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NANOTECHNOLOGY-ENABLED COMBINATION THERAPY FOR ARTHRITIS: NANOEMULSIONS, NANOPARTICLES, AND TOPICAL GEL SYSTEMS

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ABSTRACT

Arthritis is a chronic inflammatory disorder characterized by joint pain, stiffness, swelling, and progressive loss of function. Non-steroidal anti-inflammatory medications (NSAIDs), corticosteroids, and disease-modifying anti-rheumatic drugs (DMARDs) are examples of conventional therapy that are effective but frequently have low bioavailability, restricted targeting of inflamed joints, and systemic adverse effects. Through better medication delivery, greater targeting, and controlled release, nanotechnology is now recognized as a promising approach to get beyond these restrictions. The combination therapy for arthritis made possible by nanotechnology is the main theme of this review, with a focus on topical gel systems, nanoemulsions, and nanoparticles. Nanoemulsions are appropriate for topical and transdermal distribution because of their high drug solubilization, enhanced skin penetration, and quick start of action. Co-delivery of many medications is made possible by polymeric, lipid-based, and metallic nanoparticles. This results in synergistic analgesic and anti-inflammatory benefits while lowering dosages and side effects. Through surface modification and size management, these systems may be designed for targeted and prolonged release at inflammatory joints. Nanocarrier-based topical gel solutions are a patient-friendly strategy that increases local drug concentration, reduces systemic exposure, and boosts patient compliance. Combination treatment with nanocarrier-loaded gels improves therapeutic effectiveness by delivering drugs like corticosteroids, NSAIDs, and natural anti-inflammatory substances all at once. Formulation techniques, modes of action, characterisation techniques, and current developments in nanotechnology-based combination treatments for arthritis are all included in the review. Additionally highlighted are issues with stability, massive manufacturing, safety, and regulatory approval. All things considered, combination therapy enabled by nanotechnology that makes use of nanoemulsions, nanoparticles, and topical gel systems presents a promising and novel strategy for the more efficient, secure, and focused treatment of arthritis.

KEYWORDS: Nanotechnology, Arthritis therapy, Nanoemulsions, Nanoparticles, Combination therapy, Topical gel, Drug delivery systems.

1. INTRODUCTION

A collection of musculoskeletal conditions marked by joint inflammation, discomfort, stiffness, swelling, and gradual loss of function are together referred to as arthritis. It is one of the main causes of disability globally and has a substantial impact on mobility and quality of life. The two most prevalent types are rheumatoid arthritis (RA), a chronic autoimmune inflammatory illness, and osteoarthritis (OA), a degenerative joint disease. Because of its high incidence, chronic nature, and persistent socioeconomic burden, arthritis continues to be a significant public health concern despite advancements in pharmacotherapy.

1.1. Overview of Arthritis and Its Global Burden

Around the world, hundreds of millions of individuals of all ages suffer with arthritis, however the condition is more common as people age. While rheumatoid arthritis significantly increases long-term morbidity and shortens life expectancy, osteoarthritis alone is among the leading causes of years lived with disability globally. In addition to physical impairment, the illness burden also includes

psychological discomfort, decreased productivity at work, and higher healthcare costs.[1]

Delays in diagnosis and restricted access to healthcare exacerbate illness outcomes in poor nations. The combination of aging populations, sedentary lifestyles, obesity, and longer life expectancies, arthritis is becoming more common in nations like India. The financial burden consists of both direct medical expenses for medications, hospital stays, and procedures along with indirect expenditures brought on by reliance and income loss. More efficient, secure, and patient-friendly therapy approaches are therefore desperately needed.[2]

1.2. Limitations of Conventional Arthritis Therapy

The primary goals of conventional arthritis treatment are symptom management and delaying the disease's development. Non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids, disease-modifying anti-rheumatic medications (DMARDs), and biological agents are among the frequently utilized pharmacological classes. Although these treatments help lessen pain and inflammation, they have a number of significant drawbacks.[3]

- **Systemic side effects:** Gastric irritation, ulcers, kidney toxicity, and cardiovascular hazards might result from long-term NSAID usage. Corticosteroids can cause immunological suppression, diabetes, hypertension, and osteoporosis.
- **Inadequate targeting:** Instead of concentrating at the inflamed joint, the majority of traditional medications spread throughout the body, which results in low drug concentration at the target location and an increased risk of systemic toxicity.
- **Low bioavailability:** Many medications exhibit quick metabolism, poor solubility, or instability, which lowers their therapeutic efficacy.
- **Poor compliance and frequent dosage:** Rapid clearance and short half-life necessitate frequent dosing, which lowers patient adherence, particularly in chronic diseases.
- **High cost of biologics:** Despite their effectiveness, biologic treatments are costly and linked to immunological responses and infection risk.[4]

These drawbacks emphasize the need for sophisticated drug delivery methods that can boost bioavailability; decrease adverse effects, increase drug targeting, and offer long-lasting therapeutic activity.

