CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Introduction to Arthritis

The word "arthritis" refers to a collection of diseases that impact the surrounding tissues and joints. Greek words "arthro," which means joint, and "itis," which means inflammation, are the roots of the English word arthritis. Therefore, inflammation of the bones is the literal definition of arthritis. It is one of the most prevalent causes of disability globally and is a general term that encompasses over 100 distinct kinds of joint illnesses and disorders.

Individuals from every age, sexual orientation, and cultural origins are affected by arthritis. It is typified by joint pain, swelling, rigidity, and reduced range of motion. These symptoms may be intermittent or persistent, varying in severity, and ongoing. Severe cases of arthritis can result in irreversible damage to joints and disability, which would greatly lower a person's standard of living [1].

Historical Perspective of Arthritis

The human condition known as arthritis has been around for thousands of years; it is not a recent development. The bone fragments from medieval Egyptian mummies and the preserved bones of ancient creatures have been shown to contain evidence of arthritis. Various societies have recognized and managed arthritis in different ways throughout history. For instance, rheumatoid arthritis symptoms were first described by ancient Greek doctors like Hippocrates, and traditional Chinese medicine has long treated joint pain with acupuncture and herbal remedies [2-3].

Prevalence of Arthritis

Arthritis is a common ailment that impacts millions of individuals globally. The World Health Organization (WHO) estimates that over 350 million people globally have arthritis. The Centers for Disease Control and Prevention (CDC) project that 54 million adults in the US alone suffer from arthritis, and by 2040, that figure is predicted to increase to 78 million.

Arthritis is more common in women than in men, and its prevalence rises with age. But it can impact people of all ages, even young ones. One kind of arthritis that affects kids younger than 16 is called juvenile arthritis [4].

1.1.2 Types of Arthritis

There are over 100 different types of arthritis, but the most common types include:

Osteoarthritis (OA)

Osteoarthritis, the most common form of arthritis, impacts millions of individuals worldwide. Arthritis is commonly termed "worn-out" arthritis due to the degeneration of the cartilage layer that cushions the ends of the bones over time. This results in friction between the bones, leading to pain, swelling, and stiffness. Osteoarthritis predominantly impacts the spine, hands, knees, and hips.

Factors contributing to osteoarthritis (OA) include aging, obesity, genetics, joint injuries, and repetitive joint stress. Despite OA being a chronic condition that may deteriorate over time, appropriate care and lifestyle adjustments can mitigate its progression.

Rheumatoid Arthritis (RA)

Rheumatoid arthritis is an autoimmune disorder in which the immune system mistakenly attacks the synovium, the membrane lining the joints. This results in inflammation, which may damage the bones and cartilage within the joint. While rheumatoid arthritis (RA) can impact the skin, eyes, lungs, heart, and blood vessels, it predominantly affects the small joints of the hands and feet.

Rheumatoid arthritis typically manifests in individuals aged 40 to 60 and is more prevalent in women than in men. Rheumatoid arthritis is induced by an abnormal immune response, whereas osteoarthritis is primarily caused by degeneration. The exact etiology of RA remains unidentified, but a combination of environmental and genetic factors is believed to contribute.

Psoriatic Arthritis (PsA)

Individuals with psoriasis, characterized by red, scaly lesions, may develop psoriatic arthritis, a form of inflammatory arthritis. Psoriatic arthritis (PsA) can induce joint pain,

stiffness, and swelling, which are indicative of rheumatoid arthritis and can impact any joint in the body. Psoriatic arthritis (PsA) can cause alterations in the nails and inflammation in various body regions, including the eyes, alongside joint-related symptoms.

PsA is a chronic condition characterized by varying degrees of severity. Some individuals may experience only mild joint symptoms, while others may endure significant joint damage and become profoundly disabled. Early diagnosis and treatment are essential for managing PsA and preventing joint damage.

Gout

Gout is a form of arthritis characterized by the accumulation of uric acid crystals in the joints, resulting in abrupt and intense episodes of pain, swelling, and erythema. The hallux is the most frequently impacted, although gout may also involve other joints, including the ankles, knees, elbows, wrists, and fingers.

Gout is more prevalent in men than in women and frequently manifests in individuals with elevated uric acid levels in their bloodstream. Contributors to gout encompass a diet rich in purines (present in red meat, shellfish, and alcohol), obesity, specific medications, and a familial predisposition to gout.

Ankylosing Spondylitis (AS)

Ankylosing spondylitis is a form of arthritis that predominantly impacts the spine, resulting in inflammation of the vertebrae, which may cause significant, chronic pain and discomfort. In advanced instances, inflammation may lead to the fusion of spinal bones, resulting in diminished flexibility and a stooped posture. AS may also impact additional joints, including the hips, shoulders, and ribs.

AS is more prevalent in men than in women and generally commences in early adulthood. The precise etiology of AS remains unidentified; however, it is thought to result from an interplay of genetic and environmental influences.

Lupus

Lupus, or systemic lupus erythematosus (SLE), is an autoimmune disorder that can impact the joints and various organs, including the skin, kidneys, heart, and lungs. In lupus, the immune system assaults healthy tissues, resulting in inflammation and damage. Arthralgia and edema are prevalent manifestations of lupus, which may also induce fatigue, dermal eruptions, and various systemic symptoms.

Lupus is more prevalent in women than in men and usually manifests between the ages of 15 and 44. The precise etiology of lupus remains unidentified; however, it is thought to encompass a confluence of genetic, hormonal, and environmental influences [5-10].

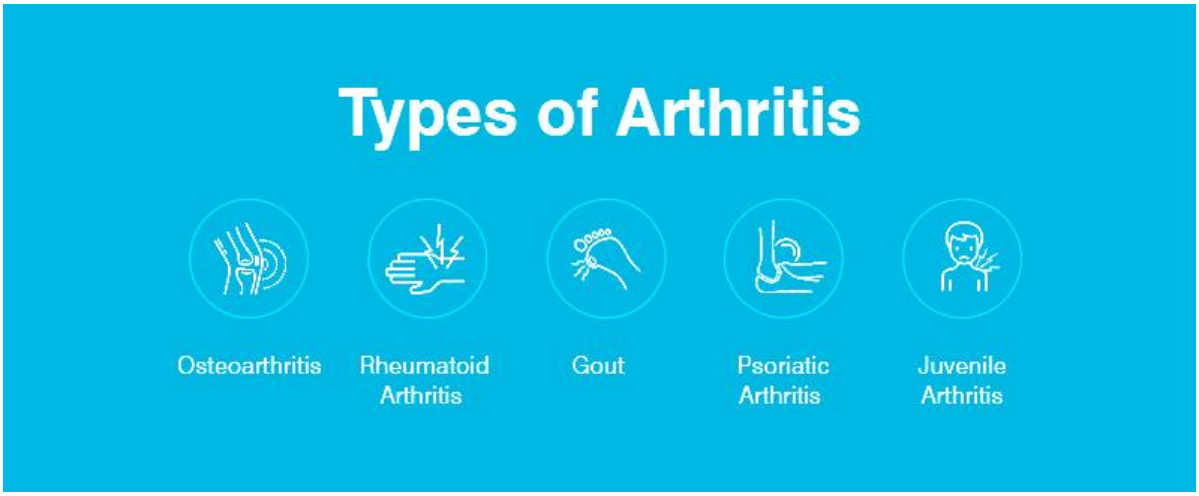

Figure 1.1: Types of Arthritis

1.1.3 Socio-Economic Impact of Arthritis

Arthritis has a significant socio-economic impact, both on individuals and society as a whole. The condition not only affects the physical health of those who suffer from it, but it also has a profound impact on their quality of life, ability to work, and financial stability.

Impact on Quality of Life

The quality of life for an individual afflicted with arthritis can be significantly diminished. Walking, dressing, and cooking can be arduous daily activities due to the pain, stiffness, and fatigue induced by the condition. This may lead to feelings of loneliness and depression due to a loss of independence and reduced ability for social interaction.

The chronic nature of arthritis results in many individuals experiencing symptoms for years, if not decades. The persistent discomfort and limitations may induce anxiety, depression, and a reduced sense of wellbeing, all of which can adversely affect mental health.

Impact on Employment

Arthritis is a predominant cause of global disability, significantly affecting employment. A significant number of individuals with arthritis are incapacitated from work or compelled to diminish their hours due to the pain and physical constraints imposed by the condition. This may result in diminished income and financial instability, which can further intensify the difficulties associated with living with arthritis. Arthritis exerts both a direct influence on employment and an indirect effect on the economy. Arthritis-related disability and absenteeism result in billions of dollars annually in lost wages and diminished economic productivity.

Healthcare Costs

Arthritis management incurs significant costs. The direct costs of arthritis encompass medical expenses such as prescription medications, physician consultations, physical therapy, and surgical procedures. Indirect costs associated with the illness also exist, including lost income and diminished productivity.

Approximately $300 billion is expended annually on medical expenses and lost income attributable to arthritis in the United States. Consequently, the management of arthritis ranks among the most expensive chronic conditions.

Impact on Families and Caregivers

Arthritis affects not only the individuals afflicted by the condition but also significantly impacts their families and caregivers. Numerous individuals with arthritis necessitate support for daily activities, imposing a considerable strain on family members and caregivers. This may result in stress, burnout, and financial hardship, particularly if the caregiver must decrease their work hours or resign from their position to offer care [11-16].

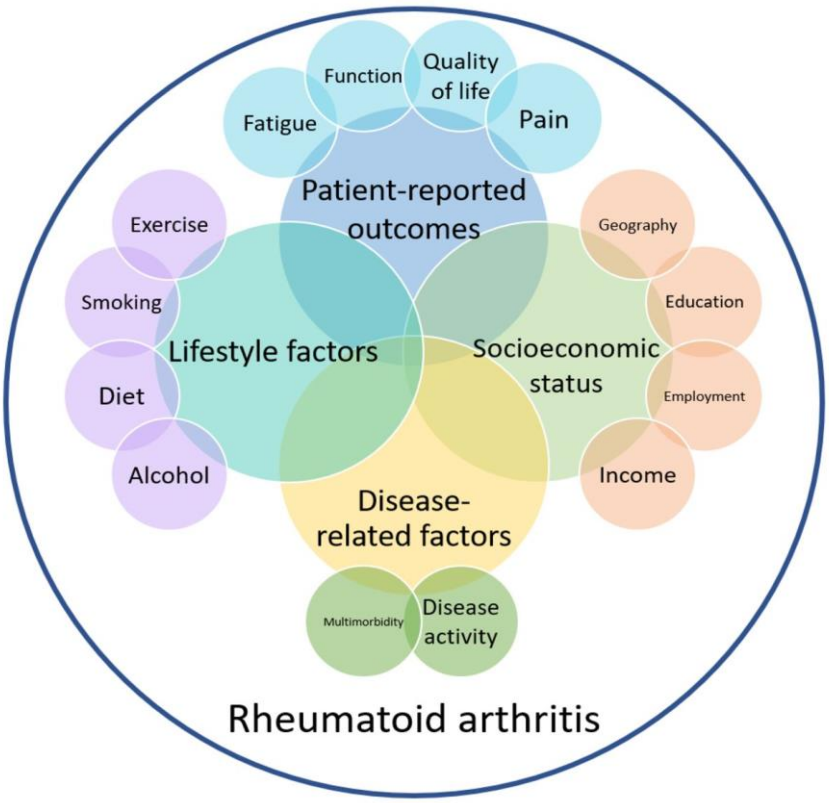

Figure 1.2: Socio-Economic factors of arthritis

1.1.4 Conventional Treatments for Arthritis

The principal objective of arthritis treatment is to alleviate symptoms such as pain and inflammation, enhance joint functionality, and avert additional joint deterioration. Traditional therapies for arthritis encompass various medications and treatments that have been utilized for many years. The treatments are primarily classified into three principal categories: Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), Corticosteroids, and Disease-Modifying Antirheumatic Drugs (DMARDs). Each class of these medications is essential for arthritis management; however, they possess considerable limitations that impact their long-term efficacy and safety.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs): NSAIDs are among the most commonly prescribed medications for arthritis. They work by blocking the enzyme cyclooxygenase (COX), which is responsible for producing prostaglandins, the chemicals in the body that cause inflammation, pain, and fever. By inhibiting these enzymes, NSAIDs reduce inflammation and pain.

