MCM EP (as the liquid lipid) and Compritol ATO 888 (as the solid lipid) in the ratio of 1:2 (w/w) and Tween 80 (as the surfactant) and PEG 400 (as the co-surfactant) in the ratio of 2:1 (w/w). A modified hot homogenization technique followed by a melt ultrasonication technique was used to prepare MT-NLC. The NLCs have a 107 ± 6 nm MPS, 0.365 ± 0.03 PDI, and 69.53% ± 1.23% EE, 13.54 ± 1.1 mV ZP. The developed aqueous dispersion of MT-NLCs was properly gelled with optimal concentrations of gelling substances Pluronics. The MT-NLC pluronic-based gel is thermosensitive, meaning it can change from a liquid to a gel state when the temperature shifts. Initially, it is in a liquid form, making it easy to inject into joints. Once inside the body, at normal body temperature, it transforms into a solid gel. The complete Freund's adjuvant (CFA)-induced arthritis model was used to study the efficacy of MT-NLC gel. A histological staining study was performed on rats' knee joints to determine the biocompatibility of the MT-NLC gel. The results of the biocompatibility study revealed that the formulation is non-toxic and biocompatible, as there was no immune cell infiltration in the synovial cavity. *In vitro* drug release studies depicted that MT-NLC gel exhibited 92.41% prolonged drug release after 108 h. Using the MT-NLC-based gel, a significant reduction in the swelling of rat joints was seen over 28 d Because of its proven efficacy results, intra-articular therapy to treat inflammatory disorders may be possible with the help of this MT-NLC-based gel.

Suto et al. [221] formulated an ibuprofen (IBU)-loaded NLC gel to improve skin penetration for OA management. The MPS and ZP of IBU-NLC were reported as 106 nm and −18.4 mV, respectively. The EE of IBU was 98.51%, while the drug loading was 9.85%. The gelling solution of carbopol 971P NF was utilized to make a gel of IBU-NLC. The *in vitro* drug release studies of IBU-NLC gel found that after 6 h, a significant proportion of IBU was diffused from the IBU-NLC, *i.e.*, 2.59 folds compared to the IBU suspension. The *ex vivo* permeation studies data revealed that the IBU-NLC gel had a 12.78-fold higher penetration rate through the excised human skin than regular IBU gel. It is evident that using IBU-NLC gel can significantly enhance drug absorption via skin and improve the effectiveness of therapy for OA and other musculoskeletal and inflammatory conditions.

10.3. *Vesicular types of lipidic nanocarriers*

They include liposomes, PLs, hyalurosomes, TRSs, bilosomes, pharmacosomes, CBSs, and ethosomes. These nanocarriers and their gel-based systems are discussed in this review. Fig. 10 depicts the types of vesicular lipidic nanocarriers along with their compositions.

10.3.1. *Liposomes and applications of gel-based liposomes*

Liposomes are vesicles comprised of outer natural bilayered phospholipids and an inner aqueous core, as shown in Fig. 10A. They can encapsulate both hydrophobic and hydrophilic drugs and improve their pharmacokinetics and pharmacodynamics [222]. Liposomes are promising nanocarriers in biomedical applications because they act as a better drug-delivery system due to their characteristic properties like biocompatible and biodegradable phospholipids, higher safety profile with no or low toxicity, and capacity to target tissue-specific delivery of therapeutic drugs [223]. Much research has been done on liposomes to reduce drug toxicity and target particular cells in the management of arthritis [125,224,225]. In comparison to conventional gels and creams, liposomal gels were discovered to increase the retention of the drug in the skin and deliver the drugs in a sustained release manner without increasing their systemic absorption. Additionally, it has been noted that incorporating liposomes into a gel matrix increases their stability (membrane integrity and mechanical stability). Furthermore, liposomal gels exhibit superior rheological properties in comparison to normal liposomal dispersions. Moreover, compared to bare liposomes in a dispersion, liposomes trapped in a gel network may exhibit higher resistance to external stimuli. When a drug is placed inside the liposomal core, and the liposomes are included in a gel network, the drug will experience a combination of transport resistances due to the liposomal bilayer and the network itself, which causes the drug to exhibit sustained release behaviour [226]. The liposome types discussed here include thermally responsible, flexible, ultra-deformable, regular, and flexible liposomes. Liposomes of MT, DEX, PD, and their gel-based systems were discussed in this review [227].

10.3.1.1. *MTTRFL and its gel form*

Shen et al. [228] developed transdermal MT-loaded thermal-responsible flexible liposomes (MTTRFL) to manage RA. MTTRFL formulation was prepared using glyceryl mono oleate as a lipid matrix and poloxamer407 as the stabilizer. The MTTRFL displayed a MPS of 90.2 nm, ZP of −30.1 and EE of 85.3%. MTTRFL formulation was incorporated into a gelling solution of carbomer 940 to formulate the gel. The prepared MTTRFLG significantly enhanced the skin permeation of MT in comparison to conventional liposomes and plain MT. MTTRFLG exhibited a sustained drug release of 70% in 24 h. The concentration of MT in the MTTRFLG was 0.5% (w/w), equivalent to the MT in the MTTRFLs. Additionally, the study findings revealed that using MTTRFLG along with microwave hyperthermia (MWH) could result in a noticeably improved RA treatment. The temperature-triggered drug release mechanism via microwave hyperthermia allows targeted drug delivery of MT to inflamed areas, such as joints affected by RA. *In vitro* cell line studies, such as *in vitro* cytotoxicity and cellular uptake of MTTRFL, were performed on EAhy926 cells (EAs). In contrast, *in vitro* anti-inflammatory activity was performed on EAs and RAW 264.7 cells. *In vitro* cytotoxicity study for MTTRFLG and free MT was performed on EAs by incubating these cells with different concentrations of MT for 24 h. The results displayed that MTTRFLG exhibited lower cytotoxicity (more cell viability) than free MT. This indicates the safety of the MTTRFLG formulation. The MTTRFL exhibited a time-dependent cellular internalization and dose-dependent cytotoxicity at tested concentrations of 0.125 to 8 μg/ml on EAs. The studies of *in vitro* anti-inflammatory activity

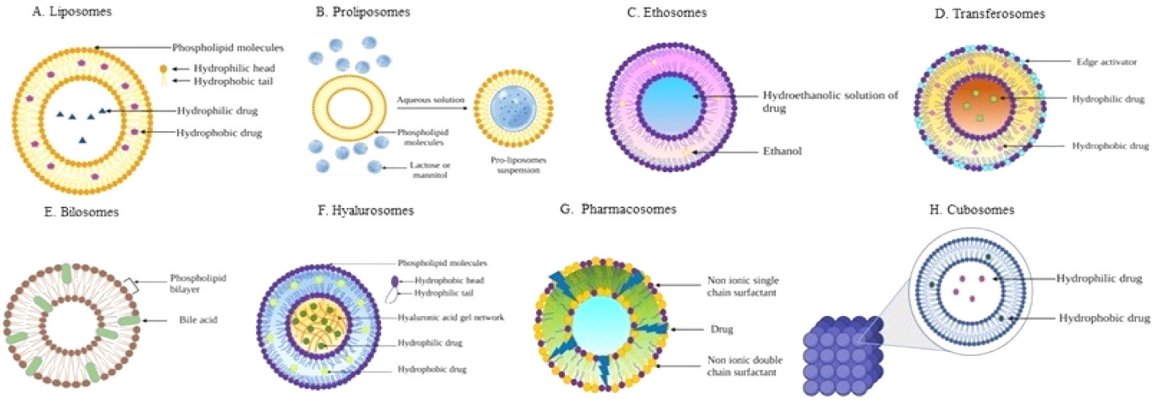

Fig. 10 – Types of vesicular lipidic nanocarriers and their compositions: (A) Liposomes, (B) PLs, (C) Ethosomes, (D) TRSs, (E) Bilosomes, (F) Hyalurosomes, (G) Pharmacosomes, and (H) CBSs.

along with MWH of MTTRFL showed a decline in TNF-α and IL-6 levels. According to the *in vivo* study results, MTTRFLG and MWH significantly reduced the TNF-α, IL-6, CD68, and RANKL levels as well as the thickness of the hind paw and improved other histopathological aspects of RA MTTRFLG loaded with MT was shown to have a longer circulation time, higher drug accumulation in inflamed joints, and lower systemic toxicity in rats with induced RA compared to free MT and conventional liposomes. Hence, a novel promising transdermal drug delivery with MTRFLG is best suited for improved treatment of RA due to its thermal-responsive properties.

10.3.1.2. MTUDL gel Zeb et al. [229] formulated MT-loaded ultra-deformable liposomes (MTUDL) to treat RA. These liposomes are incorporated in a gel matrix where the gelling agent Carbopol was used to prepare MTUDL gel, and its activity was assessed in the CFA-induced RA model. With the help of a Franz diffusion cell, the penetration of MTUDL gel over rat skin was examined. MTUDL gel showed permeation of ~164.6 µg after 24 h, which was higher as compared to MT-CLs (MT-conventional liposomes) gel (~113.3 µg) and MT-plain gel (~76.6 µg). Permeation flux of MT from MTUDL gel was found to be ~6.7 µg/cm^2/h compared to MT-CLs gel (~4.5 µg/cm^2/h) and MT plain-gel (~3.2 µg/cm^2/h). After the CFA induction, the *in vivo* anti-rheumatic effect of transdermal MTUDLG was examined in rats for 24 d. *In vivo* assessment of anti-rheumatic activity involves evaluating paw oedema scores, oedema volume, and synovial cytokine levels. The MTUDLG reduced the paw oedema score (1.18) by 3.1, 2.0 and 1.7 times when compared to diseased control (DC) rats (3.68), MT-plain-gel (2.36), and MT-CL-gel (2.04). After 24 d, the oedema volume was considerably reduced by MTUDLG (0.56 ml) compared to the DC group (1.15 ml), MT-plain-gel (1.03 ml), and MT-CL-gel (1 ml) groups. These results indicate the potential of MTUDLG in significantly reducing oedema score and paw volume in CFA-induced rats. The application of MTUDLG effectively suppressed the expression of TNF-α (6.45 times) and IL-1β (9.21 times) in the local paw tissues of treatment group rats compared to DC rats. These results aligned with the outcomes obtained from the histological evaluation of the paw tissues of treatment group rats compared to DC rats. The *in -vivo* outcomes of the designed MTUDLG suggest significant potential for effectively administering MT into inflamed joints in RA.