1.3. Role of Nanotechnology in Modern Drug Delivery

Designing and using materials at the nanoscale scale (1–1000 nm) to enhance medication delivery and therapeutic efficacy is known as nanotechnology. Nanotechnology provides creative ways to address the shortcomings of traditional treatments for arthritis. Anti-arthritic medications can be encapsulated and delivered directly to inflammatory joints using nanocarriers such nanoparticles, nanoemulsions, liposomes, solid lipid nanoparticles, polymeric nanoparticles, and nanogels.

These systems provide a number of benefits[5]

- **Targeted medication delivery:** Because of the increased permeability and retention (EPR) effect, nanoparticles can build up in inflammatory tissues. They can also be modified with ligands for active targeting.
- **Increased bioavailability:** Nanocarriers make poorly soluble medications more stable and soluble.
- **Controlled and sustained release:** By releasing medications gradually over time, dose frequency may be decreased and patient compliance can be increased.
- **Decreased systemic toxicity:** Inappropriate exposure to tissues that are healthy is reduced when medications are concentrated at the site of inflammation.
- **Improved topical and transdermal delivery:** Topical treatment is safer and more effective thanks to nanoemulsions and nanogels, which increase skin penetration.[6]

Therefore, medication delivery systems based on nanotechnology provide a viable strategy for managing arthritis in a safer, more efficient, and patient-friendly manner. Their incorporation into combination therapy, which includes topical, injectable, and oral formulations, creates new opportunities for individualized and focused treatment of arthritis.

2. PATHOPHYSIOLOGY OF ARTHRITIS

Joint inflammation, pain, stiffness, swelling, and functional impairment are the hallmarks of a set of conditions collectively referred to as arthritis. While the origins of various forms of arthritis vary, they all have pathological characteristics such bone remodeling, cartilage deterioration, synovial inflammation, and the involvement of inflammatory and immunological mediators. An initial trigger, such as mechanical stress, an immunological reaction, an infection, or a metabolic imbalance that triggers inflammatory pathways inside the joint, usually starts the illness process. Synovial hyperplasia, elevated inflammatory cytokine production, immune cell infiltration, and gradual cartilage and subchondral bone degradation result from this. Chronic inflammation causes structural alterations in joints, such as osteophyte growth, bone erosion, joint space constriction, and surrounding tissue fibrosis. These alterations eventually result in discomfort, deformity, loss of movement, and irreparable joint degeneration.[7]

2.1. Types of Arthritis

Rheumatoid Arthritis (RA): The chronic autoimmune inflammatory illness known as rheumatoid arthritis (RA) mostly affects synovial joints. When the immune system unintentionally targets joint tissues, synovitis, pannus development, cartilage degradation, and bone erosion result. RA often affects the tiny joints of the hands and

feet and is symmetrical. Systemic symptoms including exhaustion, anemia, heart problems, and lung involvement are linked to it.[8]

Osteoarthritis (OA): OA is a degenerative joint condition brought on by aging, obesity, trauma, mechanical wear and tear, and genetics. Progressive articular cartilage loss, subchondral bone thickening, osteophyte growth, and moderate inflammation are its defining characteristics. OA primarily affects weight-bearing joints, including the hands, knees, hips, and spine.[9]

Psoriatic Arthritis (PsA): Psoriasis is linked to inflammatory arthritis. Joint pain, stiffness, edema, and deformities result from both autoimmune and inflammatory processes. The spine, entheses (where tendons connect to bone), and peripheral joints may all be impacted.[10]

Other Types

- **Ankylosing spondylitis:** This condition mostly affects the sacroiliac joints and spine, causing stiffness and decreased movement.
- **Gout:** Acute inflammatory episodes brought on by monosodium urate crystal formation as a result of hyperuricemia.
- **Reactive arthritis:** This condition affects the joints, eyes, and urinary tract and develops following an infection.[11]

2.2. Inflammatory Pathways and Mediators

Immune cells, cytokines, enzymes, and signaling pathways interact intricately to control inflammation in arthritis.

- **Immune cell activation:** In inflammatory arthritis, T cells, B cells, macrophages, and synovial fibroblasts are all activated.
- **Cytokines:** Tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), IL-6, IL-17, and interferon-gamma are important pro-inflammatory cytokines. These cytokines promote bone erosion, cartilage degradation, and synovial inflammation.[12]
- **Eicosanoids:** Pain, swelling, and inflammation are caused by prostaglandins and leukotrienes that are generated by the cyclooxygenase (COX) and lipoxygenase pathways.
- **Matrix metalloproteinases (MMPs):** These enzymes break down cartilage's collagen and proteoglycans.
- **RANK/RANKL pathway:** Encourages bone resorption and osteoclast activation.[13]

The two main intracellular signaling pathways that control the production of inflammatory genes are JAK-STAT and NF-κB.

2.3. Targets for Combination Therapy

Although several pathways are involved in arthritis, single-drug treatment frequently results in insufficient control. The goal of combination treatment is to concurrently attack several phases of the disease's evolution. Important treatment targets include of:

- TNF-α, IL-1, IL-6, and IL-17 are inflammatory cytokines that are targeted by small-molecule inhibitors and biologics.
- NSAIDs target the cyclooxygenase enzymes (COX-1/COX-2) to reduce pain and inflammation.
- Immune cell activity: DMARDs that reduce immune-mediated damage include leflunomide, sulfasalazine, and methotrexate.[14]
- Intracellular signaling pathways: NF-κB modulators and JAK inhibitors lower the expression of inflammatory genes.
- Cartilage protection: substances that target oxidative stress, MMPs, and chondrocyte death.
- RANKL inhibitors are used in bone remodeling to stop bone deterioration.