- **Common NSAIDs:**
  - Ibuprofen (Advil, Motrin)
  - Naproxen (Aleve)
  - Diclofenac (Voltaren)
  - Celecoxib (Celebrex) – a selective COX-2 inhibitor
- **Mechanism of Action:**
  - NSAIDs inhibit both COX-1 and COX-2 enzymes, but it's the inhibition of COX-2 that primarily reduces inflammation and pain. However, COX-1 inhibition can lead to gastrointestinal (GI) side effects, as COX-1 is also involved in protecting the stomach lining.
- **Benefits:**
  - NSAIDs are effective in reducing pain and swelling in both osteoarthritis (OA) and rheumatoid arthritis (RA).
  - They can be used for short-term pain relief during arthritis flare-ups.
- **Limitations and Side Effects:**
  - **Gastrointestinal Issues:** Long-term use of non-selective NSAIDs can lead to stomach ulcers, bleeding, and gastritis due to COX-1 inhibition. Even COX-2 selective inhibitors, while safer for the stomach, may still cause GI issues.
  - **Cardiovascular Risks:** NSAIDs, particularly COX-2 inhibitors, have been associated with an increased risk of heart attack and stroke. This risk limits their use in patients with cardiovascular disease.
  - **Kidney Damage:** Prolonged use of NSAIDs can lead to kidney damage, especially in people with pre-existing kidney conditions or those who are dehydrated.
  - **Limited Efficacy in Disease Progression:** While NSAIDs effectively relieve symptoms, they do not slow down the progression of arthritis. They primarily address pain and inflammation without targeting the underlying disease process.

- **Why NSAIDs Alone Aren't Enough:**
    - Despite their effectiveness in managing symptoms, NSAIDs do not alter the course of the disease. For chronic conditions like rheumatoid arthritis, where joint destruction can continue silently, NSAIDs are not sufficient as a standalone therapy. Long-term use also increases the risk of serious side effects, making them unsuitable for ongoing management in many patients.

Corticosteroids: Corticosteroids, also known as steroids, are potent anti-inflammatory drugs that can be used to treat a wide range of inflammatory conditions, including arthritis. These drugs mimic the effects of cortisol, a hormone naturally produced by the adrenal glands that helps regulate inflammation in the body.

- **Common Corticosteroids:**
    - Prednisone
    - Methylprednisolone (Medrol)
    - Dexamethasone
    - Hydrocortisone
- **Mechanism of Action:**
    - Corticosteroids work by suppressing the immune system and reducing the production of inflammatory chemicals such as prostaglandins, cytokines, and interleukins. They inhibit multiple pathways involved in inflammation, making them highly effective in reducing joint swelling, pain, and other symptoms of arthritis.
- **Benefits:**
    - **Rapid Relief:** Corticosteroids provide fast and powerful relief from inflammation, which can be particularly useful during severe arthritis flare-ups.
    - **Versatile Administration:** They can be taken orally, injected directly into the affected joint, or applied topically. Intra-articular injections of corticosteroids can provide localized relief without the systemic side effects of oral medications.

- **Useful for Multiple Forms of Arthritis:** Corticosteroids are used to treat various types of arthritis, including RA, PsA, and gout.

- **Limitations and Side Effects:**
  - **Bone Loss (Osteoporosis):** Long-term use of corticosteroids can lead to a loss of bone density, increasing the risk of fractures, particularly in older adults.
  - **Increased Risk of Infections:** Corticosteroids suppress the immune system, making patients more susceptible to infections. This is a significant concern for people with chronic arthritis, who may already have compromised immune function.
  - **Weight Gain and Fluid Retention:** These drugs can cause significant weight gain, fluid retention, and changes in fat distribution (e.g., moon face, buffalo hump), which can negatively affect patients' quality of life.
  - **Insulin Resistance and Diabetes:** Prolonged corticosteroid use can lead to insulin resistance, raising blood sugar levels and potentially resulting in diabetes.
  - **Adrenal Suppression:** Long-term corticosteroid use can suppress the adrenal glands' ability to produce cortisol, leading to adrenal insufficiency. This can make it difficult for the body to cope with stress or trauma, such as surgery or infection.

- **Why Corticosteroids Aren't a Long-Term Solution:**
  - Although corticosteroids are highly effective in reducing inflammation, their severe side effects limit their use as a long-term therapy. They are typically reserved for short-term use during severe flare-ups or as a bridge therapy until slower-acting drugs (like DMARDs) take effect. Patients on long-term corticosteroids must be closely monitored for potential side effects, and efforts should be made to taper off the medication when possible.

Disease-Modifying Antirheumatic Drugs (DMARDs): DMARDs are a class of medications specifically designed to slow down the progression of rheumatoid arthritis and other autoimmune forms of arthritis. Unlike NSAIDs and corticosteroids, which primarily address symptoms, DMARDs target the underlying disease process.

- **Traditional DMARDs:**
    - Methotrexate (MTX)
    - Sulfasalazine
    - Hydroxychloroquine (Plaquenil)
    - Leflunomide (Arava)
- **Biologic DMARDs:**
    - Tumor necrosis factor (TNF) inhibitors (e.g., etanercept, adalimumab)
    - Interleukin-6 (IL-6) inhibitors (e.g., tocilizumab)
    - B-cell inhibitors (e.g., rituximab)
    - T-cell co-stimulation inhibitors (e.g., abatacept)
- **Mechanism of Action:**
    - **Traditional DMARDs:** These drugs work by suppressing the immune system, though their exact mechanisms can vary. For example, methotrexate, the most commonly used DMARD, inhibits folate metabolism, which in turn reduces the production of DNA and RNA in rapidly dividing cells, including immune cells that contribute to inflammation.
    - **Biologic DMARDs:** Biologics are engineered proteins that specifically target molecules involved in the immune response. For example, TNF inhibitors block the activity of TNF, a cytokine that plays a key role in inflammation. By targeting specific pathways in the immune system, biologics offer a more targeted approach to treatment compared to traditional DMARDs.
- **Benefits:**
    - **Disease Control:** DMARDs, particularly methotrexate and biologics, can significantly slow down or even halt the progression of rheumatoid arthritis and other inflammatory forms of arthritis. This can prevent joint damage and preserve function.
    - **Combination Therapy:** DMARDs are often used in combination with other medications, such as NSAIDs or corticosteroids, to provide comprehensive management of arthritis.

- **Improvement in Quality of Life:** By controlling the disease process, DMARDs can reduce pain, improve physical function, and enhance overall quality of life for patients with chronic arthritis.

- **Limitations and Side Effects:**
- **Slow Onset of Action:** DMARDs do not provide immediate relief. It can take weeks or even months for these medications to take full effect, which is why they are often combined with faster-acting drugs in the initial stages of treatment.
- **Immune Suppression:** Like corticosteroids, DMARDs suppress the immune system, increasing the risk of infections. Biologics, in particular, are associated with a higher risk of serious infections, such as tuberculosis.
- **Liver Toxicity:** Methotrexate and other DMARDs can cause liver damage, requiring regular monitoring of liver function. Alcohol consumption is usually discouraged for patients on methotrexate due to the increased risk of liver toxicity.
- **Blood Disorders:** DMARDs can cause blood cell abnormalities, including anemia, leukopenia (low white blood cell count), and thrombocytopenia (low platelet count). Regular blood tests are needed to monitor these potential side effects.
- **Injection and Infusion Reactions:** Biologic DMARDs are often administered by injection or infusion, which can cause local reactions at the injection site or systemic infusion reactions, including allergic responses.
- **Why DMARDs Aren't Always the Perfect Solution:**

  Although DMARDs are effective in managing disease progression, they have inherent limitations. Their immunosuppressive effects render patients more susceptible to infections, and their delayed onset of action necessitates the use of supplementary medications to manage symptoms during the initial phases of treatment. Furthermore, biologics are costly, and patient responses to them vary significantly. For certain patients, the potential for side effects surpasses the advantages, requiring a meticulous evaluation of treatment alternatives.

Janus Kinase (JAK) Inhibitors:

Janus kinase inhibitors (JAK inhibitors) are a newer class of targeted synthetic disease-modifying antirheumatic drugs (DMARDs) that specifically block the activity of Janus kinases, enzymes that play a crucial role in the immune response by transmitting signals

related to inflammation. By inhibiting these enzymes, JAK inhibitors help reduce the inflammation that leads to joint damage in rheumatoid arthritis and other autoimmune forms of arthritis.

- **Common JAK Inhibitors:**
    - Tofacitinib (Xeljanz)
    - Baricitinib (Olumiant)
    - Upadacitinib (Rinvoq)
- **Mechanism of Action:** JAK inhibitors work by blocking the JAK-STAT signaling pathway, which is involved in the production of cytokines responsible for immune-mediated inflammation. By interrupting this pathway, JAK inhibitors help prevent the overactive immune response that leads to joint damage in inflammatory arthritis.
- **Benefits:**
    - **Targeted Approach:** JAK inhibitors provide a more focused method of reducing inflammation by specifically targeting the JAK-STAT pathway, unlike traditional DMARDs that broadly suppress the immune system.
    - **Oral Administration:** Unlike biologics, which often require injections or infusions, JAK inhibitors are available in oral form, offering convenience for patients.
    - **Efficacy in Multiple Forms of Arthritis:** JAK inhibitors have shown effectiveness in treating rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.
- **Limitations and Side Effects:**
    - **Infection Risk:** Like other immunosuppressive therapies, JAK inhibitors increase the risk of serious infections, including tuberculosis and opportunistic infections.
    - **Blood Clots and Cardiovascular Risks:** JAK inhibitors, particularly at higher doses, have been associated with an increased risk of blood clots, cardiovascular events, and cancer, prompting caution in certain populations.
    - **Elevated Cholesterol Levels:** Some JAK inhibitors can raise cholesterol levels, necessitating regular monitoring of lipid profiles.

- **Liver Function and Blood Cell Abnormalities:** JAK inhibitors may cause liver enzyme elevation and changes in blood counts, requiring periodic blood tests.

- **Why JAK Inhibitors Aren't for Everyone:** Despite their effectiveness, JAK inhibitors are not suitable for all patients due to the risks associated with immunosuppression and cardiovascular issues. Close monitoring is essential for patients on these medications, and they are often used when patients do not respond adequately to traditional DMARDs or biologic therapies.

Combination Therapy: Given the limitations of each drug class, arthritis treatment often involves a combination of therapies to optimize outcomes. For example, a patient may be prescribed a DMARD to control disease progression while also taking NSAIDs for pain relief and corticosteroids for flare-ups. The goal of combination therapy is to manage symptoms effectively while minimizing side effects and preventing disease progression [17-26].

1.1.5 Need for Improved Drug Delivery

Effective management of arthritis, including osteoarthritis, rheumatoid arthritis, and other variants, necessitates the resolution of various therapeutic challenges. Notwithstanding the availability of numerous medications, many patients persist in experiencing insufficient relief, disease progression, and considerable adverse effects. A primary reason for this is the intrinsic constraints of traditional drug delivery systems, which frequently do not transport the therapeutic agent to the target location in a controlled and efficient manner. This section will examine the principal challenges related to contemporary therapies, including low bioavailability, systemic side effects, and insufficient targeted drug delivery.

1.1.5.1 Low Bioavailability:

Bioavailability denotes the fraction of a drug that reaches systemic circulation upon administration and exerts a pharmacological effect. It is the proportion of a given dose that enters the bloodstream in its active state. For a drug to be efficacious, it must be absorbed in adequate amounts, arrive at the designated target site, and persist there for a sufficient duration to produce its therapeutic effects.

Challenges with Bioavailability in Arthritis Treatment: In the context of arthritis, many drugs, particularly those administered orally, suffer from low bioavailability. Several factors contribute to this problem:

- **Poor Solubility:** Many anti-arthritic drugs have low solubility in water, making it difficult for them to be absorbed through the gastrointestinal (GI) tract when taken orally. Drugs like methotrexate, a common DMARD, face challenges with solubility, which limits the amount of the drug that can be absorbed into the bloodstream.
- **First-Pass Metabolism:** After oral administration, drugs pass through the liver before reaching systemic circulation. This process, known as first-pass metabolism, can significantly reduce the concentration of the drug that reaches the bloodstream. For instance, a significant portion of orally administered corticosteroids may be metabolized in the liver, reducing their effectiveness.
- **Variable Absorption:** The absorption of drugs can be affected by various factors such as food intake, gastric pH, and the presence of other medications. This variability can lead to inconsistent therapeutic outcomes in patients with arthritis. NSAIDs, for example, may have different absorption rates depending on whether they are taken with or without food.
- **Short Half-Life:** Some drugs have a short half-life, meaning they are quickly eliminated from the body, requiring frequent dosing. This not only affects patient compliance but also limits the drug's ability to maintain therapeutic levels in the body over time. For example, the frequent dosing required for NSAIDs can lead to poor patient adherence and fluctuating pain levels.

Impact of Low Bioavailability: The low bioavailability of many arthritis medications leads to several problems:

- **Inadequate Therapeutic Effect:** Because only a small fraction of the drug reaches the target site, the therapeutic effect may be insufficient to control the symptoms of arthritis. Patients may continue to experience pain, inflammation, and joint damage despite being on medication.
- **Higher Doses Required:** To compensate for low bioavailability, higher doses of the drug are often required, which can increase the risk of side effects and toxicity. This

is particularly concerning for drugs like NSAIDs and corticosteroids, where higher doses are associated with significant adverse effects.