10.3.1.3. DEX nanoliposomal gel Zhao et al. [88] prepared transdermal dextran sulfate (DS) modified DEX flexible liposomal (DS-FLs/DEX) hydrogel, and DS modified DEX regular liposomal DS-RLs/DEX hydrogel compared both the formulations and tested their efficacy against RA. A thin film hydration technique was used to prepare both the formulations of DS-FLs/DEX and DS-RLs/DEX. The difference in both formulations is the presence of edge activators, found only in DS-FLs/DEX, which facilitated the obtaining of flexible liposomes. The MPS of DS-FLs/DEX and DS-RLs/DEX were 112.5 nm and 122.1 nm, respectively. The polydispersity indices of DS-FLs/DEX and DS-RLs/DEX were 0.196 and 0.215. The ZP of DS-FLs/DEX and DS-RLs/DEX were found to be 2.55 and 6.65 mV. It was observed that DS-FLs/DEX and DS-RLs/DEX possess drug EE of 43% and 41%. The lower MPS, low PDI, and high drug EE% are the evaluating criteria for screening for better nanoformulation. The DS-FLs/DEX formulation exhibited low MPS, low PDI, and high EE when compared to DS-RLs/DEX. To formulate DS-FLs/DEX and DS-RLs/DEX hydrogels, the liposomal formulations were embedded in the gelling solution of carbopol 934. The optimized DS-FLs/DEX gel exhibited initial burst release followed by a sustained release of 90% DEX at 48 h. *In vivo* penetration analysis of the optimized hydrogels was performed on rats, and the skin permeation study was conducted using an *in vivo* imaging system through a fluorescence intensity technique. Thus, the measurement of fluorescence intensity provides a means to assess the penetration and permeation of a substance through the skin. Except for the control group, all the rats of different groups were treated with 1,1-dioctadecyl-3,3,3,3-tetramethyl indotricarbocyaineiodide (DIR), exhibiting yellow colour fluorescence. Fig. 11 displays the skin permeation and accumulation study of the DIR-loaded DS-FLs/DEX (DIR-DS-FLs/DEX) hydrogel and DIR-loaded DS-RLs/DEX (DIR-DS-RLs/DEX) hydrogel.

DIR-DS-FLs/DEX-treated rats exhibited the maximum yellow-coloured fluorescence intensity. In contrast, the

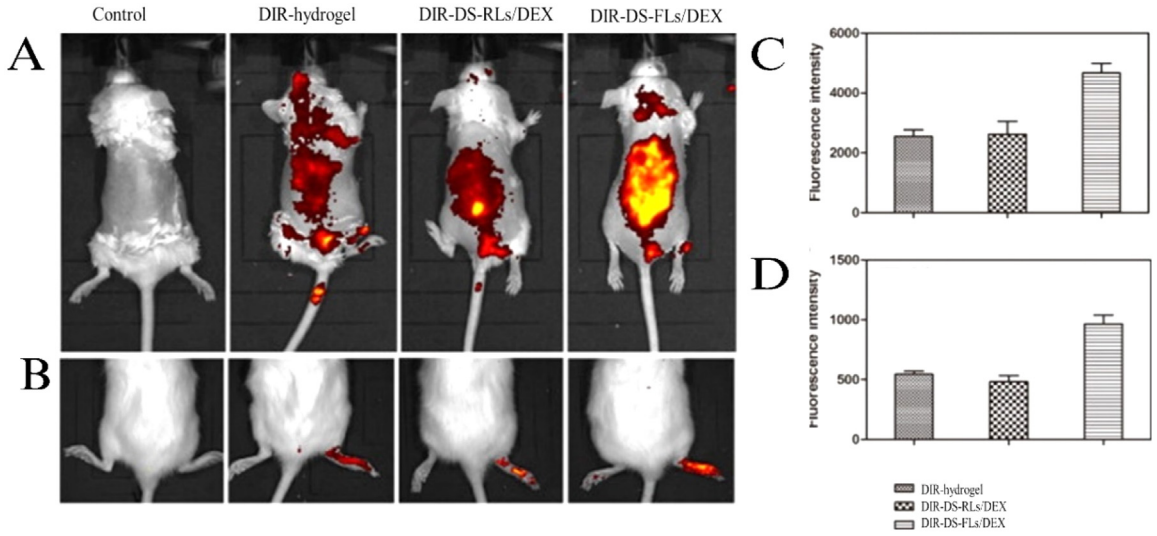

Fig. 11 – *In vivo* skin permeation and accumulation study of DIR-DS-FLs/DEX and DIR-DS-RLs/DEX hydrogels. (A) Permeation of DIR hydrogel, DIR-DS-RLs/DEX hydrogel, and DIR-DS-FLs/DEX hydrogel in the skin by using a live imaging system through DIR-loaded fluorescence imaging. (B) The accumulation of DIR-DS-RLs/DEX hydrogel and DIR-DS-FLs/DEX hydrogel in rat joints was done using a live imaging system through DIR-loaded fluorescence imaging. (C) and (D) Comparison of DIR hydrogel, DIR-DS-RLs/DEX hydrogel, and DIR-DS-FLs/DEX hydrogel in terms of *in vivo* quantitative analysis of fluorescence intensities related to their skin permeation and accumulation in the RA joints. Reproduced with permission from [88]. Copyright© 2022 The Author(s))

DIR-DS-RLs/DEX hydrogel-treated rats exhibited slight yellow-coloured fluorescence and very little yellow-coloured fluorescence in DIR hydrogel-treated rats. This is due to the excellent deformability of flexible liposomes and, thus, higher skin permeation in the case of DS-FLs/DEX hydrogel. Regular liposomes do not have a good deformability nature; therefore, less fluorescence was observed in the case of DS-RLs/DEX hydrogel. The DIR-treated hydrogel has shown very little fluorescence due to its hydrogel properties. All these skin permeation study results confirm that DIR-DS-FLs/DEX hydrogel has shown maximum yellow-coloured fluorescence due to higher skin permeability, as shown in Fig. 11A. The *in vivo* quantitative analysis of skin permeation was performed through the measurement of fluorescence intensities for various hydrogels, where the DIR-DS-FLs/DEX hydrogel exhibited the highest fluorescence intensity when compared to DIR-DS-RLs/DEX hydrogel and DIR hydrogel as shown in the Fig. 11D.

The accumulation properties of hydrogel were studied by an *in vivo* imaging system in the RA joints of rats, as shown in Fig. 11B, and its *in vivo* quantitative analysis was performed, as shown in Fig. 11C. The DIR-DS-FLs/DEX hydrogel-treated rats exhibited the maximum yellow-coloured fluorescence intensity, which was about 1.7 times (4,665 ± 324) more than the DIR-DS-RLs/DEX hydrogel-treated rats (2,623 ± 431) and about 1.8 times (2,545 ± 226.) more than the DIR hydrogel treated rats. This confirms that DIR-DS-FLs/DEX hydrogel had higher *in vivo* joint accumulation due to maximum yellow-coloured fluorescence, as shown in Fig. 11C. The histopathological study of rats showed a significant reduction in inflammation in both the treatment groups of DS-RLs/DEX and DS-FLs/DEX hydrogels, conferring their potential in arthritis therapy.

In this study, the DIR-DS-FLs/DEX gel showed the maximum fluorescence, which indicates higher *in vivo* skin permeation and joint accumulation, leading to better anti-rheumatic effects in CFA-induced RA rats. The choice of specific *in vivo* fluorescence live imaging systems and *in vitro* models in this study is driven by the need for real-time visualization, spatial tracking, and a comprehensive understanding of the gel's behaviour at both the systemic and cellular levels. By incorporating contrast agents or imaging probes into the nanocarrier structure, researchers gain the ability to perform real-time visualization of the gel's permeation and penetration. This integration enables the tracking of nanoliposomal gel distribution within the joints using imaging techniques, providing researchers with valuable insights into its behaviour *in vivo*.