In combination therapy, medications are chosen to produce synergistic effects, such as when an immunomodulator and an anti-inflammatory agent are combined, or when systemic therapy is combined with targeted topical or nanocarrier-based delivery to increase efficacy, lower dose-related toxicity, and improve persistent disease control.[15]

3. CONCEPT OF COMBINATION THERAPY IN ARTHRITIS

Using two or more therapeutic drugs with distinct mechanisms of action to treat arthritis is known as combination treatment. Targeting only one route frequently results in insufficient alleviation since arthritis is a complex illness including immune dysregulation, inflammation, cartilage degradation, and bone remodeling. Therefore, combination treatment is intended to prevent structural joint damage, decrease disease development, and control symptoms all at once. NSAIDs and DMARDs, corticosteroids and immunomodulators, biologics and conventional medications, or systemic medications with topical or targeted delivery methods like nanoformulations are examples of combination treatment in clinical practice. This strategy seeks to enhance long-term results, better disease management, and a quicker commencement of action.[15]

3.1. Rationale for Using Multiple Drugs

Combination treatment for arthritis is justified by the intricate and interrelated nature of the disease mechanisms:

- **Several pathogenic pathways:** Enzymatic cartilage degradation, immune cell activation, inflammatory cytokines, and bone resorption are all involved in arthritis. All of these mechanisms cannot be successfully blocked by a single medication.
- **Inadequate response to monotherapy:** In order to obtain sufficient disease management, many patients exhibit partial or no response to a single medication, necessitating the use of several medicines.[16]

- **Dose reduction:** By combining medications with various mechanisms, the risk of dose-related toxicity can be decreased.
- **Avoidance of disease progression:** Compared to stepwise monotherapy, early aggressive combination treatment is more successful in slowing joint degeneration.
- **Better symptom control:** Drugs that target diverse targets can treat pain, stiffness, and edema all at once.[17]

As a result, taking many medications raises the possibility of attaining thorough and long-lasting illness management.

3.2. Synergistic and Additive Effects

When medications are used simultaneously, they may have the following combined effects:

Additive effect: The sum of the various impacts equals the overall effect. For instance, a DMARD that suppresses immunological activity and an NSAID that lowers prostaglandin production combined give better symptom management than either one alone.[18]

Synergistic impact: The whole effect outweighs the sum of the individual effects. In rheumatoid arthritis, for example, methotrexate with a TNF-α inhibitor is more effective than either medication alone.[19]

Synergy can be achieved by

- Focusing on several phases of the same route.
- Using inflammatory pathways in simultaneously.
- Improving medication retention or bioavailability at the intended location, particularly when administered by cutting-edge methods like nanoparticles.
- Improved treatment results are made possible by these interactions without correspondingly raising toxicity.[20]

3.3. Advantages over Monotherapy

When compared to monotherapy, combination treatment has the following benefits:

- **Increased effectiveness:** Improved management of pain, inflammation, and the course of the illness.
- **Lower medication dosages:** By reducing exposure to high doses, the likelihood of negative consequences is decreased.
- **Quicker therapeutic response:** When long-term disease modifiers are paired with fast-acting medications, early symptom alleviation is achieved.[21]
- **Decreased medication tolerance or resistance:** This is especially important for immunomodulatory treatment.
- **Customized care:** Treatment plans can be adjusted according on comorbidities, patient response, and the severity of the illness.
- Better functional capacity, quality of life, and less long-term impairment are examples of improved patient outcomes.[22]

Consequently, combination therapy especially when combined with contemporary medication delivery technologies represents a logical and successful approach for treating complicated and long-term ailments like arthritis.

4. ROLE OF NANOTECHNOLOGY IN COMBINATION THERAPY

Although it makes it possible to co-deliver many medications with various modes of action in a single delivery system, nanotechnology is essential to improving the efficacy of combination treatment for arthritis. Drug-drug interactions, disparate pharmacokinetic profiles, and unequal drug distribution in the body are common issues with conventional combination treatment. Liposomes, solid lipid nanoparticles, nanoparticles, nanoemulsions, and nanogels are examples of nanocarriers that can encapsulate two or more medications and deliver them all to the inflamed joint in a regulated way.[23] Nanotechnology guarantees synchronized delivery, preserves ideal drug ratios at the target location, and enhances therapeutic synergy by combining many medications into a single nanosystem. Because anti-inflammatory, immunomodulatory, and cartilage-protective medications may be combined to operate concurrently on several disease pathways, this strategy is particularly helpful in the treatment of arthritis.[24]

4.1. Advantages of Nanoscale Drug Delivery

Compared to traditional formulations, nanoscale drug delivery methods have the following advantages:

- **Small size and big surface area:** The high surface-to-volume ratio of nanoparticles (1–1000 nm) enables effective drug loading and interaction with biological membranes.
- **Improved tissue penetration:** Compared to bigger particles, nanosystems are better at penetrating inflammatory synovial tissue.
- **Drug protection:** Encapsulation shields medications against deterioration, enzymatic metabolism, and early excretion.
- **Formulation flexibility:** Drugs that are lipophilic or hydrophilic can be combined in one system.
- Sustained-release nanosystems decrease the frequency of doses, which improves patient compliance.[25]

Because of these characteristics, nanotechnology is especially well suited for long-term therapy of chronic conditions like arthritis.