- **Increased Costs:** The need for higher doses and frequent administration increases the cost of treatment, both in terms of medication expenses and the need for ongoing medical monitoring.

1.1.5.2 Systemic Side Effects:

Systemic side effects refer to adverse effects that occur throughout the body, rather than being localized to the site of drug action. These side effects are often a result of the drug affecting organs and tissues other than the intended target. In arthritis treatment, systemic side effects are a major concern due to the chronic nature of the disease, which often requires long-term medication use.

Causes of Systemic Side Effects in Arthritis Therapies: Several factors contribute to the systemic side effects of arthritis medications:

- **Non-Selective Drug Action:** Many drugs used to treat arthritis, such as NSAIDs and corticosteroids, are non-selective, meaning they affect multiple systems in the body. For example, NSAIDs inhibit both COX-1 and COX-2 enzymes, which reduces inflammation but also impairs the protective functions of COX-1 in the stomach lining, leading to gastrointestinal issues.
- **Cumulative Toxicity:** Long-term use of medications, particularly in chronic diseases like arthritis, can lead to cumulative toxicity. This means that the harmful effects of the drug build up over time, increasing the risk of serious health problems. For instance, prolonged use of corticosteroids can lead to bone loss (osteoporosis), muscle weakness, and increased susceptibility to infections.
- **Widespread Distribution:** Many drugs do not specifically target the affected joints but instead circulate throughout the body. This widespread distribution increases the likelihood of side effects in other organs and systems. Methotrexate, for example, affects rapidly dividing cells throughout the body, which can lead to liver toxicity, bone marrow suppression, and gastrointestinal side effects.

Common Systemic Side Effects in Arthritis Treatment:

- **Gastrointestinal Issues:** NSAIDs are notorious for causing gastrointestinal problems, including stomach ulcers, bleeding, and gastritis. These side effects result

from the inhibition of COX-1, which plays a protective role in the stomach lining. Even with COX-2 selective inhibitors like celecoxib, GI issues can still occur.

- **Cardiovascular Risks:** Both NSAIDs and corticosteroids have been associated with increased cardiovascular risks, including heart attack and stroke. The use of COX-2 inhibitors, while reducing gastrointestinal side effects, has been linked to higher rates of cardiovascular events, making them unsuitable for some patients.
- **Bone Loss and Osteoporosis:** Long-term corticosteroid use can lead to significant bone loss, increasing the risk of fractures. This is particularly concerning for older adults with arthritis, who may already be at risk for osteoporosis.
- **Increased Risk of Infections:** Immunosuppressive drugs, such as corticosteroids and DMARDs, weaken the immune system, making patients more susceptible to infections. This is a serious concern, especially for patients on biologic DMARDs, which specifically target immune system components.
- **Hepatotoxicity:** Drugs like methotrexate can cause liver toxicity, necessitating regular liver function tests to monitor for potential damage. Patients must be cautious with alcohol consumption and other liver-toxic substances while on these medications.
- **Kidney Damage:** Prolonged use of NSAIDs can lead to kidney damage, particularly in patients with pre-existing kidney conditions. This is due to the reduction in blood flow to the kidneys, which can impair their function over time.

Impact of Systemic Side Effects: Systemic side effects can significantly impact a patient's quality of life and adherence to treatment:

- **Reduced Compliance:** Patients experiencing severe side effects may be less likely to adhere to their medication regimen, leading to suboptimal disease control and increased risk of flare-ups.
- **Need for Additional Medications:** Managing side effects often requires additional medications, which can lead to polypharmacy and increase the risk of drug interactions. For example, patients on NSAIDs may need to take proton pump inhibitors (PPIs) to protect against stomach ulcers, adding complexity to their treatment plan.

- **Increased Healthcare Costs:** The need for additional monitoring, treatments, and hospitalizations due to side effects can significantly increase healthcare costs, both for the patient and the healthcare system.

1.1.5.3 Lack of Targeted Drug Delivery:

Targeted drug delivery refers to the ability to direct a therapeutic agent specifically to the site of disease, minimizing its effects on healthy tissues. In the context of arthritis, targeted delivery would ideally focus the medication directly on the affected joints, reducing inflammation and pain without impacting other parts of the body.

Challenges with Conventional Drug Delivery Systems: Most conventional arthritis treatments lack specificity, meaning that the drug circulates throughout the body, affecting both healthy and diseased tissues. This lack of targeting results in several issues:

- **Non-Specific Action:** Traditional medications, such as oral NSAIDs, spread throughout the bloodstream and affect the entire body, leading to systemic side effects. This non-specific action limits the ability to deliver high doses directly to the affected joints without causing harm to other organs.
- **Inefficient Drug Delivery to Joints:** The delivery of drugs to the joints is often inefficient, as the blood supply to the joints is limited compared to other tissues. This makes it difficult for drugs to accumulate in sufficient concentrations at the site of inflammation, reducing their effectiveness.
- **Short Duration of Action:** Because conventional drugs are rapidly cleared from the bloodstream, their effects are often short-lived. This necessitates frequent dosing, which can be inconvenient for patients and increases the risk of side effects.
- **Variable Distribution:** The distribution of drugs can vary depending on factors such as blood flow, tissue permeability, and the presence of transport proteins. This variability can lead to inconsistent therapeutic outcomes, with some patients experiencing better relief than others.

Need for Targeted Drug Delivery Systems: Targeted drug delivery systems offer several potential advantages over conventional therapies:

- **Enhanced Efficacy:** By concentrating the drug at the site of disease, targeted delivery systems can achieve higher therapeutic concentrations in the affected joints, improving symptom relief and disease control.
- **Reduced Side Effects:** Targeted delivery minimizes exposure to healthy tissues, reducing the risk of systemic side effects. For example, a targeted NSAID delivery system could provide pain relief in the joints without causing gastrointestinal or cardiovascular issues.
- **Sustained Drug Release:** Many targeted delivery systems are designed to release the drug slowly over time, maintaining therapeutic levels in the joints for longer periods. This reduces the need for frequent dosing and improves patient compliance.
- **Personalized Medicine:** Targeted drug delivery systems can be tailored to individual patients based on factors such as disease severity, genetics, and response to treatment. This personalized approach could lead to better outcomes and fewer side effects.

Examples of Targeted Drug Delivery in Arthritis:

- **Liposomal Drug Delivery:** Liposomes are spherical vesicles that can encapsulate drugs and deliver them directly to the affected joints. This technology has been used to improve the delivery of corticosteroids and other anti-inflammatory drugs in arthritis.
- **Nanoparticles:** Nanoparticles, such as mesoporous silica nanoparticles (MSNs), offer a promising approach to targeted drug delivery in arthritis. These tiny particles can be engineered to carry drugs directly to the inflamed joints, enhancing bioavailability and reducing side effects.
- **Biodegradable Polymers:** Biodegradable polymers can be used to create drug delivery systems that release the drug slowly over time. These systems can be injected directly into the joints, providing sustained relief from arthritis symptoms.
- **Monoclonal Antibodies:** Biologic DMARDs, such as monoclonal antibodies, are designed to target specific molecules involved in the inflammatory process. By focusing on these specific targets, biologics can reduce inflammation with fewer side effects than traditional immunosuppressive drugs [27-32].

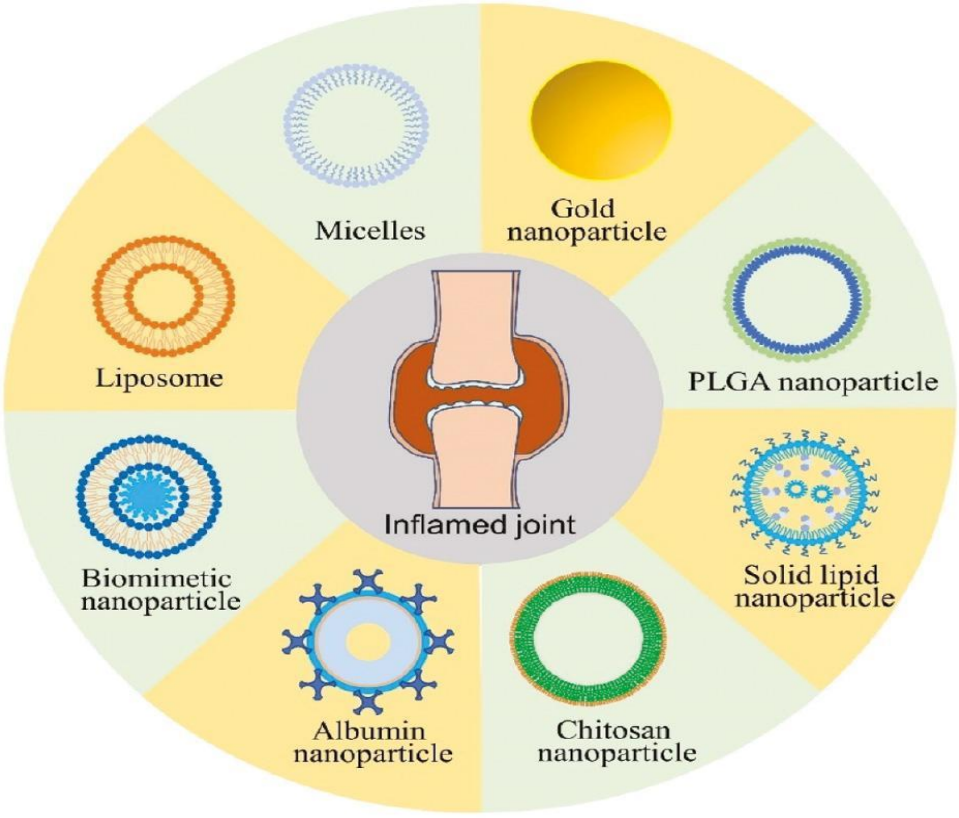

Figure 1.3: Nanoparticles used in arthritis

1.1.6 Nanotechnology in Medicine

Nanotechnology, a discipline that manipulates matter at the atomic and molecular level, has transformed various industries, particularly medicine. In recent years, nanotechnology has demonstrated significant potential in improving drug delivery systems, particularly for chronic illnesses such as cancer, cardiovascular diseases, and arthritis. This section will examine the principles of nanotechnology, its application in drug delivery systems, and its particular advantages for managing chronic diseases such as arthritis.

1.1.6.1 Understanding Nanotechnology:

Nanotechnology encompasses the design, synthesis, characterization, and application of materials and devices measuring between 1 and 100 nanometers. At this scale, materials demonstrate distinct physical, chemical, and biological properties that diverge from those of their bulk equivalents. These properties can be utilized to develop innovative drug delivery systems that enhance the efficacy and safety of therapeutic agents.

Nanotechnology facilitates meticulous regulation of the dimensions, morphology, surface characteristics, and functionality of materials. This accuracy enables scientists to engineer nanoparticles that can surmount numerous limitations inherent in traditional drug delivery systems. Nanoparticles can be designed to enhance drug solubility, safeguard drugs from degradation, improve drug absorption, and facilitate targeted drug delivery, thereby minimizing systemic side effects.

Types of Nanomaterials Used in Medicine:

- **Lipid-Based Nanoparticles:** These include liposomes and solid lipid nanoparticles (SLNs). Lipid-based nanoparticles are biocompatible and can encapsulate both hydrophilic and hydrophobic drugs, improving their solubility and stability.
- **Polymeric Nanoparticles:** These nanoparticles are made from biodegradable polymers such as poly(lactic-co-glycolic acid) (PLGA) and are used for controlled drug release. They can be engineered to release drugs over extended periods, reducing the need for frequent dosing.
- **Inorganic Nanoparticles:** Inorganic nanoparticles, such as gold nanoparticles, silica nanoparticles, and quantum dots, offer unique optical and electronic properties that can be used for imaging, diagnostics, and therapy. Mesoporous silica nanoparticles (MSNs) are particularly promising for drug delivery due to their high surface area, tunable pore size, and biocompatibility.
- **Dendrimers:** These are highly branched, tree-like molecules with multiple functional groups on their surface, allowing for the attachment of drugs, targeting ligands, and imaging agents. Dendrimers can enhance drug solubility and target specific cells or tissues.
- **Carbon-Based Nanomaterials:** These include carbon nanotubes and graphene, which have unique mechanical and electrical properties. While still in the experimental stage, these materials hold potential for drug delivery and tissue engineering applications [33-40].