10.3.2. *PLs and application of PD proliposomal gel*

Although topical liposomal formulations have been researched for various applications, their unstable nature and poor skin absorption restrict their potential for topical drug delivery. The aggregation, sedimentation, fusion, hydrolysis, and oxidation of phospholipids are only a few issues that liposomes face. To address the problems with liposomal stability, the idea of PLs was introduced [230]. PLs are a particular type of liposomal drug delivery system that is made to enhance stability. They are merely dry formulations of liposomes made up of outer phospholipids coated onto a small number of hydrophilic carrier substances like lactose or mannitol, as shown in Fig. 12. PLs can be stored as

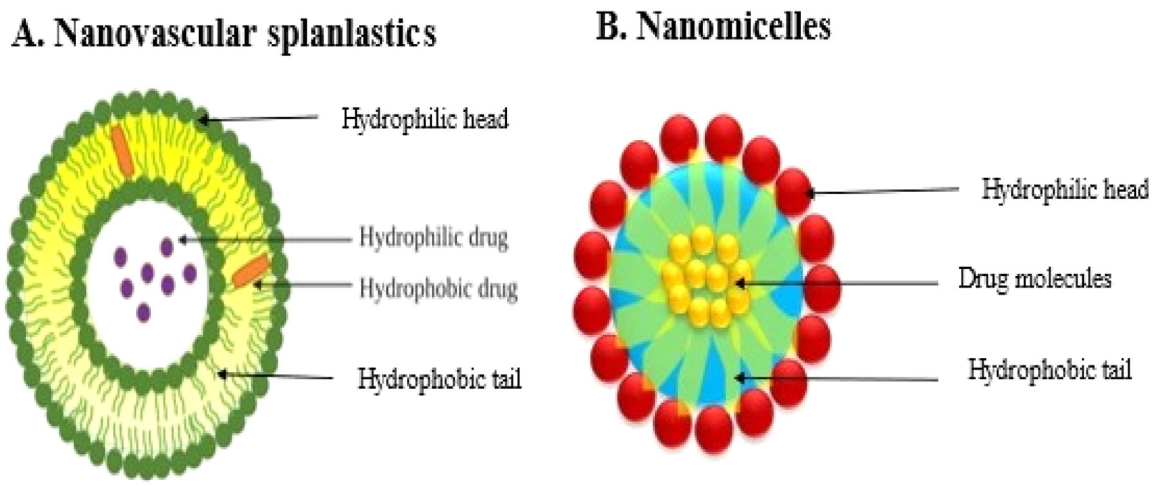

Fig. 12 – The types of surfactant-based vesicular nanocarriers and their composition. (A) NVSPLs and (B) NMs.

a dry powder and then reconstituted into liposomes by adding an aqueous solution. Therefore, PLs are defined as dry and easily flowing particles containing a dispersed system that rapidly transforms into a liposomal suspension upon contact with water [231]. In PLs, the active drug and lipid mixture (phospholipid and cholesterol) were coated by a carrier that provides free-flowing characteristics, higher stability, and solubility to the resultant vesicles compared to the conventional liposomes [232]. PLs offer several advantages over conventional liposomes, including improved stability, shelf-life, reduced costs, and ease of handling and transportation.

PLs can be prepared using many methods, including the crystal-film method, film-deposition on carrier method, fluidized-bed method, powder bed grinding method, freezing and drying method, and spray drying method [233]. Critical factors in stabilizing PLs include the choice of the carrier used and the concentration of carrier, choice of a phospholipid, the ratio of drug to a phospholipid, method of preparation such as freeze drying or spray drying, the incorporation of stabilizing agents and surfactants, storage conditions such as temperature and humidity [234,235].

Kurakula et al. [234] have developed topical PD-PLs for managing RA using a thin film deposition method on a carrier, employing a vacuum rotary evaporator. The formulation process involves several steps that include the preparation of dried mannitol powder, optimization of PD-PLs formulation with different components, drying the mixture to obtain proliposomal powder and finally, the incorporation of carbopol gelling agent into the formulation. Initially, mannitol powder was taken in a round-bottomed flask (RBF) and dried at 60–70 °C and 115 rpm under vacuum for 30 min. Subsequently, PLs were optimized using various combinations of mannitol, lecithin, and cholesterol. The optimized amounts of PD, lecithin, and cholesterol were added to the RBF, containing an organic solvent mixture of chloroform, methanol, and mannitol powder. This facilitated the penetration of the drug and lipids containing the organic solution into the porous mannitol powder. The resulting mixture was allowed to dry in a rotary evaporator to remove the organic solvent and obtain proliposomal powder. For the preparation and stabilization of PLs, the amount of addition of mannitol, phospholipids, and cholesterol was very critical. Carbopol was incorporated as a gelling substance into the PLs to obtain a gel form for improved topical application.

Developed PLs gel significantly increased the amount of PD retention in the skin compared to free PD drug-loaded gel. PD PLs gel showed 50%–80% release in 14 h compared to 90% from free drug gel. Refrigeration temperature reduces stability problems of prednisone proliposomal product compared to room temperature. Carrageenan-induced paw oedema is the model that was selected to perform an *in vivo* experiment because of its well-established and standardized relevance with more reproducibility. The carrageenan triggers the inflammation and induces it at a faster rate. The inflammatory inhibition of oedema for optimized PD was 60% compared to marketed diclofenac gel, which showed 55% inflammatory inhibition of oedema. The results of paw swelling in DC rats was 160%, whereas, in the diclofenac gel and PD PLs gel, it was 73% and 65%. These results proved that the PD PLs formulation is far superior to the marketed gel. This study proved the potential of PD PLs as an effective topical medication for RA treatment, which exhibited sustained release action and improved efficacy of anti-inflammatory activity

10.3.3. Ethosomes and application of naproxen sodium (NPXS)-loaded nanoethosomal gel

The epidermal barrier of SC, the primary drawback of transdermal drug delivery, can be significantly overcome using ethosomes. Ethosomes are ethanol-containing advanced liposomes employed to improve the drug permeation into the deeper skin layers; hence, they are designed for transdermal delivery [236]. As shown in Fig. 10C, they are composed of a phospholipid bilayer and a high amount of ethanol (usually between 20%–50%), allowing them to penetrate the skin layers more effectively than traditional liposomes [237,238]. Ethanol present in ethosomes provides vesicle flexibility, deformability, and elasticity [238].

Because of their elastic nature, these ethosomes can easily pass through pores that are smaller than their size. Ethanol acts as a penetration enhancer by disrupting the SC of the skin and allowing drugs to penetrate more easily into the deeper layers of the skin. The high concentration of ethanol in ethosomes also results in a greater fluidity of the lipid bilayer, which enhances the drug-loading capacity of the ethosomes and improves their stability. Due to the advantages of using high ethanol content, ethosomes act efficiently to enhance skin permeability [236]. In comparison to other nanocarrier drug delivery systems, such as liposomes or SLNs, ethosomes have several advantages, including their high drug-loading capacity, enhanced skin permeation, and potential for non-invasive drug delivery. They also have a low risk of toxicity due to the use of biocompatible and biodegradable materials in their composition.

To treat arthritis, Anjum et al. [239] prepared NPXS-loaded nanoethosomes by using the cold method. Phospholipids, 128.4 mg lecithin, 35.8% ethanol, and water were used for formulating NPXS nanoethosomes. Box Behnken's experimental design was used to prepare NPXS-loaded nanoethosomes. NPXS nanoethosome's MPS was found to be 129 ± 0.01 nm with 0.295 PDI, −3.29 mV ZP, and 88% EE. A carbopol 934 gel base was used to formulate NPXS nanoethosomal gel. *In vitro* drug release studies were performed for NPXS nanoethosomal gel, and NPXS release was found to be 96.573% in 24 h, which displays a sustained release profile when compared to NPXS (100%) drug release from hydroalcoholic solution in 8 h. Results of *ex vivo* skin permeation studies reported that only 54 µg NPXS was permeated from the hydroalcoholic solution in 24 h, whereas approximately 350 ug NPXS was permeated from the NPXS nanoethosomal gel. Transdermal NPXS flux from ethosomes (19.90 µg/cm^2/h) was significantly ($P < 0.05$) higher than the transdermal NPXS flux from the hydroalcoholic solution (2.92 µg/cm^2/h). These results indicate that the longer residence time of NPXS nanoethosomal gel formulation on the skin is due to its higher permeation and transdermal flux. The carrageenan-induced rat paw oedema model examined the *in vivo* anti-inflammatory efficacy of NPXS nanoethosomal gel. Due to the anti-inflammatory effect of diclofenac, the group treated with commercially marketed Voveran TPM gel experienced a gradual decrease in oedema, with oedema fluid volume reaching 1.55 ± 0.12 ml in 12 h. Another group treated with topical NPXS nanoethosomal gel exhibited further improvement in oedema, with oedema volumes falling to 1.41 ± 0.035 ml and 1.21 ± 0.01 ml in 4 h and 12 h, respectively. As a result of the above observations, the NPXS nanoethosomal gel represents a viable therapeutic strategy for managing arthritis.

10.3.4. *TRS and application of imatinib (IT)-loaded TRS gel*

TRS are more elastic ultra-deformable liposomal vesicles capable of loading both hydrophilic and lipophilic drugs designed to improve transdermal drug delivery. They are composed of a phospholipid bilayer and a small amount of an edge activator, such as sodium cholate or Tween 80, as shown in Fig. 10D. The edge activator destabilizes the lipid bilayer, making it more deformable and enabling the TRS to pass through the pores in the SC of the skin. Phosphatidylcholine is the chief lipid component in TRS [146]. Since this lipid is abundant in the human skin's membrane, it decreases hypersensitivity reactions as it is well tolerated. Lipophilic drugs can be encapsulated within either bilayers or cores, depending on lipophilicity. Utilizing surfactants in the correct ratio will increase the deformability of liposomes for enhanced drug molecule penetration into the skin. They squeeze themselves along the inter-cellular sealing lipid of SC, and additionally, their elastic nature of membranes decreases the chance of an entire vesicle rupture in the skin [240]. The main drawback of utilizing TRS topically is their liquid nature. This is avoided by incorporating TRS inside a vehicle that preserves the original vesicle structure [241].

Taymouri et al. [242] developed a transdermal gel of IT-encapsulated TRS (IT-TRS) to manage RA and decrease the frequency of oral administration and side effects of IT. Thin film hydration was used to develop IT-TRS, and the formulation has shown the MPS of 140.53 ± 0.87 nm, PDI of 0.44 ± 0.01, ZP of −17.63 ± 0.65 mV, EE of 98.7% ± 0.38%, The study results indicated that the IT-TRS nanoformulation is well-designed and developed because of its lower MPS, lower PDI, and high drug EE. The optimized IT-TRS was embedded into the gelling solution of carbopol 940 to form IT-TRS gel. In *ex vivo* studies on rat skin, it was found that the cumulative permeation of IT from IT-TRS gel was remarkably higher than that of IT gel. The flux of IT-TRS gel was found to be 15.41 ± 0.12 µg/cm^2/h, while IT gel had a considerably lower transdermal flux of 7.45 ± 0.20 µg/cm^2/h. The enhanced drug permeation from IT-TRS gel could be attributed to nanosized TRS. The cumulative drug release of IT drug from the IT-TRS gel was 55% in 24 h, whereas the drug release of IT from conventional IT gel was 100% in 24 h. The obstructive effect of the gel matrix may be the cause for the delayed release of IT from TRS gel. Furthermore, in the RA rat model, the application of IT-TRS gel led to a substantial reduction in paw oedema over the 14-d study period compared to IT gel. The increased paw weights of CFA-induced rats were reported to be 85.2%, 75.1% and 90.4%, respectively, for drug-free gel, drug-free TRS gel, and IT gel. The reduced paw weight was observed (with 42.9%) in the CFA-induced rats treated with IT-TRS gel. As the IT-TRS gel nanoformulation exhibits higher skin permeation, the effective retention of IT-TRS has been possible to show the antirheumatic effects and reduction in inflammation, which contributed to the decrease in their paw weights.