4.2. Targeted and Controlled Drug Release

Targeted and regulated medication distribution is one of the most significant benefits of nanotechnology in the treatment of arthritis.

- **Passive targeting:** Because inflamed joints have more permeability and leaky blood arteries, nanoparticles can build up at the site of inflammation (EPR impact).[26]
- **Active targeting:** Ligands that attach to receptors overexpressed in inflammatory synovial tissue, which can include antibodies, peptides, or sugars, can be added to the surface of nanocarriers.
- **Stimuli-responsive systems:** Certain nanosystems release medications in reaction to temperature, pH, enzymes, or oxidative stress, all of which are changed in arthritic joints.
- **Controlled release:** By releasing medications gradually over time, nanocarriers can sustain therapeutic dosages for prolonged periods of time.[27]

While reducing exposure to healthy tissues, this tailored and regulated administration raises medication concentration at damaged joints.

4.3. Improved Bioavailability and Reduced Toxicity

Many anti-arthritic medications have limited stability, fast metabolism, or poor water solubility, which restricts their bioavailability. These problems are addressed by nanotechnology by:

- **Improving solubility:** Lipid-based nanoparticles and nanoemulsions help poorly soluble medications dissolve.
- **Increasing absorption:** Nanocarriers improve absorption across biological barriers including the mucosa of the gastrointestinal tract and skin.[28]
- **Extending circulation time:** Surface modification, such as PEGylation, slows down the reticuloendothelial system's quick clearance.
- **Reducing systemic toxicity:** Lower total dosages are required when medications are concentrated at the inflamed joint, which lessens adverse effects such gastric, renal, and cardiovascular toxicity.
- **Safer combination therapy:** Co-administration of many medications in a single nanosystem minimizes pharmacokinetic mismatch and lowers the possibility of adverse drug responses.[29]

Thus, by enhancing efficacy, safety, and patient adherence, drug delivery methods based on nanotechnology greatly enhance combination treatment for arthritis.

5. NANOEMULSIONS IN ARTHRITIS TREATMENT

Anti-arthritic medications are increasingly being delivered by nanoemulsions, which are particularly useful for topical and transdermal treatments. They are excellent for treating chronic inflammatory diseases like arthritis because of their tiny droplet size, high kinetic stability, and capacity to solubilize both hydrophilic and lipophilic medications. sNanoemulsions are colloidal dispersions of two immiscible liquids (often water and oil) that are kinetically stable but thermodynamically unstable. They are stabilized by surfactants and co-surfactants, and their droplet sizes are generally between 20 and 200 nm.[30]

Types of nanoemulsions

- **Oil-in-water (O/W):** Lipophilic medications are frequently administered topically and orally using oil droplets scattered in an aqueous phase.[31]
- **Water-in-oil (W/O):** Water droplets scattered throughout the oil phase; helpful for moisture retention and prolonged medication release.[32]
- **Bi-continuous nanoemulsions:** Hydrophilic and lipophilic medications can be co-delivered since both water and oil form continuous phases.[33]

5.1. Formulation Methods

Depending upon the formulation needs, either high-energy or low-energy procedures can be used to create nanoemulsions. To decrease droplet size, high-energy techniques rely on outside mechanical forces. Intense shear forces are used in high-pressure homogenization to split big droplets into tiny ones. Acoustic cavitation is a technique used in ultrasonication, in which sound waves produce microbubbles that burst into tiny droplets. By forcing the liquid mixture through microchannels at high pressure, microfluidization creates uniformly sized droplets. These techniques work well, but they need a lot of energy and costly equipment.[34]

Low-energy techniques rely less on mechanical force and more on the system's inherent chemical energy. The phase inversion temperature (PIT) technique creates nanoemulsions by using temperature-induced variations in surfactant solubility. When oil, surfactant, and aqueous phase are combined under regulated circumstances, spontaneous emulsification takes place, resulting in the self-formation of nanoscale droplets.[35] Changing the ratio of the water and oil phases until phase inversion takes place is the foundation of the emulsion inversion point (EIP) approach. Drug characteristics, surfactant type, necessary droplet size, scalability, and total production cost all influence the preparation technique selection.[36]

Because nanoemulsions may contain both lipophilic and hydrophilic medications, they can be used in combination treatment. Hydrophilic medications are integrated in the aqueous phase, whereas lipophilic medications are often dissolved in the oil phase. Multiple medications with distinct qualities can be delivered simultaneously by co-loading them in various stages.[37] The use of surfactants in nanoemulsions improves drug solubility, which results in improved formulation performance and high drug loading efficiency. Because of the protective surfactant layer around the droplets and the extremely tiny droplet size, nanoemulsions are kinetically stable. However, processes including phase separation, Ostwald ripening, and coalescence can still lead to instability. Optimizing the oil phase, adding the right stabilizers, and choosing the right surfactant and co-surfactant system may all increase stability. Long-term stability and reliable therapeutic results are guaranteed by a well-designed formulation.[38]