1.1.6.2 Nanotechnology in Arthritis Treatment:

Challenges in Treating Arthritis: Osteoarthritis (OA) and rheumatoid arthritis (RA) in particular are chronic inflammatory diseases that cause swelling, stiffness, and pain in the joints. NSAIDs, corticosteroids, and DMARDs are examples of conventional treatments for arthritis that frequently have drawbacks like low bioavailability, systemic side effects, and lack of targeted delivery. Improving patients' quality of life and achieving long-term disease control are challenging due to these issues.

How Nanotechnology Can Address These Challenges: Nanotechnology offers several advantages in the treatment of arthritis:

- **Targeted Delivery to Inflamed Joints:** Anti-inflammatory medications can be delivered straight to the site of inflammation by using specially designed nanoparticles that are intended to target inflammatory joints. This minimizes side effects and lessens the requirement for high systemic doses. To guarantee that they accumulate in the inflammatory joints, MSNs, for instance, can be functionalized with targeting ligands and loaded with anti-inflammatory medications.
- **Improved Drug Retention in Joints:** The quick clearance of medications from the joints, which requires frequent dosing, is one of the difficulties in treating arthritis. Because they cling to joint tissues and release the drug gradually, nanoparticles can enhance drug retention in the joints. This lessens the need for repeated injections and offers long-lasting symptom relief.
- **Reduced Systemic Exposure:** By targeting the drug directly to the affected joints, nanotechnology can reduce systemic exposure to the drug, minimizing the risk of side effects. This is particularly important for drugs like corticosteroids, which can cause significant systemic toxicity when used long-term.
- **Combination Therapy:** Nanoparticles can be designed to carry multiple drugs, allowing for combination therapy in a single formulation. For example, a nanoparticle could deliver both an anti-inflammatory drug and a disease-modifying agent, providing comprehensive treatment for arthritis.

Examples of Nanotechnology in Arthritis Treatment:

- **Liposomal Delivery of Methotrexate:** Methotrexate is a commonly used DMARD for the treatment of RA, but its systemic side effects limit its long-term use.

Liposomal formulations of methotrexate have been developed to target the drug directly to the inflamed joints, reducing its toxicity and improving its efficacy.

- **Mesoporous Silica Nanoparticles (MSNs):** MSNs are particularly promising for arthritis treatment due to their high surface area, tunable pore size, and biocompatibility. MSNs can be loaded with anti-inflammatory drugs and functionalized with targeting ligands to ensure they accumulate in the inflamed joints. This targeted delivery improves drug bioavailability and reduces the risk of systemic side effects.
- **Gold Nanoparticles for RA:** Gold nanoparticles have been studied for their potential in treating RA due to their anti-inflammatory properties. These nanoparticles can be functionalized with drugs and targeting ligands, allowing for targeted delivery to the inflamed joints. Gold nanoparticles also have the potential to be used for imaging, providing a theranostic approach to RA treatment.

1.1.6.3 Future Directions in Nanotechnology-Based Drug Delivery:

Personalized Medicine: Because it makes it possible to create medication delivery systems that are specifically suited to each patient's needs, nanotechnology holds the promise of revolutionizing personalized medicine. Nanoparticles can be tailored to deliver the right medication at the right dose to the right patient by taking into account variables like genetics, the severity of the disease, and the patient's response to treatment. This individualized approach may result in fewer side effects and improved treatment outcomes.

Smart Drug Delivery Systems: The "smart" nanoparticles of the next generation of drug delivery systems will probably be able to react to particular stimuli, like modifications to pH, temperature, or enzymatic activity, in order to release the drug at the intended site. The effectiveness of treatment could be enhanced by these intelligent systems by giving precise control over medication delivery.

Nanotechnology in Regenerative Medicine: In addition to drug delivery, nanotechnology holds promise for regenerative medicine applications in arthritis treatment. For example, nanoparticles can be used to deliver growth factors or stem cells to damaged joint tissues, promoting tissue repair and regeneration. This could potentially reverse the damage caused by arthritis and restore joint function.

Safety and Regulatory Considerations: Although there are numerous advantages to nanotechnology, there are additionally safety and legal issues that need to be resolved. There is still much to learn about the long-term health benefits of nanoparticles, especially with regard to their potential toxicity and rate of accumulation in the body. Additionally, regulatory bodies are attempting to create standards for the creation and acceptance of medication delivery systems based on nanotechnology [41-48].

1.2 Concept of Mesoporous Silica Nanoparticles (MSNs)

1.2.1 Introduction to MSNs:

Mesoporous Silica Nanoparticles (MSNs) are advanced materials characterized by a highly ordered porous structure with pores ranging from 2 to 50 nanometers in diameter, as per the International Union of Pure and Applied Chemistry (IUPAC) nomenclature. These nanoparticles have garnered significant interest in the pharmaceutical and biomedical fields due to their unique properties, which make them suitable for various applications, including drug delivery, catalysis, and imaging.

Structure of MSNs: MSNs are made by a silica (SiO_2) structure with a repeating, highly ordered pore network. During the templating process, which produces these pores, block copolymers or surfactants which create tiny particles in solution are frequently used. Silica precursors, like tetraethyl orthosilicate (TEOS), condense around the micelles during synthesis. After the surfactant is removed, a distinct mesoporous structure is left behind.

Properties of MSNs:

1. **High Surface Area and Pore Volume:** MSNs exhibit a high surface area (usually between 500-1500 m^2/g) and large pore volume, which allows for high drug-loading capacities. The extensive surface area provides ample space for drug molecules to adsorb or be encapsulated, enhancing the drug delivery potential of these nanoparticles.
2. **Tunable Pore Size:** One of the key advantages of MSNs is the ability to precisely control the pore size during synthesis. This tunability allows for the optimization of the pore size to match the dimensions of various drug molecules, improving loading efficiency and release kinetics. Adjusting factors such as the concentration of the surfactant, the pH of the solution, and the type of silica precursor can achieve this customization.

3. **Biocompatibility and Safety:** MSNs are appropriate for use in biomedical applications because they are typically regarded as nontoxic and biocompatible. However, the size, shape, surface functionalization, and administration route of MSNs can all affect their safety profile. Research has demonstrated that when synthesized correctly, MSNs do not cause appreciable toxicity either in vivo or in vitro; however, more studies are required to completely comprehend their long-term safety.
4. **Thermal and Mechanical Stability:** MSNs exhibit excellent thermal and mechanical stability due to their rigid silica framework. This stability ensures that the structural integrity of the nanoparticles is maintained under various physiological conditions, which is crucial for consistent drug release and effectiveness in therapeutic applications.
5. **Surface Functionalization:** It is simple to add different functional groups to the surface of MSNs in order to improve their interaction with particular drugs or target tissues. A surface can be made more functional by adding amine, carboxyl, or thiol groups, that may boost biocompatibility, target specific drugs, or improve drug loading. For instance, through electrostatic interactions, amine-functionalized MSNs can increase the effectiveness of loading of negatively charged molecule of drug [49-60].

1.2.2 Historical Development of Mesoporous Silica Nanoparticles (MSNs):

Overview of the Discovery and Development of MSNs in Drug Delivery Systems

Early Discovery and Background:

The journey of Mesoporous Silica Nanoparticles (MSNs) began with the development of mesoporous materials in the early 1990s by researchers at Mobil Oil Corporation. In 1992, they introduced the Mobil Composition of Matter (MCM) series, including MCM-41, which featured an ordered mesoporous structure with a high surface area and uniform pore sizes ranging from 2 to 10 nm. This discovery marked a significant advancement in material science, as it allowed the creation of materials with precisely controlled porosity and surface characteristics.

The initial interest in mesoporous silica materials was driven by their potential applications in catalysis, separation processes, and adsorption due to their large surface area and customizable pore sizes. However, as the field of nanotechnology evolved, the unique properties of mesoporous silica—such as their high surface area, tunable pore size, and

ability to be functionalized—caught the attention of researchers in the pharmaceutical sciences for their potential as drug delivery carriers.

Initial Applications in Drug Delivery:

The first significant exploration of MSNs in drug delivery systems was reported in the early 2000s. In 2001, Vallet-Regi and colleagues published pioneering work highlighting the use of MCM-41 mesoporous silica as a drug delivery system. They demonstrated that MSNs could effectively encapsulate therapeutic agents within their porous structure, providing a novel strategy for enhancing drug solubility and controlling drug release.

Their work showed that MSNs could be loaded with a variety of drugs, including both hydrophilic and hydrophobic compounds, making them versatile carriers for different types of therapeutic agents. This early research established the potential of MSNs as a promising platform for drug delivery, paving the way for further exploration and development in the field.

Advancements in Synthesis and Functionalization:

Following the initial studies, researchers focused on optimizing the synthesis and functionalization of MSNs to improve their performance in drug delivery applications. Advances in synthesis techniques allowed for better control over the particle size, pore diameter, and surface properties of MSNs. Techniques such as sol-gel processing, microemulsion, and templating methods were refined to produce MSNs with specific characteristics tailored to different therapeutic needs.

One of the critical developments during this period was the introduction of surface functionalization techniques. By modifying the surface of MSNs with various functional groups (e.g., amine, carboxyl, thiol), researchers could enhance the interaction between the nanoparticles and the drug molecules, improve biocompatibility, and enable targeted delivery to specific tissues or cells. Surface functionalization also opened up the possibility of conjugating targeting ligands, such as antibodies or peptides, to MSNs, allowing for more precise delivery of drugs to diseased tissues while minimizing systemic side effects.

Emergence of MSNs in Targeted and Controlled Drug Delivery:

The next phase of MSN development focused on their role in targeted and controlled drug delivery systems. Researchers began exploring the use of MSNs for delivering drugs to specific sites within the body, such as tumors or inflamed tissues. This targeted approach

aimed to increase the therapeutic efficacy of drugs while reducing their toxicity by concentrating the drug at the site of action.

To achieve targeted delivery, MSNs were functionalized with targeting ligands that could recognize and bind to specific receptors on the surface of target cells. For example, MSNs functionalized with folic acid were used to target cancer cells that overexpress folate receptors, leading to more efficient drug delivery to tumors.

Additionally, the ability to tune the release profile of drugs from MSNs became a significant area of research. By modifying the pore size and surface properties, as well as incorporating responsive materials such as polymers or gatekeepers that could respond to environmental triggers (e.g., pH, temperature, enzymes), researchers were able to develop MSNs that released their drug payload in a controlled and sustained manner. This feature was particularly valuable for achieving prolonged therapeutic effects and reducing the frequency of drug administration.

Integration of MSNs in Multifunctional and Theragnostic Platforms:

As the field progressed, the concept of multifunctional MSNs emerged, where MSNs were engineered to perform multiple roles simultaneously, such as drug delivery, imaging, and therapy. These multifunctional MSNs were designed to carry therapeutic agents, imaging contrast agents, and targeting ligands, creating a single platform that could diagnose, deliver treatment, and monitor therapeutic outcomes.

The term "theragnostic" was coined to describe this integration of therapy and diagnostics in a single system. MSNs were at the forefront of this innovation, particularly in cancer treatment, where they were used for simultaneous drug delivery and imaging using techniques like magnetic resonance imaging (MRI) or fluorescence imaging. This capability allowed for real-time tracking of the nanoparticles within the body, providing valuable information on the biodistribution and accumulation of the therapeutic agents at the target site.

Current Trends and Future Directions:

Today, MSNs continue to be a focal point of research in drug delivery, with ongoing efforts to enhance their functionality, safety, and efficacy. Some of the current trends include the development of MSNs with stimuli-responsive properties, where the release of the drug is triggered by specific internal or external stimuli such as changes in pH, temperature, light, or

magnetic fields. This approach aims to further refine the control over drug release, making MSNs even more precise in their therapeutic action.

MSNs are being explored for applications beyond traditional drug delivery, including gene delivery, protein delivery, and as carriers for vaccines. The versatility of MSNs allows them to be adapted for various biomedical applications, making them a highly valuable tool in the advancement of personalized medicine [61-67].

1.2.3 MSNs in Drug Delivery:

In recent years, mesoporous silica nanoparticles (MSNs) have emerged as a prominent nanocarrier in the field of drug delivery due to their distinctive properties. These nanoparticles offer numerous advantages over other types of nanoparticles, such as liposomes, polymeric nanoparticles, and metal-based nanoparticles. The unique characteristics of MSNs, including their biocompatibility, biodegradability, and non-toxicity, make them a superior choice for drug delivery applications, particularly in the development of targeted therapies.

Advantages of MSNs Over Other Nanoparticles

1. **Biocompatibility:**
    - MSNs are primarily composed of silica (SiO_2), a material recognized for its excellent biocompatibility. Silica is naturally present in the human body in trace amounts, which reduces the risk of adverse reactions when used as a drug carrier.
    - The surface of MSNs can be easily modified with various functional groups, such as amine or carboxyl groups, to enhance their interaction with biological tissues. This surface modification can further improve their compatibility with the human body.
    - Unlike some metal-based nanoparticles, which can accumulate in organs and potentially cause toxicity, MSNs are less likely to induce immune responses or other toxic effects due to their biocompatible nature.
2. **Biodegradability:**
    - MSNs are recognized for their biodegradable characteristics. Upon administration, they progressively break down into non-toxic silicic acid under

physiological conditions, which is subsequently eliminated from the body via standard metabolic pathways. This degradation process is advantageous for reducing long-term accumulation and toxicity.