10.3.5. *Bilosomes and application of fluticasone propionate bilosomal gel*

Bilosomes are nanosized, ultra-deformable vesicles made of bile salts, as shown in Fig. 10E. Bile salts produce extremely stable vesicles for transdermal application, which act as edge activators [243,244]. Modulating the phospholipid vesicular nanocarriers with bile salt incorporation is helpful in increasing drug diffusion through the skin. The stability of vesicular nanocarriers can be improved by adding them to gels [245]

AbuBakr et al. [246] developed a fluticasone propionate-loaded bilosomal formulation (FPB) using the thin-film evaporation method to evaluate the skin permeation. Optimization of FPB was conducted using Draper-Lin's

small composite design. FPB was loaded into the gelling solution of carbopol gel to formulate FPB gel. EE was found to be 84.72% ± 4.36%. ZP and 112.5 were found to be + 53.70 ± 1.47 mV and 268.13 ± 3.55 nm with PDI value 0.34 ± 0.02. The flux and deposition of FP on the skin were 5.89 ± 0.45 (μg/cm^2/h) and 16.21±1.27 (μg/cm^2/h), respectively. The FP dispersion showed significantly lower skin flux (1.81 ± 0.15 μg/cm^2/h) and skin deposition (7.02 ± 0.83 μg/cm^2/h). The FPB gel and standard FP gel showed fluxes of 5.14 ± 0.29 and 1.44 ± 0.26 μg/cm^2/h and skin deposition values of 15.67 ± 2.14 and 6.85 ± 1.24 μg/cm^2/h respectively. These results showed the highest permeability and higher skin deposition of FPB gel across skin layers.

10.3.6. Hyalurosomes

Hyalurosomes are modified liposomes made up of outer phospholipid vesicles and an inner aqueous core where the HA is entrapped in it in the form of gel material, as shown in Fig. 10F. Therefore, in simple, hyaluosomes are regarded as gel-core-like liposomes, which can combine some of the benefits of gel formulations and liposomes in a single drug delivery system. This feature enables controlled drug release, contributing to improved drug delivery. The structure of hyalurosomes, when analyzed by cryo-transmission electron microscopy (cryo-TEM), will be displayed like a core-shell type with a darker coat inside and a lighter shell. The hyaluronate vesicle size will be smaller when analyzed by cryo-TEM compared to the size analyzed by Zetasizer. This is due to the dryness of the sample without hydration layers outside when analyzed through cryo-TEM. However, the core containing HA will retain the water, which will not completely evaporate even after drying by cryo-TEM. The spherical shape retained after removing the bilipid layer confirms the spherical gel core [247]. The gelated structure of HA in the core of hyalurosomes can be assessed by cryo-TEM and confocal fluorescence microscopy. AFM microscopy imaging confirms the gel core of hyalurosomes [247]. Hyaluosomes are reported to have higher EE when compared to liposomes and other modified liposomes like ethosomes and TRSs [248]. This is because of the HA gel core in hyalurosomes, which contributes to the minimal leakage or no leakage of drugs that got entrapped in them. HA is a key component in synovial fluid and cartilage. Its viscoelastic properties contribute to the shock-absorbing and lubricating functions of synovial fluid. Invasive Injectable HA supplementation is employed in treating joint diseases such as OA and RA. This is due to the characteristic decrease in HA concentrations in the synovial fluid associated with these diseases, resulting in diminished elasticity and viscosity of the synovial fluid. Hence, noninvasive transdermally permeated hyaluosomes find a potential benefit in OA and RA

A patent [249] was published regarding the study on the evaluation of nanohyalurosomal gel against RA. The invention relates to the design and development of a nano-hyalurosomal formulation of TFC and boric acid, followed by formulating its gel using the gelling solution of carbopol 934. The *in vivo* study results showed a significant reduction in inflammatory cytokines like TNF-α and interleukins IL-6 and IL1-β. The study results also exhibited a pronounced reduction in swelling. This is due to the hyalurosomal formulation, where HA is supplemented, which might be beneficial to restore the declined levels of HA in RA. Additionally, boric acid has anti-inflammatory properties. These findings highlight the potential of boric acid and tofacitinib citrate as the combinatorial approach for managing RA.

10.3.7. Pharmacosomes and applications of gel-based pharmacosomes

The word “pharmacosome” comes from the Greek words “pharmakon” for drug and “soma” for the carrier. Pharmacosomes are nothing but colloidal suspensions of drugs where there is a covalent connection between drugs and lipids, which is shown in Fig. 10G. They are pharmaceutical amphiphilic lipid vesicular systems. They may exist as ultrafine vesicular, micellar, or hexagonal aggregates, which further depend on the chemical structure of the drug-lipid complex. The active hydrogens of the drug will bind to molecules of phospholipids, forming phospholipid complexes (PLC) in pharmacosomes. Pharmacosome vesicles can incorporate both hydrophilic and hydrophobic substances [250]. Pharmacosomes are fast growing as one of the lipid-based promising vesicular carriers due to their benefits in terms of enhanced stability characteristics, increased EE, minimal drug leakage, and drug-lipid conjugation. It aids in improving the drug’s biological characteristics and increasing its bioavailability. Any pharmaceutically active drug substance with OH, NH_2 or COOH active functional groups in its chemical structure is eligible for loading into pharmacosomes [251]. The covalent connection between the drug and the lipid is the unique feature of pharmacosomes. This covalent bonding not only increases the stability of pharmacosomes but also increases their effectiveness [252].

10.3.7.1. Etoricoxib (ETC) pharmacosomal gel Soman et al. [253] prepared pharmacosomes of ETC by thin film hydration method in which soya lecithin (phospholipid) was used. Carbopol 934 and triethanolamine were used to prepare pharmacosomal gel. To measure the drug release was carried out on the Franz diffusion cell. The range for EE of pharmacosome was 81%–90.20%. The range of yield for all formulations was found to be 91.32%–94.91%. It was observed that 86.13% of the ETC was diffused through the pharmacosomal ETC gel. The ETC drug release was significantly impacted by the soya lecithin, dichloromethane, and polymer concentrations that are used to prepare ETC pharmacosomes.

10.3.7.2. ETD pharmacosomal gel Latha et al. [254] formulated etodolac (ETD) pharm acosomal gel for the treatment of RA and compared it with the pure drug gel and marketed diclofenac gel. A gelling solution of carbopol 934 is employed to formulate the gels. The formulation was optimized using solvents like acetone, dichloromethane, methanol: chloroform (8:2), and drug: lecithin ratio. *In vitro* studies revealed that pharmacosomal formulations showed slower drug release than pure drug gel of ETD. The plain drug gel of ETD exhibited a 98.6% drug release in 24 h, whereas the optimized pharmacosomal gel exhibited 59.9% in 24 h. The active hydrogens of the etodolac drug bind with phospholipid molecules of the vesicular system in pharmacosomes, leading

to ETD-PLC formation. The complexation involved in ETD-PLC might afford an additional barrier so that drug release from the vesicular structure of pharmacosomes is delayed, exhibiting the sustained release behaviour. The *ex vivo* skin permeation studies revealed that ETD pharmacosomal gel exhibited higher skin permeation and higher skin deposition compared to pure drug gel and diclofenac gels.

During the progression of arthritis, the immune cells neutrophils are abundant at the site of inflammation. The proteinase activity exhibited by lysosomes of neutrophils is high and causes protein denaturation, which is a process related to the triggering of inflammation and finally causes tissue damage. The CFA-induced paw and ankle oedema model was selected to estimate the *in vivo* anti-inflammatory effect on Wistar-albino rats for 14 d In this study, anti-inflammatory effect evaluation is related to the inhibition of protein denaturation exhibited by neutrophils, where the results of it were found to be 54.96% for ETD formulation compared to 47.1% for etodolac and 41.6% of diclofenac. Thus, ETD pharmacosomal gel exhibited higher anti-arthritic potential by maximum inhibition of protein denaturation, indicating its capacity to prevent disease progression. When storage conditions of the ETD pharmacosomal gel were compared at room temperature of 26 °C and refrigerated temperatures of 2–8 °C, the physical testing data revealed a reduction in viscosity and an increase in spreadability at rising temperatures. When kept in a refrigerated condition, ETD pharmacosomes displayed higher stability and improved efficacy that can be utilized effectively in the treatment of RA.

10.3.8. CBS and application of ketoprofen (KTP) loaded cubogel

CBS are self-assembling bicontinuous cubic liquid crystalline structures with sizes between 100 nm and 500 nm. CBS is composed of a cubic liquid crystalline phase of lipids and water. Two non-intersecting water channels surrounded by lipid bilayers that are folded or curved into a highly ordered 3D structure give a cubic structure for CBS, as shown in Fig. 10H. This 3D cubic structure offers unique properties to CBS, such as high internal surface area and the ability to entrap and solubilize both lipid-soluble and water-soluble drugs. A particular type of amphiphilic lipids is utilized to prepare CBS [255,256]. CBS has more benefits, including the ability to incorporate a wide range of drugs such as water-soluble, lipid-soluble, and amphiphilic drugs; thermodynamically stable; and the inclusion of biodegradable lipids that form nanovesicles with enhanced permeation power. They are also used as nanocarriers for targeted drug delivery. The higher drug loading of CBS is due to its cubic structure [256].