5.2. Applications in Topical and Transdermal Delivery

When delivering anti-arthritic medications topically or transdermally, nanoemulsions are especially helpful:

- Increased medication penetration through the disruption of stratum corneum lipids by small droplet size and surfactants.
- **Localized action:** Reduces systemic exposure by delivering medication directly to afflicted joints.
- **Better patient compliance:** Compared to injections, this method is non-invasive and simple to administer.
- **Sustained release:** Offers extended medication release at the place of application.
- **Versatility:** For improved skin retention, it may be made into gels or creams.[39]

Examples include NSAIDs, corticosteroids, and herbal anti-inflammatory drugs in nanoemulsion-based gels for the treatment of arthritic pain, inflammation, and stiffness.

6. NANOPARTICLES FOR ARTHRITIS THERAPY

The purpose of nanoparticles, which are submicron-sized carriers (usually 10–1000 nm), is to enhance the administration of anti-arthritic medications. They improve the solubility, stability, targeting, and controlled release of drugs, which makes them ideal for long-term inflammatory conditions like arthritis. Depending on the material composition and therapeutic requirements, several kinds of nanoparticles are used.[40]

6.1. Polymeric Nanoparticles

As a result of their biocompatibility, biodegradability, and easily adjustable characteristics, polymeric nanoparticles which may be made from synthetic or natural polymers are often utilized in drug administration. Alginate, gelatin, dextran, and albumin are examples of natural polymers, whereas PLGA, PLA, PEG, PCL, chitosan, and Eudragit are often utilized synthetic polymers. These polymers enable the creation of nanoparticles with regulated surface charge, size, and release properties.[41] Polymeric nanoparticles provide a number of benefits, including the capacity to alter their surface with ligands for active targeting, regulated and prolonged drug release, and protection against chemical and enzymatic degradation. Additionally, they exhibit remarkable formulation repeatability and strong physical stability. NSAIDs, corticosteroids, and DMARDs such as methotrexate are administered using polymeric nanoparticles in the treatment of arthritis. Better disease management and patient compliance result from their longer anti-inflammatory impact, less systemic adverse effects, and increased medication accumulation in inflammatory joints.[42]

6.2. Lipid-Based Nanoparticles

Lipid-based nanoparticle systems are exceedingly biocompatible and can be used for topical and systemic medication delivery in the treatment of arthritis. Solid lipids stabilized with surfactants are used to create solid lipid nanoparticles (SLN), which offer both high physical stability and controlled drug release. They may be employed in oral, injectable, and topical formulations and are particularly well suited for the delivery of lipophilic anti-arthritic medications. The second generation of SLN, known as nanostructured lipid carriers (NLC), is made up of both liquid and solid lipids.[43] This structure provides better long-term stability, lowers drug ejection during storage, and permits greater drug loading. Liposomes are spherical vesicles made of phospholipid bilayers that may contain lipophilic medications inside the bilayer membrane and hydrophilic drugs in their watery core. They are capable of being surface-modified for targeted distribution to inflammatory joints and are biodegradable and biocompatible. Because of their safety, adaptability, and efficacy, lipid-based nanoparticles are generally utilized to administer NSAIDs, corticosteroids, and biologics in arthritis.[44]

6.3. Metallic and Inorganic Nanoparticles

Regardless of their distinct physicochemical and biological characteristics, metallic and inorganic nanoparticles can be used in sophisticated medication delivery and diagnostic applications. Iron oxide, silica nanoparticles, gold, and silver are typical examples. Gold nanoparticles can improve the therapeutic impact of loaded medications and have anti-inflammatory and antioxidant properties. Iron oxide nanoparticles are particularly helpful for imaging and targeted administration with magnetic guiding, allowing for theranostics a combination of diagnostic and treatment. Silver nanoparticles have antibacterial and anti-inflammatory properties, whereas silica nanoparticles offer a large surface area for drug loading. However, the possible toxicity and buildup of metallic and inorganic nanoparticles in organs, which might have long-term negative consequences, is a big issue. Therefore, prior to clinical use, meticulous design, surface modification, and thorough safety evaluation are crucial.[45]

Nanoparticles are extremely useful for combination therapy in arthritis because they allow the co-delivery of several medications in a single system. Different medications can be administered using layered or hybrid nanoparticles, or they can be put into distinct compartments like lipid and aqueous phases or core and shell architectures. It is possible for one medicine to be encapsulated inside the nanoparticle while another be conjugated to its surface. This method minimizes systemic adverse effects, decreases dose frequency, improves synergistic or additive therapeutic benefits, and preserves an ideal medication ratio at the target location. Additionally, it reduces medication pharmacokinetic mismatch. In comparison with single-drug systems, nanoparticles can co-deliver an anti-inflammatory medication with a DMARD or antioxidant in arthritis treatment, improving pain relief, reducing inflammation, and slowing joint degradation.[46]