- The degradation rate can be managed by modifying the density of the silica network and the extent of surface functionalization. The ability to tune biodegradation offers significant benefits for customizing the rate at which drugs are released to meet specific therapeutic requirements.

3. **Non-Toxicity:**
    - One of the most critical aspects of any drug delivery system is its safety profile. MSNs have been extensively studied and generally regarded as non-toxic at doses relevant for drug delivery.
    - The non-toxic nature of MSNs is attributed to their composition and the mild conditions under which they operate. Unlike certain metal-based nanoparticles that may release harmful ions, MSNs remain stable and do not leach toxic components into the body.
    - Several in vitro and in vivo studies have confirmed that MSNs do not cause significant cytotoxicity or inflammatory responses when used at appropriate concentrations, making them a safer alternative compared to other nanoparticle systems.
4. **High Drug Loading Capacity:**
    - MSNs exhibit a high surface area and substantial pore volume, enabling them to accommodate considerable quantities of drugs in comparison to other nanoparticles. The substantial loading capacity facilitates the delivery of a greater dose of the therapeutic agent to the target site, thereby improving the treatment's efficacy.
    - The adjustable pore size of MSNs allows for the encapsulation of a diverse array of molecules, including small drugs as well as larger biomolecules such as proteins and peptides. This versatility presents a clear advantage compared to other nanoparticles, which may face restrictions regarding the types or sizes of drugs they are capable of transporting.

5. **Controlled and Sustained Release:**
    - The porous structure of MSNs facilitates the controlled release of the encapsulated drug. Modifying the pore size, surface chemistry, or incorporating stimuli-responsive gates allows for precise tuning of release kinetics, facilitating sustained drug release, minimizing dosing frequency, and enhancing patient compliance.
    - This controlled release capability is particularly beneficial for chronic conditions such as arthritis, where sustained delivery of anti-inflammatory or disease-modifying drugs can help manage symptoms and improve quality of life.

6. **Versatility in Functionalization:**
    - MSNs offer a high degree of functional versatility due to their easily modifiable surface. They can be functionalized with targeting ligands, such as antibodies, peptides, or small molecules, that recognize specific markers on diseased cells, enhancing targeted drug delivery.
    - Functionalization can also impart additional properties, such as stealth characteristics to evade the immune system or magnetism for externally guided delivery, which are not readily achievable with many other nanoparticle types.
7. **Stability and Robustness:**
    - MSNs are chemically and physically stable under a wide range of conditions, including varying pH levels, temperatures, and biological environments. This stability ensures that the nanoparticles retain their integrity and do not release the drug prematurely before reaching the target site.
    - Unlike liposomes or polymeric nanoparticles, which can be sensitive to environmental changes, MSNs maintain their structure and function, providing a reliable platform for drug delivery.
8. **Cost-Effectiveness:**
    - The synthesis of MSNs is relatively simple and cost-effective, utilizing readily available materials and straightforward chemical processes. This makes them an economically viable option for large-scale production compared to some other

types of nanoparticles that require complex and expensive manufacturing techniques.

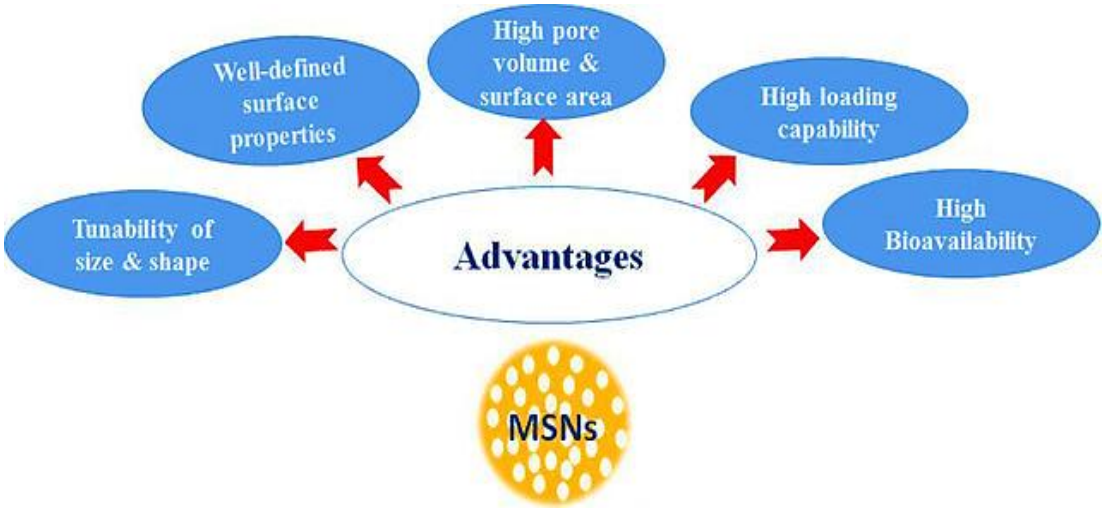

Figure 1.4: Advantages of MSNs

1.3 Challenges in Drug Delivery for Arthritis

1.3.1 Challenges in Topical and Systemic Delivery:

Introduction to Arthritis and Drug Delivery Needs:

Arthritis is a chronic inflammatory condition that affects millions of people worldwide, causing pain, stiffness, and swelling in the joints. Effective management of arthritis often requires long-term medication to reduce inflammation, relieve pain, and slow disease progression. However, the efficient delivery of therapeutic agents directly to the inflamed joints remains a significant challenge due to various biological and physicochemical barriers. The primary obstacles in delivering drugs for arthritis treatment include poor drug solubility, inadequate permeability through biological membranes, and insufficient retention at the target site. Addressing these challenges is crucial for developing more effective therapies that can provide sustained relief and improve the quality of life for patients with arthritis.

1.3.1.1 Poor Drug Solubility:

One of the major issues in drug delivery for arthritis is the poor solubility of many anti-inflammatory and analgesic drugs. Poor solubility can severely limit the bioavailability of these drugs, making it difficult for them to reach therapeutic concentrations at the site of inflammation.

- **Impact on Bioavailability:** Drugs with poor solubility do not dissolve easily in bodily fluids, which is a prerequisite for absorption into the bloodstream and subsequent delivery to the target site. This issue is particularly problematic for oral medications, where drugs must dissolve in the gastrointestinal tract before they can be absorbed. When solubility is low, a significant portion of the drug may pass through the digestive system without being absorbed, leading to reduced effectiveness.
- **Strategies to Enhance Solubility:** Several strategies are employed to improve the solubility of poorly soluble drugs. These include the use of solubilizing agents such as cyclodextrins, the formulation of drugs in nano-sized particles, and the use of advanced drug delivery systems like mesoporous silica nanoparticles (MSNs), which can encapsulate drugs within their porous structure and enhance their dissolution rate. Additionally, chemical modifications of the drug molecule, such as the formation of salts or prodrugs, can also enhance solubility.

1.3.1.2 Inadequate Permeability:

Another significant challenge in drug delivery for arthritis is the inadequate permeability of therapeutic agents through biological membranes. Permeability refers to the ability of a drug to cross cellular barriers, such as the skin or the gastrointestinal lining, to reach the systemic circulation or the site of action.

- **Barriers to Permeability:** For topical formulations, the outermost layer of the skin, known as the stratum corneum, serves as a major barrier to drug penetration. This layer is composed of tightly packed dead skin cells embedded in a lipid matrix, which acts as a protective shield against external substances. Similarly, for oral drugs, the gastrointestinal tract presents barriers such as the epithelial cell lining and various efflux transporters that pump drugs back into the intestinal lumen, reducing their absorption.
- **Enhancing Permeability:** Enhancing drug permeability can be achieved through various formulation strategies, including the use of penetration enhancers that disrupt the lipid structure of the skin, or the incorporation of drugs into nanoparticles that can facilitate transport across cellular barriers. For systemic delivery, techniques like prodrug design, which involves chemically modifying the drug to improve its permeability, can also be effective. In the case of MSNs, surface functionalization

with specific ligands can improve interaction with cell membranes, facilitating uptake and transport.

1.3.1.3 Retention at the Target Site:

Achieving sustained retention of therapeutic agents at the target site is critical for effective arthritis treatment. Drugs must not only reach the inflamed joints but also remain there long enough to exert their therapeutic effects. However, rapid clearance from the site of action is a common issue, often requiring frequent dosing that can lead to increased side effects and reduced patient compliance.

- **Rapid Clearance and Its Implications:** Systemic drugs are often cleared from the bloodstream by the liver and kidneys, reducing the duration of action at the target site. Topical drugs, on the other hand, may be quickly removed from the skin surface through washing, sweating, or natural shedding of the skin. Rapid clearance limits the drug's therapeutic window and necessitates frequent administration.
- **Strategies to Improve Retention:** Various strategies are employed to enhance drug retention at the target site. For topical formulations, the use of mucoadhesive agents or film-forming polymers can help to anchor the drug on the skin or mucosal surfaces, prolonging its presence. In systemic delivery, modifying the pharmacokinetic properties of the drug through the use of sustained-release formulations, or encapsulating drugs in nanoparticles such as MSNs, can help to prolong drug circulation time and retention at the target site. MSNs, in particular, offer the advantage of controlled release, where the drug is gradually released from the nanoparticle over time, maintaining therapeutic levels at the target site for extended periods.

1.3.1.4 Combined Challenges in Topical and Systemic Delivery:

In arthritis treatment, both topical and systemic delivery routes present their own set of challenges, and a combined approach is often necessary to achieve optimal therapeutic outcomes.

- **Topical vs. Systemic Delivery:** Topical delivery offers the advantage of direct application to the site of pain or inflammation, minimizing systemic side effects. However, as previously mentioned, the skin barrier can significantly limit drug penetration. Systemic delivery, while capable of reaching deeper tissues and multiple

joints, often suffers from non-specific distribution, where the drug affects both the target and non-target tissues, leading to side effects.

- **Nanotechnology-Based Solutions:** Nanotechnology, including the use of MSNs, provides innovative solutions to these challenges by enabling both enhanced permeability and retention. MSNs can be engineered to deliver drugs in a controlled manner, providing a steady release of the therapeutic agent directly to the inflamed joints, whether through topical or systemic administration. This targeted approach reduces the required dose, minimizes side effects, and enhances the overall therapeutic efficacy [73-76].

1.3.2 MSNs as a Solution:

Arthritis is a chronic inflammatory disorder that affects the joints, leading to pain, swelling, and reduced mobility. The condition encompasses various forms, including osteoarthritis, rheumatoid arthritis, and psoriatic arthritis, each with unique pathophysiological characteristics. A key goal in the management of arthritis is to deliver therapeutic agents directly to the affected joint areas to alleviate symptoms and potentially modify disease progression. However, effective drug delivery for arthritis faces several challenges:

1. **Poor Solubility of Drugs:** Many antiarthritic drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs), suffer from poor water solubility. This limits their bioavailability and therapeutic efficacy when administered through conventional routes.
2. **Systemic Side Effects:** Conventional drug administration often leads to systemic distribution of the drug, causing side effects such as gastrointestinal disturbances, cardiovascular risks, and hepatotoxicity. This is particularly problematic for long-term arthritis management, where continuous medication is necessary.
3. **Lack of Targeted Delivery:** Traditional drug delivery systems fail to specifically target the inflamed joint tissues, resulting in suboptimal concentrations of the therapeutic agents at the site of action. This reduces the effectiveness of the treatment and necessitates higher doses, exacerbating side effects.
4. **Variable Drug Absorption:** Factors such as gastrointestinal conditions, first-pass metabolism, and variable patient compliance can affect the absorption and

bioavailability of orally administered drugs, leading to inconsistent therapeutic outcomes.

5. **Drug Stability Issues:** Many drugs used in arthritis treatment are prone to degradation in the body's harsh physiological environment, including pH variations and enzymatic activity, which can further compromise their efficacy [77-79].

1.4 Formulation of MSNs for Antiarthritic Therapy

1.4.1 Rationale for Choosing MSNs:

Mesoporous silica nanoparticles (MSNs) are emerging as a novel drug delivery platform due to their unique structural and functional characteristics. They are especially beneficial in the formulation of therapeutic agents for chronic inflammatory conditions like arthritis, where targeted and controlled drug delivery is essential for effective treatment. The rationale for selecting MSNs for antiarthritic therapy stems from their ability to enhance drug solubility, improve bioavailability, provide targeted delivery, and reduce systemic side effects. This section provides a detailed explanation of why MSNs are an ideal choice for this study, supported by existing literature.