Karthika et al. [257] formulated the topical formulation of KTP-loaded cubogel to evaluate the release behaviour of the drug from the gel. Employing a top-down approach, CBS dispersions were created using various amounts of the lipid phase GM (Glyceryl monooleate), the non-ionic surfactant poloxamer 407, and water as the aqueous phase. To develop cubosomal hydrogel, the optimal formulae were added to a hydrogel made of carbopol 934, and KTP cubogel was prepared using a cold mechanical method. KTP CBS diameter was reported with a MPS of 61.1 nm. The reported ZP was −46.7 mv. With a homogeneous particle size distribution, the optimized KTP cubosomal formulation displayed a low PDI of 0.443. All batches have an EE between 59.02% and 86.45%. The concentration of GM and poloxamer 407 affected the EE of KTP into cubic NPs. Both the CBS-enriched gel and the normal carbopol 934 gels were determined to have 92.12% and 90.44% of the total drug content, respectively. The KTP plain gel exhibited 91.67% ± 0.16% in 7 h, whereas the KTP loaded cubogel exhibited 89.04% ± 0.03% in 12 h. These observations showed that compared to KTP-loaded plain gel, KTP-loaded cubogel exhibited prolonged release of KTP. Thus, the outcomes of this study suggested that cubogel, which has been loaded with KTP, may be used as a topical gel to treat diseases related to arthritis

10.4. *Surfactant-based vesicular type of nanocarriers*

It includes nano vesicular spanlastics (NVSPLs) and nanomicelles (NMs) which have vesicular structure and are generally prepared from self-assembly of surfactant monomers (Fig. 12).

10.4.1. NVSPL and application of celecoxib (CBL) nvspl gel

The nano vesicular spanlastics (NVSPLs) are elastic, deformable surfactant-based nanovesicles. They may be either unilamellar or multilamellar and have liposomal-like concentric bilayers, as shown in Fig. 12. They represent a unique category of vesicular carriers designed to serve as a site-specific drug delivery system, delivering the drugs precisely to the intended target areas. The production of innovative SPL surfactant-based delivery vehicles offers a non-invasive method of delivering the drug to the target place without the need for repeated dosing [258].

Alaaeldin et al. [259] developed topical CBL nano vesicular spanlastics (NVSPL) to evaluate the anti-inflammatory effect in the CFA-induced arthritis model in rats. The spraying method was used to prepare CBL-NVSPL using surfactants Span 60, Tween 80 and Brij 35 (edge activators). CBL-NVSPL vesicles were incorporated into carbopol to form a gel. Different inflammatory agents like TNF-α and COX-2 were examined in the tissues of animal paws before and after treatment. EE and particle size of spanlastics nanovesicles were 83.6% ± 2.3% and 112.5 ± 3.6 nm, respectively. Transdermal flux of CBL-NVSPL gel was found to be 6.9 ± 0.25 μg/cm^2/h, while celecoxib niosomes containing gel and unprocessed celecoxib loaded gel showed 5.2 ± 0.12 μg/cm^2/h and 0.64 ± 0.09 μg/cm^2/h. Oedema reduction of SPL gel was found to be 73.45% ± 2.6%, and for celecoxib-loaded niosomal gel was found to be 64.1% ± 3.5%. Celecoxib-loaded SPL gel has shown superior efficacy in lowering oedema and regulating arthritic markers in a rat model of severe CFA-induced arthritis

10.4.2. NMs and application of MT-loaded NMs-based gel

NMs are colloidal structures at the nanoscale that spontaneously self-assemble through the organization of amphiphilic molecules when dispersed in aqueous solutions [260,261]. Because of the amphiphilic surfactant monomer, these NMs possess both a hydrophilic head and a hydrophobic tail [262] enabling them to arrange into spherical or ellipsoidal

vesicular structures, as shown in Fig. 12. They are employed as pharmaceutical carriers to solubilise hydrophobic drug molecules [261] due to their capacity to either avoid or reduce drug degradation and decrease undesirable side effects [274].

NMs have shown their potential as nanocarriers for drug delivery owing to their small size and capacity to effectively entrap lipophilic drugs in their hydrophobic core, thereby enhancing solubility with the assistance of their outer hydrophilic portion [262]. Apart from the small size and lipophilic drug solubilization, NMs are also involved in improving drug delivery by facilitating improvement in pharmacokinetic properties and maintaining stability. NMs are reportedly better than other administration methods because they are easier to prepare, more drug-soluble, less toxic, have longer circulation times, and are easier to target [263].

Qindeel et al. [158] prepared MT-loaded NMs using the nanoprecipitation technique to treat RA. The MPS of NMs was found to be 31 nm, and drug EE was 91%. To formulate a transdermal gel, MT-NMs were loaded into the gelling solution of carbopol 934. Eucalyptus oil is utilized as a permeation enhancer, which reversibly breaks down the intercellular lipid structures between the corneocytes of the SC and alters the shape of intercellular protein domains. *In vitro*, a hemolytic assay was done to ensure that the formulation for systemic delivery of MT was safe because the MT-NMs were exposed to systemic circulation through the transdermal route. At concentrations between 3.12 and 50 µg/ml, MT-NMs did not cause hemolysis ($\leq$ 22.5%). The anionic character of the NMs may cause decreased hemolysis in NM formulation. MT-NMs. Skin permeation study results showed that free MT-loaded hydrogel showed extremely low permeation (59 µg/cm^2/h) in comparison to the permeation of MT-loaded hydrogel with eucalyptus oil (150 µg/cm^2/h) and MT-NMs hydrogel (573 µg/cm^2/h). However, the MT-NMs hydrogel in combination with Eucalyptus oil has shown remarkable permeation up to 946 µg/cm^2/h when compared to other formulations of hydrogels. So, it has been proven that adding eucalyptus oil and loading MT into NMs can considerably increase free drug MT's ability to permeate the skin.

The *in vivo* study in mice was carried out for 21 d Applying MT-NMs hydrogel containing eucalyptus oil in an RA mouse model revealed that NMs preferentially accumulated in inflamed joints. Unlike free MT, MT-NMs exhibited substantial improvements in pharmacokinetics (4.34-fold greater half-life and 3.68-fold higher AUC. The pharmacodynamics of this formulation are evidenced by reduced inflammatory cytokine expression, enhanced oxidation protection, restored behavioural responses, favourable radiological analysis, and reduced hepatotoxicity. These findings suggest that the MT-NMs transdermal hydrogel holds promise as an effective agent against RA.

10.5. *Polymeric type of nanocarriers*

They include NCs, NPs, NGs, and NSPs. Fig. 13 displays the different types of polymeric nanocarriers and their compositions.

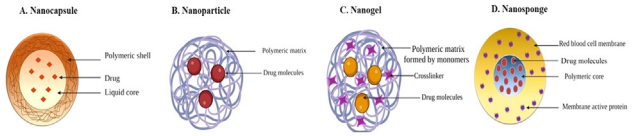

Fig. 13 – Types of polymeric nanocarriers and their compositions: (A) NCs, (B) NPs, (C) NGs, and (D) NSPs.

10.5.1. *NCs and application NC-based gel*

NCs belong to the nanoparticulate system type, comprised of a polymeric shell surrounding a liquid or solid core, as shown in Fig. 13. The polymeric shell is made up of either natural polymers or synthetic polymers. Various biocompatible polymers such as PLGA or CS can also be designed to prepare NCs that control the release of drugs. NCs exist in various sizes, ranging in size between 10 and 1,000 nm [264] and offer several advantages, including sustained release, drug selectivity and protection, targeting, increased drug bioavailability, enhanced *in vitro/in vivo* stability, and reduced toxicity. Due to the polymeric wall of the particle, NCs exhibit a constant rate of drug release [265]

Lenz et al. [266] formulated a topical nimesulide-loaded NC gel to study anti-inflammatory activity in arthritis. The nanoprecipitation method was used to prepare colloidal nimesulide-NC. The optimized nimuselide-NC particles displayed 3,44.6 $\pm$ 4.33 nm particle size with 0.251 $\pm$ 0.002 PDI and EE of 99%. To make nimesulide-loaded NC gel (nimesulide-NCG), Carbopol 934 gelling solution was used. Using nimesulide-NCG, the inflammation inhibition in the chronic arthritis model was found to be 81.5%. Paw oedema volume was studied by using the carrageenan model. The nimesulide-NCG treatment groups showed about an 83% reduction in oedema. Anti-inflammatory activity was also determined by evaluating paw volume. Paw volume reduction obtained was 31% for nimesulide-NCG. Topical nimesulide-NCG anti-inflammatory efficacy was enhanced in the *in vivo* models of chronic inflammation

10.5.2. *NPs and application of gel-based NPs*

The formulation containing particles ranging between 1 and 100 nm in size are known as NPs, and because of their tunable small size, they might differ from the bulk material [267]. Compared to the particles at higher scales, the NPs show distinct physical, chemical, and biological characteristics because of their miniature size range of nanoscale structures. The unique characteristics of NPs are due to a relatively larger specific surface area, surface-to-volume ratio, increased reactivity or stability in a chemical process, and enhanced mechanical strength [268]. The structure of NP contains a polymeric matrix where the drugs are loaded, as shown in Fig. 12. A larger surface area is crucial in achieving a high drug-loading capacity [269]. Consequently, NPs can accommodate a significant quantity of therapeutic agents, thereby enhancing drug delivery efficiency. Additionally, the elevated surface-to-volume ratio of NPs influences their interaction with the biological environment, promoting improved absorption and distribution in tissues. NPs reactivity enables the design of formulations with tunable release kinetics, ensuring a

controlled drug delivery [269]. NPs are likewise superb contenders in the case of nanocarrier systems because they expand the payload efficiency of the drugs through covalent bonding or encapsulation. The incorporation of NPs into hydrogels has drawn a lot of interest. Hydrogels give additional flexibility to enhance the overall therapeutic efficacy in addition to maintaining the structural integrity and functions of the enclosed NPs [270].