Table 1: Nanoparticles for Arthritis Therapy.[47]

Type of Nanoparticle	Composition / Examples	Key Features	Applications in Arthritis
Polymeric Nanoparticles	Synthetic: PLGA, PLA, PEG, PCL, Chitosan, Eudragit; Natural: Alginate, Gelatin, Dextran, Albumin	Biocompatible, controlled release, surface modifiable, high stability	Delivery of NSAIDs, corticosteroids, DMARDs (e.g., methotrexate); improved joint targeting, reduced systemic toxicity
Solid Lipid Nanoparticles (SLN)	Solid lipids + surfactants	Controlled release, good physical stability, suitable for lipophilic drugs	Oral, injectable, and topical delivery of anti-arthritic drugs
Nanostructured Lipid Carriers (NLC)	Solid + liquid lipids	Higher drug loading, less drug expulsion, better long-term stability	Enhanced delivery of NSAIDs and corticosteroids
Liposomes	Phospholipid bilayer vesicles	Carry hydrophilic and lipophilic drugs, biodegradable, targetable	Delivery of NSAIDs, steroids, biologics
Metallic Nanoparticles	Gold, Silver	Anti-inflammatory, antioxidant activity	Pain and inflammation reduction
Inorganic Nanoparticles	Iron oxide, Silica	Imaging, magnetic targeting, drug delivery	Theranostics, targeted arthritis therapy
Co-delivery Nanoparticles	Core–shell, layered, hybrid systems	Deliver multiple drugs together	Combination therapy with NSAIDs + DMARDs or antioxidants; better synergy and lower toxicity

7. TOPICAL GEL SYSTEMS WITH NANOCARRIERS

In the treatment of arthritis, topical therapy is crucial, particularly for localized pain and inflammation. Systemic adverse effects such stomach irritation, renal toxicity, cardiovascular hazards, and immunological suppression are frequently brought on by oral and injectable treatments. By applying medication directly to the afflicted joint, topical administration offers a high local drug concentration with less systemic exposure. It enhances patient compliance, especially in older and chronic arthritic patients, and is non-invasive and simple to administer. For osteoarthritis and moderately to severely inflammatory arthritis that affects superficial joints like the hands, ankles, and knees, topical systems are particularly helpful.[48]

7.1. Types of Gels and Gelling Agents

Topical gels are semi-solid systems that provide good spreadability, cooling effect, and patient acceptability.

Types of gels

- **Hydrogels:** Water-based systems suitable for hydrophilic drugs
- **Organogels:** Oil-based systems for lipophilic drugs
- **Emulgels:** Emulsion incorporated into a gel base, suitable for both hydrophilic and lipophilic drugs.[49]

Common gelling agents

- Synthetic: Carbopol, Poloxamer, HPMC, CMC, PVA
- Natural: Aloe vera gel, xanthan gum, guar gum, sodium alginate, tragacanth

Gelling agents control viscosity, spreadability, stability, and drug release behavior.

7.2. Incorporation of Nanoemulsions and Nanoparticles into Gels

Nanocarriers such as nanoemulsions and nanoparticles can be incorporated into gel bases to form nanogel or nanoemulgel systems.

- **Nanoemulsion-based gels (Nanoemulgels):** Nanoemulsions containing drug are mixed with a gel base to improve skin penetration and stability.
- **Nanoparticle-loaded gels:** Drug-loaded polymeric or lipid nanoparticles are dispersed uniformly in a gel matrix.[50]

Advantages

- Combines benefits of nanocarriers and gels
- Improves drug solubility and stability
- Provides controlled and sustained drug release
- Enhances penetration through stratum corneum
- Improves patient acceptability.[51]

Such systems are used to deliver NSAIDs, corticosteroids, herbal extracts, and combination drugs for arthritis.

7.3 Skin Permeation and Retention

The drug's capacity to penetrate the skin barrier and stay at the target location is essential for topical treatment to be effective.

- **The function of nanocarriers:** Their small size makes it easier for them to pass via intercellular lipid channels and skin pores.
- **Surfactants and penetration enhancers:** Found in nanoemulsions, they increase permeability by upsetting the lipids in the stratum corneum.
- **Occlusive effect:** The gel base hydrates the skin and enhances medication dispersion by holding onto moisture.

- **Depot formation:** Long-term medication retention and sustained release can be achieved by nanoparticles building up in epidermal layers.
- **Localized action:** Side effects are minimized by a high medication concentration at the joint site with less systemic absorption.[52]

Therefore, topical gel solutions including nanocarriers offer a safe, efficient, and patient-friendly method of treating localized arthritis.

8. MECHANISMS OF ACTION OF NANOCARRIER-BASED COMBINATION THERAPY

By effectively delivering many medications to the afflicted joint while reducing systemic exposure, nanocarrier-based combination therapy enhances the treatment of arthritis. Enhanced penetration, extended retention, regulated release, and specific targeting of inflammatory tissues are the basis of its mode of action.

8.1. Enhanced Penetration and Retention in Joints

In addition to their extremely tiny particle sizes, nanocarriers like nanoparticles and nanoemulsions can more successfully cross biological barriers than traditional formulations.