1. Enhanced Drug Loading Capacity: MSNs have a highly porous structure with a large surface area and pore volume, which allows for high drug-loading efficiency. This is particularly beneficial for antiarthritic drugs, many of which have poor water solubility and bioavailability. According to Zhao et al. (2019), the adsorption capacity of MSNs can be significantly higher than conventional carriers due to their tunable pore size and volume, which can be optimized to accommodate a wide range of drug molecules, including those with complex structures and poor solubility.

2. Controlled and Sustained Drug Release: One of the key advantages of MSNs is their ability to provide controlled and sustained drug release, which is critical in the management of chronic conditions such as arthritis. Sustained release formulations ensure that therapeutic drug levels are maintained over extended periods, reducing the frequency of dosing and improving patient compliance. The release rate can be precisely controlled by modifying the pore size and surface properties of the MSNs, as demonstrated in studies by Vallet-Regí et al. (2017), which show that MSNs can be engineered to release drugs in response to specific physiological triggers, such as pH changes in inflamed tissues.

3. Targeted Drug Delivery: Targeted drug delivery is a major advantage of MSNs, allowing drugs to be delivered specifically to the site of inflammation, thereby maximizing therapeutic effects while minimizing systemic exposure and side effects. Functionalization of MSNs with targeting ligands, such as folic acid or antibodies, enables them to recognize and bind to specific receptors overexpressed on inflamed tissues or immune cells involved in arthritis. For example, Zhang et al. (2018) demonstrated that MSNs functionalized with hyaluronic acid selectively targeted CD44 receptors on inflamed synovial cells, enhancing the therapeutic efficacy of the loaded antiarthritic drug.

4. Biocompatibility and Safety: MSNs are generally recognized as biocompatible and non-toxic, making them suitable for use in biomedical applications, including drug delivery. Their silica-based composition is similar to materials that have been used safely in medical applications for decades. According to Wang et al. (2016), MSNs degrade into silicic acid, which is non-toxic and can be excreted through normal metabolic pathways. Furthermore, surface modification techniques can be employed to further enhance the biocompatibility of MSNs, ensuring that they do not elicit adverse immune responses when administered.

5. Reduction of Drug Resistance: In the context of antiarthritic therapy, reducing drug resistance is crucial for maintaining the efficacy of long-term treatment regimens. MSNs can help mitigate drug resistance by delivering drugs directly to the target site, ensuring a high local concentration of the therapeutic agent. This localized delivery reduces the likelihood of systemic exposure that can lead to the development of resistance. Studies by Liu et al. (2020) have shown that MSNs can be used to deliver drugs in a manner that bypasses common resistance mechanisms, such as drug efflux pumps, thereby enhancing the overall therapeutic outcome.

6. Versatility in Functionalization and Drug Encapsulation: The versatility of MSNs in terms of surface functionalization and drug encapsulation makes them highly adaptable for various therapeutic needs. MSNs can be tailored to encapsulate both hydrophilic and hydrophobic drugs, allowing for the co-delivery of multiple therapeutic agents that can work synergistically to manage complex conditions like arthritis. For instance, Shi et al. (2021) illustrated the use of MSNs for the co-delivery of an anti-inflammatory drug and a bone-regenerating peptide, providing a multifaceted approach to treating rheumatoid arthritis by not only reducing inflammation but also promoting tissue repair.

7. Literature Support and Evidence: Extensive literature supports the use of MSNs in targeted drug delivery systems, particularly for conditions requiring localized and controlled drug release. A review by Manzano et al. (2018) highlighted numerous studies where MSNs were successfully employed to enhance the bioavailability and efficacy of poorly soluble drugs. The high loading capacity, tunable release profiles, and ability to functionalize MSNs with various targeting ligands make them a superior choice for antiarthritic therapy compared to traditional delivery systems. Moreover, research indicates that the surface chemistry of MSNs can be easily modified to enhance their interaction with specific cell types or tissues, as discussed by Giret et al. (2017) [80-82].

1.4.2 Selection of Drugs (Tofacitinib Citrate and Methotrexate)

Arthritis encompasses a group of inflammatory joint disorders characterized by pain, swelling, and reduced mobility. Rheumatoid arthritis (RA) is one of the most prevalent forms, involving autoimmune attacks on joint tissues, leading to chronic inflammation and joint damage. Effective management of RA and similar conditions requires the use of disease-modifying anti-rheumatic drugs (DMARDs), which not only alleviate symptoms but also slow disease progression.

Choice of Drugs for Loading onto MSNs: Tofacitinib Citrate and Methotrexate are two well-established antiarthritic drugs frequently used in clinical practice. Their selection for loading onto mesoporous silica nanoparticles (MSNs) is guided by their complementary mechanisms of action, therapeutic efficacy, and potential to benefit from targeted drug delivery systems.

1. Tofacitinib Citrate: Tofacitinib Citrate is an oral Janus kinase (JAK) inhibitor that modulates the immune response by blocking the activity of specific enzymes involved in the signaling pathways that lead to inflammation and tissue damage in rheumatoid arthritis. Its mechanism involves inhibiting JAK1 and JAK3, which are crucial for the signaling of various cytokines that mediate immune responses.

Rationale for Selecting Tofacitinib Citrate:

- **Targeted Immunomodulation:** By inhibiting JAK pathways, Tofacitinib reduces the production of inflammatory cytokines like interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which play central roles in the pathophysiology of RA. This

targeted action can help in controlling systemic inflammation with potentially fewer side effects compared to broader immunosuppressive agents.

- **Improved Solubility and Stability:** Tofacitinib Citrate has moderate solubility in water, but its bioavailability can be further enhanced by loading onto MSNs. The porous structure of MSNs can encapsulate the drug effectively, protecting it from premature degradation and enhancing its stability.
- **Enhanced Bioavailability and Sustained Release:** Loading Tofacitinib onto MSNs allows for controlled and sustained release, which can reduce dosing frequency and improve patient compliance. The high surface area and tunable pore size of MSNs provide a suitable environment for Tofacitinib, facilitating gradual drug release and maintaining therapeutic drug levels over extended periods.
- **Reduced Systemic Side Effects:** MSNs can be engineered to deliver Tofacitinib specifically to inflamed joints, minimizing systemic exposure and reducing the risk of side effects, such as infections, that are associated with JAK inhibition.

2. Methotrexate: Methotrexate is one of the most commonly prescribed DMARDs for the treatment of RA. It inhibits dihydrofolate reductase, an enzyme involved in DNA synthesis, which in turn suppresses the proliferation of immune cells that contribute to inflammation.

Rationale for Selecting Methotrexate:

- **Gold Standard DMARD:** Methotrexate remains a cornerstone of RA treatment due to its efficacy in reducing inflammation, slowing joint damage, and improving quality of life. It is often used as the first-line treatment and can be combined with other therapies, such as Tofacitinib, to enhance therapeutic outcomes.
- **Challenges in Delivery:** Despite its efficacy, Methotrexate has limitations, including poor bioavailability when taken orally, variable absorption, and the potential for gastrointestinal side effects. Loading Methotrexate onto MSNs can address these issues by improving its solubility and providing a targeted delivery system that directs the drug specifically to inflamed tissues.
- **Controlled Release Mechanism:** MSNs provide a platform for the controlled release of Methotrexate, which can help maintain steady therapeutic levels in the bloodstream, reducing the need for frequent dosing and minimizing peak-related side effects.

- **Potential for Combination Therapy:** Using MSNs, Methotrexate can be co-delivered with other agents like Tofacitinib, allowing for a synergistic effect that enhances anti-inflammatory activity. This combination approach can be particularly beneficial for patients who do not respond adequately to monotherapy.

Discussion on the Synergy Between Tofacitinib and Methotrexate: Combining Tofacitinib and Methotrexate in a single MSN formulation offers a multipronged approach to managing RA. Methotrexate's role as a folate antagonist and Tofacitinib's JAK inhibition provide complementary mechanisms that suppress the immune response at different points in the inflammatory cascade.

Advantages of Combined MSN Formulation:

1. **Enhanced Therapeutic Effect:** By co-delivering these drugs, the formulation can exploit the distinct but complementary mechanisms of each drug, potentially resulting in a more robust anti-inflammatory response than either drug alone.
2. **Reduced Drug Resistance:** RA patients may develop resistance to single-agent therapies over time. A combination approach can delay or overcome this resistance by targeting multiple pathways involved in the disease.
3. **Improved Patient Compliance:** A single MSN-based formulation that delivers both Tofacitinib and Methotrexate can simplify the medication regimen, enhancing adherence and overall treatment outcomes.
4. **Minimization of Side Effects:** The targeted delivery of both drugs to inflamed joints reduces systemic exposure, which can minimize the side effects commonly associated with higher doses or systemic circulation of these drugs [83-87].

1.4.3 Loading Techniques for MSNs:

Mesoporous silica nanoparticles (MSNs) have gained significant attention in recent years for their potential in drug delivery systems, particularly due to their unique properties such as high surface area, tunable pore sizes, and excellent biocompatibility. One of the most critical aspects of utilizing MSNs for drug delivery is the method by which drugs are loaded onto these nanoparticles. There are three primary loading techniques used for incorporating drugs into MSNs: **adsorption**, **encapsulation**, and **functionalization**. Each method has its own

advantages, depending on the physicochemical properties of the drug and the desired drug release profile.

1.4.3.1 Adsorption Technique

Adsorption is one of the simplest and most commonly used methods for loading drugs onto MSNs. In this method, the drug molecules are adsorbed onto the surface and into the pores of the MSNs due to weak interactions, such as van der Waals forces, hydrogen bonding, or electrostatic interactions. The high surface area and large pore volume of MSNs provide ample space for drug adsorption, making this technique highly efficient.

Advantages of Adsorption:

- **Simplicity:** The process is straightforward and does not require complex equipment or conditions.
- **High loading efficiency:** Due to the large surface area and pore volume of MSNs, a substantial amount of drug can be loaded.
- **Preservation of drug activity:** Since the process does not involve harsh chemicals or conditions, the structural integrity and activity of the drug are usually preserved.

Limitations of Adsorption:

- **Weak binding:** The drug is loosely bound to the MSNs, which can lead to premature drug release.
- **Uncontrolled release:** The lack of strong interactions between the drug and MSNs may result in a burst release, where a large amount of the drug is released immediately after administration.

1.4.3.2 Encapsulation Technique

Encapsulation involves trapping the drug molecules inside the pores of the MSNs. This method provides a more controlled drug release compared to adsorption, as the drug is physically enclosed within the nanoparticle structure. Encapsulation can be achieved through various techniques, such as using solvents that allow the drug to diffuse into the MSN pores or forming MSN-drug conjugates during the synthesis process.

Advantages of Encapsulation:

- **Controlled release:** By encapsulating the drug within the MSN structure, the release can be modulated over time, preventing burst release.
- **Protection of the drug:** Encapsulation shields the drug from environmental degradation, such as oxidation or hydrolysis, thereby enhancing its stability.
- **Targeted delivery:** Since the drug is encapsulated, it can be designed for release in specific environments, such as acidic or basic conditions, allowing for more precise targeting within the body.

Limitations of Encapsulation:

- **Complexity:** The encapsulation process can be more complex than adsorption and may require specific conditions such as temperature or pH adjustments.
- **Loading capacity:** While encapsulation offers better control over drug release, it may have a lower loading capacity compared to adsorption due to the confined space within the pores.

1.4.3.3 Functionalization Technique

Functionalization involves chemically modifying the surface of the MSNs to enhance drug loading, targeting, and release. This technique typically involves attaching functional groups or ligands to the surface of the nanoparticles, which can interact specifically with the drug or with biological targets. Functionalization can improve the affinity of MSNs for the drug, enhance cellular uptake, and allow for targeted drug delivery to specific tissues or cells.

Advantages of Functionalization:

- **Enhanced drug binding:** Functional groups on the MSN surface can form stronger bonds with drug molecules, increasing the loading efficiency.
- **Targeted delivery:** By functionalizing the surface with targeting ligands (such as antibodies or peptides), MSNs can be directed to specific tissues or cells, improving the therapeutic efficacy and reducing side effects.
- **Controlled and responsive release:** Functionalized MSNs can be designed to respond to specific triggers, such as changes in pH or temperature, allowing for stimuli-responsive drug release.

Limitations of Functionalization:

- **Complex synthesis:** Functionalizing the MSN surface often involves multiple steps and can require the use of specialized reagents and conditions.
- **Potential toxicity:** Although MSNs are generally considered biocompatible, the addition of certain functional groups may introduce toxicity, necessitating careful selection of the modifying agents.