10.5.2.1. MT NPs loaded gel Chaudhary et al. [271] prepared topical MT NPs loaded gel (MT-NPsG) to treat RA. To prepare MT-NPsG, the formulation of MT NPs is added to the gelling solution of carbopol 934. After the CFA-induced arthritis model was developed, the MT-NPs gel was applied to the treatment group of rats for 21 d. The therapeutic potential of MT-NPsG was evaluated through anti-inflammatory effect in CFA-induced rats and compared with MT gel and DEX gel. The formulation's anti-inflammatory activity was assessed based on the inhibition of oedema and arthritic score. The MT-NPsG markedly inhibited paw oedema compared to MT gel and DEX gel. The formulation MT-NPsG successfully decreased the inflammatory interleukins like IL-1β, IL-6 and TNF-α in the synovial fluid of CFA-induced treatment group rats. The results have shown that the anti-arthritic activity of MT-NPsG was much superior to that of the existing marketed MT and DEX gel.

10.5.2.2. INDM-loaded NPs gel Nagai et al. [272] used a bead mill to develop INDM-loaded NPs (INDM-NPs). These NPs were subsequently incorporated with carbopol-containing menthol to make transdermal INDM-NPs-Menthol gel, which was evaluated to assess the permeation. INDM-NPs are incorporated with carbopol solution without menthol to prepare INDM-NPs gel, which is used as a comparator to determine the efficacy of INDM-NPs-Menthol gel. In an *in vitro* rat skin permeation experiment, the $AUC_{0-24\ h}$ of the INDM-NPs-Menthol gel was found to be 2.8 times greater than that of the INDM-NPs gel. Additionally, the penetration rate of the INDM-NPs-Menthol gel was 3.9 times higher than that of the INDM-NPs gel. The results clearly explain that menthol-containing gel has significantly enhanced permeation. The inclusion of menthol can increase intercellular spaces in the SC of the skin and enhance the INDM permeability. Additionally, the energy-dependency of skin penetration of INDM-NPs was also demonstrated. The INDM-NPs-Menthol gel and INDM-NPs gel exhibited reduced drug permeability at 4 °C compared to body temperature 37 °C, demonstrating that energy-dependent endocytosis is the mechanism through which INDM-NPs penetrate the skin.

10.5.2.3. KTP-loaded NPs gel To treat RA, Gul et al. [273] developed NPs co-loaded with KTP and CDS using the ion coagulation method, regarded as KTP-CDS-NPs. These KTP-CDS-NPs, along with argan oil (AO) were incorporated into an HPMC gel matrix to create a transdermal emulgel of KTP-CDS-NPs-AOG for managing arthritis. KTP-CDS-NPs, without AO, were incorporated into an HPMC gel matrix to formulate gel, regarded as KTP-CDS-NPsG, and used for comparative study. Franz diffusion cell was used to perform the *ex vivo* permeability study for the emulgel on mice's skin. The drug permeability coefficient values of commercially available Fastum® gel, KTP-CDS-NPsG and KTP-CDS-NPs-AOG emulgel are 0.36 ± 0.03, 0.69 ± 0.02 and 0.90 ± 0.03, respectively. The transdermal flux values of commercially available Fastum® gel, KTP-CDS-NPsG and KTP-CDS-NPs-AOG emulgel are 17.83 ± 1.41, 34.56 ± 0.86 and 44.82 ± 1.62, respectively. These results showed a significant increase in the transdermal flux of KTP-CDS-NPsG and KTP-CDS-NPs-AOG emulgel by 1.92 and 2.49 folds, respectively, compared to the marketed gel. The permeability coefficient also significantly increased for KTP-CDS-NPsG and KTP-CDS-NPs-AOG emulgel by 2 and 3 folds, respectively, compared to the marketed gel. Thus, the enhanced penetration of this KTP-CDS-NPs-AOG emulgel can be attributed to several factors. Firstly, CDS can hydrate the skin's SC, leading to reversible changes in the conformation of keratin and the formation of channels that facilitate the penetration of KTP. Additionally, the oleic and linoleic components present in AO can interact with the lipids in the SC skin layer, promoting permeation through the pericellular pathway. The synergistic effect observed in the prepared emulgels can be attributed to the combination of KTP, CDS and AO. KTP, as a NSAID, exhibits typical anti-inflammatory properties. CDS helps to down-regulate the expression of inflammatory factors and supports cartilage protein synthesis. Furthermore, AO possesses natural anti-inflammatory activity. This anti-inflammatory property of AO synergistically contributes to the treatment of RA when incorporated into a formulation containing the anti-inflammatory KTP and CDS. Therefore, the synergistic effect of KTP, CDS, and AO in the emulgel formulation could provide a better option for treating RA.

10.5.2.4. Clodronate-loaded CS NPs gel Russo et al. [274] formulated CS NPs loaded with the drug clodronate and incorporated them into a thermoreversible gel matrix of poloxamer. The CS NPs' size range was 200–300 nm, and ZP was 21.0 ± 1.3 mV. The purpose was to evaluate the efficacy of this formulation against arthritis by injecting it through intra-articular administration. The developed formulation exhibited enhanced retention of clodronate within the joint, leading to an improved therapeutic index and reduced risk of side effects. The significant drug loading of clodronate CS NPs was achieved with almost 31% (w/w). The drug EE of clodronate CS NPs was approximately 50%. This is because the drug clodronate acts as a structuring agent for this nanoparticulate system, which aided in the significant drug loading and EE.

10.5.3. NGs, their applications and differences from NPs and conventional hydrogels

NGs are majorly 3D cross-linked polymer networks of smart hydrogel particles with a nanometer-sized space, as shown in Fig. 12 [275]. Therefore, NGs are also regarded as hydrogel NPs or nanohydrogels [276]. Therefore, NGs are advantageous because of the combined properties of gels and colloidal NPs, such as high surface-to-volume ratio and small size [193]. In simple terms, NGs are 3D networks that can entrap substances such as drugs, nanocarriers, polymers, and dispersed liquid phases [277].

These NGs have more potential due to the hydrogel feature of high water content and biopolymeric matrix that mimics the extracellular environment found in osteo-cartilage tissues and possibly cell adhesion, hence finding potential in arthritic conditions [275]. The higher water content is related to fluid-like transport properties for the drugs or nanocarriers, which are smaller than the gel pore size. This facilitates the delivery of drugs or nanocarriers to the inflamed synovium by undergoing swelling and deswelling mechanisms [276]. The retention of high-water content in NGs provides a feature that behaves like natural tissue and mimics the 3D ECM of cartilage, which reduces the immunological responses at the injection site or applied site [275]. When injected, the water-retaining property of NGs improves joint lubrication and a soothing effect in the inflamed tissues of the synovium. The major component of synovial fluid is water. The water reduces the friction and imparts the joint lubrication [105,278,279].

10.5.3.1. NGs applications CDS is one of the natural biopolymers in the cartilage of joints. It helps in reducing cartilage degeneration. The inclusion of anti-inflammatory biopolymeric matrices in NGs has beneficial effects on arthritis. For example, Ma et al. [280] prepared an anti-inflammatory NG using CDS combined with gelatin and coated NG with an M2 macrophage membrane to manage OA. The biopolymeric matrix of gelatin-CDS NG-coated M2 macrophage membrane exhibited potential therapeutic effects such as a reduction of inflammatory cytokines and long residence time of NG in the joints of the OA-affected mouse model. Both gelatin and CDS used in this study are biopolymers [281]. Thus, the water-retaining property and biopolymeric matrix make NGs a suitable biocompatible drug delivery in arthritis management.

Nanorapid NGs, marketed by Vivifi Life Sciences, is a topical pain-relieving medication designed to alleviate pain and inflammation. This gel is specifically indicated for treating conditions such as RA, ankylosing spondylitis, and OA. This gel composition includes diclofenac, linseed oil, menthol, and methyl salicylate. Commonly utilized polymers for NG preparation include CS, gelatin, alginate, PVA and carbomers [282,283].

NO is an inflammatory mediator in the pathogenesis of RA; hence, scavenging NO is essential to reduce the inflammation of RA. Yeo et al. [177] formulated NO-scavenging (Scav) NG. They prepared an intra-articular NO-responsive NG containing acrylamide and a NO-cleavable crosslinker (NOCL) using a polymerization method to treat RA. In the presence of endogenous NO of synovial RA joint, the prepared NG gets cleaved by using a NO-cleavable crosslinker (NOCL), which is regarded as NO-Scav-NG. To compare the efficacy of NO-Scav-NG, the researchers used marketed intra-articular DEX injection, and they also developed the control NG where the NG cannot capture the NO, which is regarded as NOX gel. The NO-Scav-NG significantly exhibited the capability of scavenging NO by two folds when compared to NOX gel and effectively reduced the inflammatory mediators against macrophages *in vitro* study. *In vivo* studies have been conducted on a mouse model of RA for 35 d Clinical scores were examined by monitoring each mouse paw's redness and degree of swelling for 35 d After a 35-d treatment period, NO-Scav NG-treated mice showed the lowest cytokine levels of TNF-α and IL-6 in the serum of blood samples compared to the other treatment groups administering NOX gel and DEX. The NO-Scav-NG exhibited a marked therapeutic effect in reducing inflammation-like redness and swelling compared to the marketed drug DEX. X-ray analysis highlighted the potential of NO-Scav-NG by demonstrating reduced cartilage damage compared to NOX and DEX. The histological analysis study revealed that the damaged chondrocyte layers and immune cell infiltration were observed in NOX-treated paw tissues, whereas less damaged chondrocytes and less immune cell infiltration were observed in the DEX group. However, compared to NOX and DEX-treated groups, the NO-Scav-NG exhibited no immune cell infiltration and chondrocyte layers, similar to healthy rats' histological analysis. These findings highlight the promising role of the NO-Scav-NG as a potential treatment approach for RA by reducing inflammation.