- Better tissue penetration: Because of the increased permeability and retention (EPR) effect, nanocarriers can concentrate in joints by passing through the leaky vasculature of inflammatory synovial tissue.[53]
- Skin penetration (topical systems): Sweat glands, hair follicles, and intercellular lipid routes allow nanoparticles and droplets to enter the skin.
- Extended retention: Due to decreased lymphatic outflow and contact with inflammatory cells, nanocarriers are held in inflammatory joints after they have accumulated.
- Depot effect: By creating local drug reservoirs, nanocarriers enable medications to stay at therapeutic levels for extended periods of time.[54]

8.2. Controlled and Sustained Release

Instead of releasing medications all at once, nanocarriers are made to release them gradually.

- Matrix-controlled release: The medication progressively diffuses from the lipid or polymer matrix.
- Degradation-controlled release: As biodegradable polymers decompose, drugs are released.[55]
- Stimuli-responsive release: Certain systems release medications in reaction to oxidative stress, temperature, pH, or enzymes found in inflammatory joints.
- Synchronized release in combination therapy: To preserve the ideal therapeutic ratio, many medications might be delivered in a predetermined order or at comparable rates.[56]

Controlled release keeps therapeutic levels constant, minimizes peak-related toxicity, and lowers the frequency of doses.

8.3. Targeting Inflamed Tissues

Targeting preserves healthy tissues while increasing medication concentration in damaged joints

- Passive targeting: Because inflamed joints have more vascular permeability, nanocarriers can naturally build up there.
- Active targeting: Surface modification using ligands (antibodies, peptides, sugars) that attach to immune or inflammatory synovial cell receptors.[57]
- Cell-specific uptake: Nanoparticles are easily absorbed by synovial fibroblasts and macrophages.
- Microenvironment targeting: Drugs are released preferentially in inflammatory tissue via systems that are sensitive to acidic pH, enzymes, or reactive oxygen species.

These methods provide enhanced long-term management of arthritis, less toxicity, and increased effectiveness in nanocarrier-based combination treatment.[58]

9. EVALUATION AND CHARACTERIZATION OF NANOCARRIER-BASED SYSTEMS

To guarantee the quality, safety, and efficacy of nanocarrier-based combination treatment for arthritis, proper assessment and characterization are crucial. These investigations verify the formulation's appropriate physical characteristics, controlled drug release, ability to cross biological barriers, and ability to provide the intended therapeutic effect.[59]

9.1. Physicochemical Characterization

The fundamental characteristics of nanocarriers are determined by physicochemical characterisation

- Dynamic light scattering (DLS) is used to measure particle size and size distribution. Better penetration, stability, and targeting capabilities are guaranteed by small and consistent particle sizes.
- Polydispersity index (PDI): Shows how uniform the particles are. Narrow size distribution and improved formulation stability are indicated by lower PDI.[60]
- Zeta potential: Predicts physical stability and measures surface charge. Aggregation is inhibited by a high absolute zeta potential.
- Morphology and shape: To verify spherical or uniform structure, TEM, SEM, or AFM were used.[61]
- The amount of drug loaded and held in nanocarriers is determined by the entrapment efficiency and drug content.
- For gels, pH, viscosity, and spreadability are crucial for patient acceptance and skin compatibility.
- Stability studies: Conducted to assess chemical and physical stability over time at various humidity and temperature levels.[62]

9.2. In Vitro and Ex Vivo Studies

These studies evaluate drug release, permeation, and biological interaction before animal testing.

In Vitro Studies

- Drug release studies: These are conducted to examine the release pattern (immediate, sustained, or controlled) utilizing diffusion cells or dialysis membranes.
- Release kinetics: Information suited to Higuchi, Korsmeyer-Peppas, zero-order, and first-order models.[63]
- Cell culture studies: Assess anti-inflammatory activity, cellular uptake, and cytotoxicity in fibroblast, synoviocyte, or macrophage cells.
- Anti-inflammatory activity: Determined by lowering cytokines in cell models, including TNF-α, IL-1, and IL-6.[64]

Ex Vivo Studies

- Skin permeation studies: These are carried out with animal or human cadaver skin and Franz diffusion cells.
- Permeation parameters: Drug retention in skin layers, flux, and permeability coefficient are computed.
- Skin irritation tests: Verify topical compositions' compatibility and safety.[65]

9.3. In Vivo Evaluation

Therapeutic efficacy and safety in animal models are validated by in vivo research.

- Animal models of arthritis: Freund's adjuvant-induced arthritis, collagen-induced arthritis, and osteoarthritis caused by monosodium iodoacetate are common models.
- Pharmacokinetic studies: Assess drug levels in tissues and blood throughout time.
- Biodistribution studies: Ascertain whether nanocarriers have accumulated in joints and other organs.[66]
- Pharmacodynamic studies: Assess the decrease in inflammatory markers, joint stiffness, discomfort, and edema.
- Histopathological investigations: Look for bone erosion, synovial inflammation, and cartilage protection in joint tissues.
- Toxicity studies: Evaluate immunological responses, organ damage, and acute and long-term toxicity.[67]

These assessment and characterization investigations guarantee the safety, stability, efficacy, and suitability of nanocarrier-based combination therapy for clinical use in the treatment of arthritis.