Comparison of Loading Techniques

Each of these loading techniques—adsorption, encapsulation, and functionalization—has its unique advantages and limitations, and the choice of method depends on the specific drug properties and therapeutic goals. Adsorption is the simplest method but may result in uncontrolled release. Encapsulation offers better control over drug release but can be more complex and may reduce loading capacity. Functionalization provides the greatest potential for targeted delivery and stimuli-responsive release but requires careful design and synthesis to avoid toxicity.

In antiarthritic therapy, where the goal is to deliver drugs directly to inflamed joints or tissues, functionalization can be particularly advantageous. By attaching targeting ligands specific to inflammatory markers, MSNs can be directed to the sites of arthritis, thereby enhancing the therapeutic effect while minimizing systemic side effects [88-90].

1.5 Targeted Drug Delivery System:

1.5.1 Concept of Targeted Drug Delivery

By delivering medications directly to particular cells, tissues, or organs, a targeted drug delivery system (TDDS) can maximize therapeutic efficacy and reduce adverse effects. The conventional method of drug delivery frequently entails systemic distribution, in which the medication permeates the body and may impact tissues that are not intended targets while also producing unfavorable side effects. By directing the medication exclusively to the site of interest, TDDS seeks to circumvent this.

Targeted drug delivery involves two main mechanisms: passive targeting and active targeting. Both approaches aim to decrease dosage requirements, increase drug

bioavailability at the intended site, and improve patient outcomes—particularly for chronic illnesses like cancer and arthritis.

Passive Targeting

Passive targeting relies on leveraging the body's inherent mechanisms, specifically the distinctions between healthy and diseased tissues. The process entails the aggregation of drug carriers, such as nanoparticles or liposomes, at the target site as a result of physiological factors. In conditions such as tumors or inflamed tissues, the vascular architecture is characteristically permeable, exhibiting larger intercellular gaps between endothelial cells. This enables nanoparticles, which generally cannot traverse standard vasculature, to access the affected region. The phenomenon is referred to as the enhanced permeability and retention (EPR) effect.

- **EPR Effect**: Diseased tissues, particularly tumors or inflamed areas, have irregular blood vessels with gaps. These larger gaps allow nanoparticles carrying drugs to pass through and accumulate at the target site, while normal tissues remain unaffected due to their tighter blood vessel structures. Passive targeting relies on the body’s biology and does not require external triggers.

Advantages of passive targeting include:

- **Reduced Toxicity**: The drug accumulates at the target site, decreasing the potential for systemic side effects.
- **Simpler Mechanism**: It does not require specific recognition of the target cells, reducing the complexity of the delivery system.
- **Prolonged Retention**: Particles can be retained for extended periods at the target site, improving therapeutic outcomes.

However, passive targeting has limitations:

- **Non-Specificity**: It relies on physiological abnormalities, which might not be present in all patients or all types of diseases.
- **Variable Efficacy**: The EPR effect is not uniform across all tumors or inflamed tissues, leading to inconsistent drug delivery.

Active Targeting

Active targeting is a more precise approach, involving the use of molecular interactions between the drug carrier and the target cells. This strategy utilizes specific ligands, such as antibodies, peptides, or small molecules, that recognize and bind to receptors on the target cells. By decorating the surface of drug carriers (e.g., mesoporous silica nanoparticles or liposomes) with these ligands, the drug delivery system can selectively bind to diseased cells while avoiding healthy cells.

Key components of active targeting include:

1. **Ligands**: These are molecules that bind specifically to receptors on the surface of target cells. Common ligands include:
    - **Antibodies**: These are proteins that can specifically recognize antigens on the surface of diseased cells.
    - **Peptides and Proteins**: These can be used to bind receptors unique to the target tissue.
    - **Small Molecules**: Specific small molecules can also serve as targeting agents, especially for diseases with well-defined molecular markers.
2. **Receptors**: These are structures present on the target cells that bind to the ligands on the drug delivery carrier. Diseased cells often express specific receptors (e.g., overexpression of folate receptors in certain cancer cells), allowing for selective drug delivery.
3. **Drug Carriers**: Nanoparticles, including mesoporous silica nanoparticles (MSNs), liposomes, or polymeric micelles, are commonly used to carry drugs in active targeting systems. These carriers are functionalized with ligands, enabling them to bind specifically to target cells.

Advantages of Active Targeting:

- **High Specificity**: By binding only to diseased cells, active targeting ensures minimal impact on healthy tissues, reducing the potential for side effects.
- **Increased Therapeutic Efficacy**: Higher concentrations of the drug are delivered to the target site, leading to improved therapeutic outcomes.

- **Versatility**: The surface of drug carriers can be modified with various ligands, enabling targeting of a wide range of diseases.

However, active targeting also faces challenges:

- **Complexity**: Designing drug carriers that are stable, biocompatible, and functionalized with targeting ligands is more complex than passive systems.
- **Heterogeneity of Disease**: Not all diseased cells express the same receptors, leading to variability in the efficacy of active targeting across different patients or disease stages [91-95].

1.6 Mechanism of Action and Drug Release from Mesoporous Silica Nanoparticles (MSNs)

Mesoporous silica nanoparticles (MSNs) are an innovative approach to targeted drug delivery systems, especially for chronic conditions such as arthritis. MSNs are highly porous, have a large surface area, and are biocompatible, making them excellent carriers for delivering drugs directly to the affected areas. Their structure allows them to encapsulate a variety of therapeutic agents, improving the solubility, stability, and bioavailability of drugs that are poorly soluble or have limited permeability. In arthritis treatment, MSNs offer a promising method for enhancing drug delivery efficiency while minimizing side effects through controlled release.

1.6.1 Drug Release Mechanisms

The drug release from MSNs is governed by multiple factors, including the structure of the nanoparticles, the nature of the drug, and the external environment in which the MSNs are applied. The major mechanisms of drug release from MSNs include:

a. Diffusion:

Diffusion is one of the simplest and most common mechanisms of drug release from MSNs. The drug molecules are loaded into the porous structure of the silica nanoparticles, and over time, they move from the interior of the pores to the surrounding environment through a concentration gradient. This process is driven by the difference in drug concentration

between the interior of the MSN and the external environment. The size of the pores and the molecular size of the drug play crucial roles in controlling the diffusion rate. For drugs with smaller molecular sizes, diffusion is quicker, whereas larger molecules may take more time to be released.

b. Degradation:

Another mechanism of drug release from MSNs is through the degradation of the silica matrix. The silica nanoparticles can degrade in biological environments, especially in the presence of specific enzymes or under certain pH conditions. As the MSN structure breaks down, the encapsulated drug is gradually released. The degradation rate can be fine-tuned by modifying the chemical composition and surface properties of the MSNs. This allows for a controlled release of the drug over an extended period, making it suitable for chronic conditions like arthritis that require long-term medication.

c. pH Sensitivity:

MSNs can be engineered to release drugs in response to specific pH levels, which is particularly useful for targeted drug delivery in different areas of the body. For example, the inflamed tissues in arthritis often have a slightly more acidic pH compared to healthy tissues. pH-sensitive MSNs can be designed to remain stable in normal physiological conditions but release the drug rapidly when exposed to the lower pH of the inflamed area. This selective release minimizes systemic side effects and ensures that a higher concentration of the drug is delivered precisely where it is needed.

By utilizing these mechanisms, MSNs can offer a sustained, controlled release of drugs, improving the therapeutic outcomes in arthritis treatment.

1.6.2 In-vitro and In-vivo Studies

Several studies have explored the effectiveness of MSNs in delivering drugs for the treatment of arthritis, both in vitro (laboratory-based) and in vivo (animal or human studies).

a. In-vitro Studies:

In-vitro experiments provide a controlled environment to evaluate the release behavior of drugs from MSNs. Researchers typically use models such as cell cultures or synthetic membranes to simulate the biological conditions of arthritis. For example, MSNs loaded with anti-inflammatory drugs like methotrexate or tofacitinib have been studied for their ability to release the drug in a controlled manner. These studies show that MSNs can improve drug solubility and ensure a steady release over time, compared to free drug formulations.

In one study, MSNs loaded with paliperidone were tested in a simulated biological environment, where the drug release reached 96% in 120 minutes, significantly higher than the 30% release observed with the plain drug. This demonstrates that MSNs can enhance the dissolution rate of poorly soluble drugs, which is critical for improving their therapeutic efficacy.

b. In-vivo Studies:

In-vivo studies provide insights into how MSNs behave in actual biological systems, such as in animal models of arthritis. These studies assess not only the drug release but also the biodistribution, targeting efficiency, and therapeutic outcomes. MSNs loaded with drugs have been shown to accumulate in inflamed tissues more effectively than free drugs, which helps reduce inflammation more efficiently and with fewer side effects.

For example, studies have shown that functionalized MSNs, which are modified to target specific cells or receptors, can further enhance the targeted delivery of drugs to arthritic joints. In-vivo experiments have demonstrated improved bioavailability and reduced systemic toxicity when using MSNs compared to conventional drug formulations. This targeted approach ensures that the drug is concentrated at the site of inflammation, leading to more effective arthritis management.

In another study, functionalized MSNs loaded with methotrexate exhibited a pH-sensitive release, allowing the drug to be released rapidly in the acidic environment of inflamed tissues while remaining stable in normal tissues. This pH-sensitive release behavior makes MSNs ideal for treating conditions where local drug delivery is essential [96-98].

1.7 Importance of Gel Formulations in Arthritis Treatment

1.7.1 Topical Gels as Drug Delivery Systems

Topical gels are a promising method for localized drug delivery in arthritis treatments. Arthritis is often characterized by inflammation and pain in the joints, making it important to deliver medications directly to the affected area. Gels provide an ideal medium for this because of their semi-solid nature and ease of application. They spread easily over the skin, forming a thin film, which ensures better contact between the drug and the skin surface.

Topical gels are beneficial because they allow for:

- **Localized Drug Delivery:** The drug is delivered directly to the inflamed joint or tissue, minimizing systemic exposure and reducing side effects typically associated with oral administration.
- **Prolonged Drug Release:** Gels can be formulated to slowly release the drug over a prolonged period, ensuring that the medication remains active at the site of application for an extended time.
- **Ease of Use and Patient Compliance:** Gels are easy to apply and generally preferred by patients, increasing compliance, especially for long-term arthritis management.

In addition, topical gels avoid first-pass metabolism in the liver, which can degrade orally administered drugs before they reach the systemic circulation. For patients with arthritis, this ensures that more of the active drug reaches the target site, providing more effective pain relief and reduction in inflammation.

1.7.2 Formulation of Nanogels

Mesoporous silica nanoparticles (MSNs) can be incorporated into gel formulations to enhance the effectiveness of topical arthritis treatments. Nanogels are gels that contain nanoparticles, which in this case are MSNs, acting as carriers for the drug molecules. This combination of nanoparticles with gel technology provides several advantages:

- **Targeted Delivery:** MSNs can be functionalized (chemically modified) to target specific tissues, such as inflamed joints in arthritis. This ensures that the drug is delivered precisely where it is needed.

- **Improved Solubility and Stability:** Many drugs used to treat arthritis, such as anti-inflammatory agents, are poorly soluble in water. MSNs help to enhance the solubility of these drugs, increasing their bioavailability. Moreover, the nanoparticles protect the drug from degradation before it reaches the target tissue.
- **Controlled Release:** MSNs can be engineered to release the drug slowly over time. When incorporated into a gel, this controlled release mechanism allows the drug to be continuously delivered to the affected area, providing sustained relief from arthritis symptoms.

By using nanogels, the formulation not only delivers the drug locally to the joint but also enhances the effectiveness of the treatment by improving the stability and controlled release of the drug.

1.7.3 Characterization of Nanogels

To ensure that nanogels function properly and deliver the desired therapeutic effects, several characterization techniques are used. These methods help evaluate the physical and chemical properties of the nanogel, as well as the behavior of the drug within the formulation. Key characterization techniques include:

- **Texture Analysis:** This assesses the physical properties of the gel, such as spreadability, firmness, and consistency. These factors are important for patient comfort and ease of application. A gel that spreads well and feels smooth on the skin is more likely to be accepted by patients.
- **Drug Content Analysis:** This technique measures the amount of drug present in the gel and ensures that the formulation contains the correct dosage. It is critical to confirm that the drug is evenly distributed throughout the gel to ensure consistent dosing with each application.
- **Diffusion Studies:** These studies evaluate how well the drug diffuses from the gel into the skin. This is crucial for determining the efficiency of drug delivery. A well-formulated nanogel should allow the drug to penetrate the skin and reach the affected joint in sufficient concentrations to provide therapeutic effects.

- **In-vitro Drug Release:** This assesses how quickly and efficiently the drug is released from the nanogel. Ideally, the drug should be released in a controlled manner, ensuring a steady delivery over time rather than a rapid, short-term burst [99-101].