Many studies have demonstrated that NGs are efficient because of their high stability, superior drug loading capacity, biological consistency, and responsiveness to various stimuli like ionic strength, pH, and temperature [284].

10.5.3.2. Diffrences between NGs and NPs NGs and NPs, both are nanoscale materials but differ in structure, composition, and properties. NGs are 3D networks of crosslinked polymers forming gel-like structures at the nanoscale, whereas NPs are particles with nanoscale dimensions and diverse structures, which can be solid, hollow, or porous [194]. The composition of NGs includes hydrophilic or amphiphilic polymers (forming a gel-like network) with crosslinkers. The composition of NPs includes various materials such as metals, polymers, lipids, or ceramics. The NGs can efficiently encapsulate multiple bioactive substances with distinct physical properties within the same carrier. This capability is less frequently observed in other nanocarrier types, including micelles, liposomes, dendrimers, or SLNs [276]. NGs have the ability to swell and deswell due to the hydration feature, which is not observed in NPs.

10.5.3.3. Differences between NGs and conventional hydrogels NGs and conventional hydrogels differ primarily in size and structure, with NGs being nanoscale hydrogel particles (1 to 100 nanometers) [285], while conventional hydrogels are larger and macroscopic [286]. The smaller dimensions of NGs contribute to their faster responsiveness due to the quicker diffusion of molecules within the gel matrix, allowing for prompt responses to external stimuli. This stimuli-responsiveness makes NGs suitable for controlled drug release in a spatial and stimuli-dependent manner [287]. The surface of NGs can be easily modified with functional groups, ligands, or targeting moieties. Chemical modifications allow NGs to incorporate ligands for targeted or triggered drug delivery, showcasing their potential in biomedical systems compared to conventional hydrogels [288]. The unique feature of NGs is their soft structure, which plays a crucial role in modifying biodistribution properties. By altering the chemical structure of the NG, the degree of softness can be tailored. *In vivo*, softer NGs deform easily, passing physiological barriers, resulting in longer circulation and lower splenic accumulation [289]. In simple, NGs are superior to conventional hydrogels

due to their relatively high drug encapsulation capacity, uniformity, tunable size, softness, minimal toxicity, stability in the presence of serum, and stimuli responsiveness [276].

10.5.4. *NSPs and MT-NSPs loaded gel*

NSPs are solid, cross-linked, polymeric nano-sized porous structures that encapsulate the drug within their polymeric core, surrounded by a red blood cell (RBC) membrane [290]. Therefore, NSPs are defined as supramolecular 3D hyper-reticulated nanoporous structures with spongy surfaces. They are composed of a 3D scaffold made of polyester that can break down gradually. These polyesters are dissolved in a solution along with a crosslinker to create porous NSPs in which drugs can be incorporated [291]. They have a spherical colloidal structure and porous nature [292]. To prepare NSPs, the polymer should be conjugated with a crosslinker. They elicit a high solubilization capacity for poorly soluble drugs. Cyclodextrin, the most commonly employed polymer in NSP preparation, possesses a porous structure and an outer hydrophilic and inner hydrophobic core. The poorly soluble drugs or bioactives are entrapped in the core, but the outer hydrophilic shell imparts hydrophilicity, significantly enhancing solubility [293,294]. NSPs are capable of promoting the prolonged release of hydrophobic drugs [295]. They can combine a variety of drugs and release them in a controlled and predictable manner [290]. Topical NSPs can increase patient compliance and deliver adequate patient benefits by minimizing repeated doses and side effects [296].

Banjare et al. [297] formulated a cyclodextrin-based NSPs gel system loaded with MT, which was administered intra-articularly in a mouse model of RA. The stirring method was used to prepare MT-NSPs. The PLF-127 was used to prepare thermosensitive MT-NSPs gel. At the injection site, the sol is transformed into a thick, viscous gel that forms a depot and releases the drug in a regulated manner. An inclined test tube method was used to measure the nano gelation time. *In vitro* drug release studies of MT, MT-NS, and MT-NS gel were analyzed under the pH conditions of 7.4 and 6.8. The cumulative release of MT drug from MT-NSPs and MT-NS gel in 72 h was found to be 67.67% ± 0.77% and 55.19% ± 1.74% at pH 7.4, respectively, whereas it was 63.52% ± 3.41% and 55.89% ± 1.36% at pH 6.8, respectively. The results indicated that MT-NSP gel exhibited sustained drug release at both pH conditions without significant changes. The efficacy of the developed formulation was assessed through an MTT test on macrophage cell lines, and it was found to be more effective and nontoxic to macrophage cell lines. To further validate these findings, an *in vivo* study was performed for MT-NSPs gel, confirming the superior anti-arthritic activity by accumulating in the joints for longer retention.

11. Challenges and considerations for clinical applications

The experimental development of gel-based nanocarrier systems is advancing rapidly, yet significant challenges persist in the transition of these platforms to enter the clinical level. The following are the several key challenges associated with gel-based nanocarriers that must be addressed, along with considerations to overcome them.

Efficacy: Animal model efficacy does not guarantee similar outcomes in humans, which is challenging. This is due to physiological differences and molecular target variations in animals and humans. When translating from animal models to humans, modification of formulations for human administration is crucial. Considering the need for dose adjustments is based on the differences in human physiology [298,299].

Scale-up challenges and cost of production: Moving from small-scale laboratory production to large-scale clinical manufacturing poses challenges in terms of scalability and cost-effectiveness. The cost required to manufacture gel-based nanoformulations, including the raw materials and production processes, must be economically viable for widespread clinical use. Therefore, optimization of manufacturing processes for scalability, cost-effectiveness, and reproducibility of nanomedicines should be considered to meet the demands of clinical applications, such as consistency of products with desirable properties [300]. Maintaining uniformity and consistency in large-scale batches poses more significant challenges than smaller-scale production. Variability in raw materials, mixing processes, and other factors can impact the overall homogeneity of the gel system as well as gelation kinetics; thereby, batch-to-batch consistency is more challenging [301]. Monitoring and ensuring the consistency of critical quality attributes across batches should be considered to meet regulatory standards. The complexity of the dosage form design significantly influences the successful translation of nanomedicine to the clinic, regardless of its therapeutic activity [298]. Therefore, simplification in formulation design is required to allow efficient and reproducible large-scale manufacturing [298].

Formulation design of gel-based nanocarrier system: Maintaining consistent viscosity is crucial for accurate dosing and effective application of gel systems. Additionally, viscosity is important during transit to the target site and adapts to the local microenvironment. Hence, variability in viscosity is challenging. Injectable gel-based nanocarriers must have a sufficiently low viscosity to be introduced via a needle but contain sufficient elasticity for *in situ* conditions to maintain their injected volume and sustain repetitive load. [302,303]. Hence, optimization of gel systems with suitable gel components to achieve the desired viscosity and injectability is considered. Achieving the desired viscosity while incorporating nanocarriers can be complex. Optimization of the formulation design by carefully balancing the concentrations of gelants and nanocarriers is considered using statistical designs like Box-Behnken [304]. Gels should possess optimum mechanical strength (which depends on rheological behaviour) when intended for topical or transdermal administration. Gels often experience changes in rheological properties *in vivo* environment due to stimuli-responsive factors such as temperature, pH, and biological interactions. Hence, the rheological behaviour of gels and the stimuli-responsiveness of gels that can adapt to changes in the microenvironment should be considered. While transitioning gel-based nanocarriers to the clinic, attention should be given to nanocarriers as they have to be

Table 1 – Types of nanocarriers with their loaded drugs and gelling agents used to produce gel-based nanocarrier systems.

Nanocarrier type and its gel form	Drug	Gelling agent	Type of animal model used	Outcome	Ref.
Lipidic carriers (Micellar type); NE and NEG	MT-MgO	Carbopol 940 (Confers sustained release-gelling agent increases the viscosity of the formulation, which makes it challenging to release the drug)	CFA-induced arthritis rat model	Reduction in inflammation, enhanced joint mobility, and decreased discomfort.	[203]
	Valdecoxib	Carbopol 940(confers stability and sustained release)	Carrageenan-induced hind paw oedema rat model	Inhibition of oedema by valdecoxib NEG was very high as compared to free drug and free drug-loaded conventional gel.	[204]
	MT	Badam gum (confers sustained release and stability)	–	Sustained drug release behaviour exhibited by MT-NEG. Good stability of MT NEG is achieved.	[205]
	DF	Xanthan gum (confers sustained release)	Carrageenan-induced paw oedema model; Histamine-induced paw oedema model; Formalin-induced paw oedema model	Skin penetration was noticeably higher for DIF-IC-loaded NEG formulations than for DIF-loaded NEG. Better *in vivo* anti-inflammatory efficacy was exhibited by the DIF-IC NEG containing XG.	[206]
	TF	Carbopol 934 (confers sustained release)	–	*In vitro* drug release, 89.64% ± 0.97% sustained drug release of TF was obtained in 24 h	[207]
	DST	Carbopol ETD 2020(confers sustained release)	CFA-induced arthritis model	DST NEG showed enhanced skin permeation, *in vitro* sustained drug release, and decreased TNF levels.	[208]
Lipidic carriers (Particulate type) SLNs	ETC	Carbopol 934 and HPMC (confers sustained release, HPMC also acts as a stabilizing agent.	–	The ETC SLNs gel containing carbopol showed better permeation as compared to the ETC SLNs gel containing HPMC.	[213]
	CQ	Sodium carboxy methyl cellulose (confers high drug retention)	CFA-induced arthritis rat model	CQ-SLNs gel has the highest drug retention in the skin compared to CQ phosphate gel. Less bone and cartilage degeneration was seen in the radiographic and histopathological analyses of the arthritic rats that were treated with CQ SLN gel than in those treated with CQ phosphate gel.	[214]
Lipidic carriers (Particulate type) NLCs	MT	Pluronics (Confers thermos-responsive properties to gels)	CFA-induced arthritis model	Good spreadability of MT NLC gel The MT-NLC gel showed a reduction in paw oedema over 28 d, which has the potential to treat RA.	[220]
	IBU	Carbopol 971P NF (Confers stability)	–	IBU NLC gel showed better permeation through the skin, which might be suitable as a vehicle to load anti-arthritic drugs.	[221]
Lipidic carriers(Vesicular type) Liposomes	MT	Carbomer 940 (confers stability)	–	MTTRFL showed excellent skin permeation, longer circulation time, and higher drug retention in inflamed joints.	[228]
	MT	Carbopol	Adjuvant-induced RA model	MTUDLG showed enhanced anti-inflammatory activity and improved skin permeation in an adjuvant-induced rat model.	[229]