10. RECENT RESEARCH AND CLINICAL PROGRESS

Nanocarrier-based systems, including polymeric nanoparticles, lipid nanoparticles, nanoemulsions, and nanogels, have been extensively investigated in recent preclinical studies for the treatment of arthritis. Nanocarriers preferentially collect in inflammatory joints because of increased vascular permeability, according to research utilizing animal models such as collagen-induced arthritis, adjuvant-induced arthritis, and osteoarthritis models. When compared to traditional formulations, these systems exhibit superior analgesic and anti-inflammatory properties and enable efficient co-delivery of many medications.[68]

- Enhanced joint retention and targeting
- A significant decrease in inflammatory markers (IL-1, IL-6, TNF-α)
- Improved mobility and pain alleviation Reduced systemic toxicity
- Synergistic effect that works well in combination treatment.[69]

Clinical Trials and Marketed Products

Certain medicines developed using nanotechnology have made their way into clinical trials and the market. For better targeting and lower toxicity, liposomal and nanoparticle-based corticosteroid, NSAID, and methotrexate formulations are being researched. There are already a number of NSAID topical nanoformulations that offer greater skin penetration and quicker pain relief than traditional gels.

- Clinical research on liposomal anti-inflammatory medications.
- Methotrexate nanoparticles are being studied.
- Topical nano-NSAID gels that are sold improved effectiveness and patient adherence.[70]

11. CHALLENGES AND LIMITATIONS

Stability and Scalability: Aggregation, drug leakage, and particle size changes during storage are some of the issues that nanocarrier systems may encounter. It is challenging to scale up production from the laboratory to the industrial level because of complicated procedures, expensive costs, and the requirement for stringent formulation parameter control.

- Chemical and physical instability
- The challenge of large-scale production
- Exorbitant production costs
- Variation from batch to batch.[71]

Toxicity and Safety Issues: Certain nanoparticles, particularly inorganic and metallic ones, have the potential to build up in organs and result in long-term toxicity. The size, content, surface charge, and dosage of nanocarriers all affect their safety. There is currently a dearth of long-term human safety data.

- The possibility of organ buildup
- Potential immunological responses
- Limited information on long-term toxicity
- A thorough safety assessment is required.[72]

Regulatory Issues: The absence of set rules makes it difficult to obtain regulatory approval for nanomedicines. Advanced testing techniques are needed to evaluate complicated nanocarriers, which increases the time and expense of product certification.

- The lack of an explicit regulatory framework
- A complex evaluation of quality
- Prolonged approval processes
- Exorbitant development costs.[73]

12. FUTURE PERSPECTIVES

Advanced Targeting Strategies: By adding ligands to nanocarriers that selectively attach to inflammatory synovial tissue or immune cells, future research aims to increase targeting efficiency. Additionally, stimuli-responsive systems that release medications in reaction to oxidative stress, pH, or enzymes are being created.

- Active targeting based on ligand
- Systems that are sensitive to pH and enzymes
- Dual-targeting strategies
- Improved site-specific medication administration

Personalized Nanomedicine: The goal of personalized nanomedicine is to tailor care according to patient-specific characteristics such immunological profile, genetics, and disease severity. Drug combinations and dosages that are appropriate for each patient can be administered using nanocarriers.

- Customized medication combinations
- Dosage tailored to each patient
- A better reaction to treatment
- Fewer negative consequences

13. CONCLUSION

Combination therapy made possible by nanotechnology offers a prospective breakthrough in the treatment of arthritis by overcoming the drawbacks of traditional methods. Drug penetration, retention in inflammatory joints, and overall treatment effectiveness can all be enhanced by the targeted and controlled delivery of numerous medications using topical gel systems, nanoemulsions, and nanoparticles. These systems encourage synergistic or additive effects of combination medications, improve bioavailability, enable prolonged drug release, and lessen systemic toxicity. Therefore, in managing chronic arthritis, nanocarrier-based formulations provide better symptom control, less frequent dosage, and more patient compliance.

Even while preclinical and early clinical research has made great strides, issues including long-term safety, stability, large-scale production, and regulatory approval still need to be resolved. However, these obstacles should be removed by continued research in stimuli-responsive systems, better targeting techniques, and customized nanomedicine. Combination therapy facilitated by nanotechnology is expected to play a major role in the medical management of arthritis in the future, providing safer, more effective, and patient-centered therapeutic alternatives that can greatly enhance the standard of life for arthritis patients.

All things considered, the use of nanotechnology in combination therapy has the potential to completely change the way that arthritis is managed from a symptom-based approach to a targeted, disease-modifying one. Nanocarrier systems can aid in early intervention, halt the course of illness, and reduce long-term joint damage by precisely delivering many medications to inflammatory joints. Nanotechnology-based combination medicines are anticipated to close the gap between laboratory innovation and practical clinical practice with more multidisciplinary research, clinical validation, and regulatory backing, increasing the effectiveness and accessibility of advanced arthritis therapy.

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