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Table 1 (*continued*)

Nanocarrier type and its gel form	Drug	Gelling agent	Type of animal model used	Outcome	Ref.
	DEX	Carbopol 934	CFA-induced rats	The fluorescence live imaging system revealed a better accumulation of flexible liposomes in the rat joints.	[88]
Lipidic carriers (Vesicular type) PLs	PD	Carbopol (confers sustained release)	Carrageenan-induced paw edema	The suggested PD proliposomal gel of PD demonstrated sustained release along with improved anti-inflammatory action, indicating that it may be useful as a topical treatment for the management of RA.	[234]
Lipidic carriers (Vesicular type) Ethosomes	NPXS	Carbopol 934	Carrageenan-induced rat paw oedema model	The transdermal flux of NPS ethosomes was ~10 times higher than the hydroethanolic solution. Additionally, compared to commercially available diclofenac gel, the improved ethosomal gel showed a better percentage suppression of swelling paw oedema in the *in vivo* pharmacodynamic analysis, which has shown a potential to treat RA.	[239]
Lipidic carriers (Vesicular type) TRS	IT	Carbopol 940	CFA-induced arthritis model	Imatinib TRS gel showed enhanced drug permeability and reduced paw swelling, which could be a promising treatment for RA.	[242]
Lipidic carriers (Vesicular type) Bilosomes	FP	Carbopol	Carrageenan-induced rat model	FPB gel showed complete recovery in the histology of arthritic joints and reduced cytokine levels, which would be the best option for treating arthritis.	[246]
Lipidic carriers (Vesicular type) Hyalurosomes	TFC and boric acid	Carbopol 934 and HA (confers sustained release)	CFA-induced rat model	TFC and BA hyalurosomal gel reduces the IL-6, IL1-$\beta$and TNF-α levels	[249]
Lipidic carriers (Vesicular type) Pharmacosomes	ETC	Carbopol 934	–	The ETC-pharmacosomal gel has a prolonged release mechanism. It demonstrates increased EE and improved drug release.	[253]
	ETD	Carbopol 934	CFA-induced paw and ankle oedema model	ETD-pharmacosomal gel sustained release behaviour, enhanced skin permeation, inhibition of protein denaturation (*in vivo* anti-inflammatory effect)	[254]
Lipidic carriers (Vesicular type) CBS	KTP	Carbopol 934 (confers sustained release)	–	Carbopol was used to prepare KTP cubogel, which showed prolonged drug release.	[257]
Surfactant-based vesicular nanocarriers NVSPL	CBL	Carbopol	CFA-induced rat model	CBL NVSPL gel showed a reduction in swelling and suppression of cytokines levels in the rat. Gel incorporating NVSPLs offers a more effective site-specific treatment for the topical management of RA.	[259]

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Table 1 (*continued*)

Nanocarrier type and its gel form	Drug	Gelling agent	Type of animal model used	Outcome	Ref.
Surfactant-based vesicular nanocarriers NMs	MT	Carbopol 934	CFA-induced RA mice model	MT-NM gel showed a reduction in paw thickness and clinical score. The drug had the highest accumulation in inflamed joints. These results suggest that it could be a promising agent against RA.	[158]
Polymeric nanocarriers NCs	Nimesulide	Carbopol 934	Carrageenan model	In models of chronic inflammation, topical nimesulide exhibited enhanced anti-inflammatory efficacy upon nanoencapsulation.	[266]
Polymeric nanocarriers NPs	MT	Carbopol 934	Complete Freund's Adjuvant–induced arthritis rats' model	Compared to MT gel and DEX gel, MT-NPs gel substantially decreased the inhibition of edema.	[271]
	INDM)	Carbopol 934	Adjuvant-induced arthritis rat	INDM-NPs-Menthol gel exhibited enhanced permeation than INDM-NPs gel	[272]
	KTP	HPMC	–	KTP NPs Gel showed enhanced skin penetration as compared to the marketed formulation.	[273]
	Clodronate	Poloxamer (confer thermos-responsive properties)	–	The gel showed prolonged drug release compared to free drugs and reduced cytokine levels.	[274]
Polymeric nanocarriers NGs	NO scav NG	–	Collagen-induced arthritis mouse model	The lowest cytokines levels were observed in mice treated with NO-Scav NG. The onset of RA was reduced with therapy of NO-Scav NG.	[177]
Polymeric nanocarriers NSPs	MT NSPs	PLF-127	CFA-induced RA model	Results OF MT-NS gel suggested sustained drug release with an enhanced drug retention time.	[297]

incorporated into gel systems. The nanocarriers should be easily scalable for manufacturing and ensure high control over their physicochemical properties (such as MPS, PDI, morphology, drug EE and charge). As nanocarriers enter the cells and influence molecular pathways, a thorough evaluation of synthetic polymers and lipids is necessary to assess potential short-term and long-term toxicity in the clinical context [298,304].

Stability: Maintaining the stability of gel-based nanocarriers during storage and transportation is critical for clinical application. Developing formulations that exhibit long-term stability should be considered.

Drug Release: Achieving controlled and predictable drug release from gels is essential for maintaining therapeutic efficacy. Balancing the release rate to maintain therapeutic levels without causing toxicity or underdosing is a significant challenge. Optimization of the gel formulation to control drug release kinetics should be considered by employing strategies like stimuli-responsive gel-based nanofor mulations.

Biocompatibility: Gel components and any encapsulated drugs or nanocarriers should not cause compatibility issues and biocompatibility issues like immune responses, toxicity, and adverse reactions in the body. Hence, considering the compatibility and biocompatibility of different components of gel-based systems is essential.

Regulatory Approval: Meeting regulatory requirements is a complex process that involves demonstrating the safety and efficacy of the gel-based nanoformulations. Developing a robust regulatory strategy early in the development process should be considered. Comprehensive data (like *in vitro, in vivo* and *ex vivo* protocols) on the formulation's performance and safety is necessary for regulatory approval [298].

These challenges and considerations must be addressed to ensure their safety, efficacy, and practicality, contributing to the successful translation of gel-based nanocarriers into clinical applications (Table 1).

12. Future research focuses on clinical trials and scalability

To overcome the challenges associated with gel-based nanocarriers, future research in this field with a focus on

clinical trials and scalability could explore several promising areas. Addressing the following areas can contribute to advancing gel-based nanocarriers as clinically viable drug delivery systems, ultimately enhancing patient outcomes and expanding the possibilities for personalized and effective therapeutic interventions.

Patient convenient: As gel-based systems are easy to apply and patient convenient, the gel-based nanocarriers should be designed as non-invasive, easy to use, and easily manageable by patients to promote adherence to the treatment.

Scalability: Scalable and cost-effective manufacturing processes should be developed to produce gel-based nanocarriers at a clinical scale. Continuous manufacturing approaches should be investigated to enhance efficiency and decrease variation between the batches. Robust quality control methods should be established to ensure consistency in large-scale production.

Novel materials for gel-based nanocarriers with improved biocompatibility, stability, and controlled drug release should be investigated. The development of biodegradable gels to address concerns related to the persistence of nanomaterials in the body should be explored.

Appropriate clinical endpoints and biomarkers to assess treatment responses and patient outcomes should be defined while selecting a clinical trial design. Regulatory challenges related to the testing and approving complex nanoformulations should be addressed.

13. Conclusion

Arthritis is a chronic joint disorder where the inflammation worsens and causes cartilage degradation. It poses challenges for traditional oral or systemic drug delivery due to associated side effects. A gel-based nanocarrier system is more promising as it combines both the advantages of gels and nanocarriers. This approach minimizes the risk of oral and systemic side effects, particularly when therapy is localized (intra-articular, topical, transdermal) for arthritis management. Localized drug delivery ensures specific targeting of inflamed joints in OA and RA, enhancing therapeutic efficacy. Gel-based nanocarriers discussed in this review notably have demonstrated effectiveness in arthritis treatment by delivering anti-inflammatory drugs or NSAIDs, showcasing advantages such as localized drug delivery, prolonged and targeted release, and reduced systemic side effects. Overall, the use of a gel-based nanocarrier system can improve drug efficacy, increase patient convenience, and potentially reduce healthcare costs. While the benefits make gel-based nanoengineered therapy attractive for arthritis management, challenges must be addressed in translating these systems to the clinical level. Scale-up issues, stability, regulatory approval, gelation kinetics, and batch-to-batch consistency are among the considerations for manufacturing gel-based nanoformulations. Despite the promising evidence, further research is essential to fully understand the clinical potential, emphasizing the need for continued investigation into gel-based nanocarriers in arthritis management.

Conflict of interest

Authors declared no conflict of interest.

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