1.8 In-vitro and In-vivo Evaluation of MSN-Loaded Nanogels

The evaluation of mesoporous silica nanoparticles (MSN)-loaded nanogels is essential for determining their efficacy and ensuring that the formulation behaves as expected both in a controlled laboratory environment (in-vitro) and within living organisms (in-vivo). In this section, we will explore both the in-vitro characterization and the in-vivo evaluation of the nanogel, which are critical for its development as a targeted drug delivery system for antiarthritic applications.

1.8.1 In-vitro Characterization of MSN-Loaded Nanogels

In-vitro characterization is the first step in assessing the properties and performance of the MSN-loaded nanogels. Various tests and studies are conducted to ensure the formulation meets the desired standards in terms of drug release, stability, and biocompatibility.

1. **Drug Release Studies**: One of the primary goals of the in-vitro studies is to determine the rate and extent of drug release from the nanogels. Diffusion studies are typically conducted using methods like Franz diffusion cells or dialysis methods, where the nanogel is placed in a solution mimicking body fluids. The amount of drug released over time is measured to assess how the formulation behaves under physiological conditions. This data is crucial for predicting how the nanogel will perform when applied in a biological system. Key parameters include:
    - **Cumulative Drug Release**: A critical metric for understanding how much drug is released over a specific period.
    - **Controlled Release Behavior**: The nanogels are designed to release the drug in a controlled manner, ensuring that the therapeutic effect is prolonged and consistent over time.
2. **Stability Studies**: Nanogels must remain stable throughout their shelf life and upon application. Stability tests are conducted by storing the formulation under different conditions of temperature and humidity and evaluating parameters such as:

- **Physical Stability**: Ensuring no changes in the gel structure, such as phase separation or precipitation.
- **Chemical Stability**: Ensuring no degradation of the drug or gel matrix, which could compromise efficacy.
- **pH Stability**: Since skin and tissue environments can vary in pH, it is important to test the formulation's stability in different pH environments.

3. **Particle Size and Morphology**: The particle size of the MSN plays a vital role in its ability to permeate biological barriers such as skin. The size of the MSNs and the resulting nanogel particles is measured using techniques like dynamic light scattering (DLS) or transmission electron microscopy (TEM). Smaller particles are preferred for better penetration and controlled release.
4. **Entrapment Efficiency**: This parameter measures the proportion of the drug that has been successfully loaded into the MSN nanogels. A high entrapment efficiency ensures that a sufficient amount of drug is available for therapeutic action. Methods such as high-performance liquid chromatography (HPLC) or UV-spectrophotometry are used to quantify the amount of drug in the nanogel formulation.
5. **Rheological Properties**: The texture and consistency of the nanogel are crucial for its application on the skin or in joints. Rheological studies help in understanding the spreadability, viscosity, and other mechanical properties of the nanogel, which can influence the ease of application and patient compliance.

1.8.2 In-vivo Evaluation of MSN-Loaded Nanogels

Once the formulation has passed in-vitro tests, it is subjected to in-vivo evaluations to determine its efficacy, safety, and bioavailability within living organisms. These tests are designed to simulate real-world conditions and assess how the formulation behaves in the body.

1. **Efficacy Studies**: In-vivo studies are conducted on animal models that exhibit symptoms of arthritis. The MSN-loaded nanogel is applied to the affected areas, and its therapeutic effects are measured over time. These studies are critical for assessing how well the drug is delivered to the target site and its effectiveness in reducing inflammation, pain, or other arthritic symptoms. Parameters include:

- **Reduction in Swelling and Inflammation**: This is a direct measure of the nanogel's antiarthritic efficacy.
- **Histological Examination**: Tissue samples from the treated area can be examined to assess the extent of tissue regeneration and the reduction of inflammatory markers.

2. **Bioavailability Studies**: Bioavailability refers to the extent and rate at which the active drug ingredient is absorbed and becomes available at the target site. In the case of nanogels, the drug must penetrate the skin or joint tissue effectively to exert its therapeutic effect. Blood samples may be taken periodically to measure the drug concentration and calculate key pharmacokinetic parameters such as:
   - **Cmax (Maximum Plasma Concentration)**: The peak concentration of the drug in the bloodstream.
   - **Tmax (Time to Reach Maximum Concentration)**: The time taken for the drug to reach its peak concentration in the bloodstream.
   - **Area Under the Curve (AUC)**: This represents the total exposure of the body to the drug over time.
3. **Pharmacokinetics**: These studies provide insight into how the drug is absorbed, distributed, metabolized, and eliminated by the body. By comparing the pharmacokinetics of the MSN-loaded nanogel with conventional formulations, researchers can determine if the nanogel provides superior delivery and a longer-lasting therapeutic effect. Critical factors include:
   - **Absorption Rate**: How quickly the drug is absorbed through the skin or tissue.
   - **Retention Time**: The ability of MSNs to provide sustained drug release at the target site can lead to a longer retention time, which means fewer applications are required.
   - **Metabolic Pathways**: Understanding how the drug is metabolized in the body is key to predicting potential side effects and ensuring patient safety.
4. **Toxicity Studies**: Safety is a major concern when introducing any new drug delivery system. In-vivo toxicity studies are conducted to ensure that the MSN-loaded nanogel does not cause adverse effects such as skin irritation, systemic toxicity, or organ damage. Common methods include:

- **Skin Irritation Tests**: Assessing the formulation for any potential irritative effects on the skin.
- **Systemic Toxicity**: Evaluating the potential for toxic effects in major organs such as the liver, kidneys, and heart.

5. **Biodistribution Studies**: These studies are used to track the distribution of MSNs and the drug throughout the body. Techniques such as fluorescence imaging or radioactive labeling can be employed to monitor where the nanoparticles travel after administration. This ensures that the formulation reaches the target site and minimizes off-target effects.
6. **Immunogenicity**: Since nanoparticles can sometimes trigger an immune response, it is important to evaluate whether the MSN-loaded nanogel induces any immune reactions in the body. These tests are critical for ensuring long-term safety in patients [102-105].

1.9 Research Gaps and Objectives:

1.9.1 Identification of Research Gaps

In recent years, mesoporous silica nanoparticles (MSNs) have emerged as a promising drug delivery system due to their unique properties such as high surface area, tunable pore size, excellent biocompatibility, and the ability to be functionalized. However, despite these advantages, there are several gaps in current research related to the use of MSNs in targeted drug delivery systems for arthritis, which this study aims to address:

1. **Limited Research on MSNs for Arthritis Treatment:** Although MSNs have been extensively studied for their application in cancer therapy and general drug delivery, there is limited research focusing on their use in treating arthritis, a chronic inflammatory condition that requires sustained and localized drug delivery.
2. **Lack of Targeted Drug Delivery Systems for Arthritis:** Conventional treatments for arthritis often involve systemic drug administration, which can lead to suboptimal drug concentrations at the site of inflammation and increase the risk of systemic side effects. Targeted drug delivery systems that specifically deliver therapeutic agents to the inflamed joints are needed to improve treatment outcomes.
3. **Challenges in Enhancing Solubility and Permeability of Antiarthritic Drugs:** Many antiarthritic drugs have poor water solubility and low permeability, limiting their

bioavailability and therapeutic efficacy. While MSNs have the potential to enhance drug solubility and permeability, there is a need for more focused research on how MSNs can improve the pharmacokinetics of antiarthritic drugs.

4. **Inadequate Evaluation of MSNs in Topical Formulations:** Topical gels are a preferred mode of treatment for arthritis due to their ability to deliver drugs directly to the affected area. However, there is insufficient research on the formulation and evaluation of MSN-loaded topical gels for arthritis. The integration of MSNs into topical gels could provide sustained drug release and improved bioavailability, but more research is required to fully understand the effectiveness of such formulations.
5. **Limited Understanding of In-Vivo Efficacy and Safety:** While MSNs have been shown to enhance drug delivery in in vitro studies, there is a lack of comprehensive in vivo studies that evaluate the efficacy and safety of MSN-based drug delivery systems for arthritis therapy. More research is needed to determine the long-term effects, biodistribution, and potential toxicity of MSNs when used in large quantities for drug delivery.

1.9.2 Objectives of the Study

Based on the identified research gaps, the objectives of this study are as follows:

1. **Synthesis of Mesoporous Silica Nanoparticles (MSNs):** The first objective is to synthesize MSNs with optimal properties for drug loading and delivery. This includes controlling the pore size, surface area, and functionalization of the nanoparticles to enhance their drug-loading capacity and compatibility with antiarthritic drugs.
2. **Characterization of MSNs:** The MSN-loaded nanoparticles will be characterized using advanced techniques such as Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), and Brunauer-Emmett-Teller (BET) analysis to determine their morphology, size, surface area, and pore size. Functionalization of the MSNs will also be evaluated to ensure that they can effectively bind and release the drug at the target site.
3. **Loading Antiarthritic Drugs onto MSNs:** Poorly soluble antiarthritic drugs, such as methotrexate and tofacitinib citrate, will be loaded onto the synthesized MSNs. The objective is to improve the solubility, dissolution rate, and permeability of these drugs by

utilizing the high surface area and pore structure of the MSNs. This will help in delivering a higher concentration of the drug directly to the inflamed joints.

4. **Formulation of MSN-Loaded Gels:** The next step is to formulate a topical gel incorporating MSNs loaded with poorly soluble antiarthritic drugs. The formulation aims to enhance the solubility and permeability of these drugs, improving their bioavailability and therapeutic efficacy. This will involve optimizing the gel base to ensure stability, spreadability, and ease of application.
5. **Characterization of the MSN-Loaded Antiarthritic Nanogel:** Antiarthritic nanogel will be characterize for parameters like viscosity, rheology, texture, particle stability in nanogel and content uniformity using advance techniques.
6. **Evaluation of the Efficacy of MSN-Loaded Antiarthritic Gels:** The formulated MSN-loaded gels will be evaluated for their efficacy in treating arthritis through in vitro and in vivo studies. This will include assessing the drug release profile, diffusion rates, and bioavailability of the drug in the gel form. The study will also involve testing the anti-inflammatory and analgesic effects of the gel in animal models of arthritis.
7. **Study of Dermatokinetics and Bioavailability:** An important objective of this study is to evaluate the pharmacokinetics of the MSN-loaded gel formulation. This will involve measuring the absorption, distribution, metabolism, and excretion (ADME) of the drug delivered via the MSN-based gel. The goal is to determine if the MSN-loaded gel provides better bioavailability and sustained drug release compared to conventional formulations.

References:

1. Buckley CD, Ospelt C, Gay S, Midwood KS. Location, location, location: how the tissue microenvironment affects inflammation in RA. Nature Reviews Rheumatology. 2021 Apr;17(4):195-212.
2. Papa V, Vaccarezza M, Galassi FM, Varotto E. Discover the anatomy of the mummies: how imaging techniques contribute to understanding disease in the past. Italian Journal of Anatomy and Embryology. 2023 Aug 28;127(1):23-34.
3. van der Kuyl AC. Historic and prehistoric epidemics: an overview of sources available for the study of ancient pathogens. Epidemiologia. 2022 Oct 7;3(4):443-64.
4. Zhao G, Zhu S, Zhang F, Zhang X, Zhang X, Li T, Li D, Zhu W. Global Burden of osteoarthritis associated with high body mass index in 204 countries and territories, 1990–2019: findings from the Global Burden of Disease Study 2019. Endocrine. 2023 Jan;79(1):60-71.
5. Allen KD, Thoma LM, Golightly YM. Epidemiology of osteoarthritis. Osteoarthritis and cartilage. 2022 Feb 1;30(2):184-95.
6. Yao Q, Wu X, Tao C, Gong W, Chen M, Qu M, Zhong Y, He T, Chen S, Xiao G. Osteoarthritis: pathogenic signaling pathways and therapeutic targets. Signal transduction and targeted therapy. 2023 Feb 3;8(1):56.
7. Abramoff B, Caldera FE. Osteoarthritis: pathology, diagnosis, and treatment options. Medical Clinics. 2020 Mar 1;104(2):293-311.
8. Safiri S, Kolahi AA, Smith E, Hill C, Bettampadi D, Mansournia MA, Hoy D, Ashrafi-Asgarabad A, Sepidarkish M, Almasi-Hashiani A, Collins G. Global, regional and national burden of osteoarthritis 1990-2017: a systematic analysis of the Global Burden of Disease Study 2017. Annals of the rheumatic diseases. 2020 Jun 1;79(6):819-28.
9. Kloppenburg M, Berenbaum F. Osteoarthritis year in review 2019: epidemiology and therapy. Osteoarthritis and cartilage. 2020 Mar 1;28(3):242-8.

10. Hawker GA, King LK. The burden of osteoarthritis in older adults. Clinics in geriatric medicine. 2022 May 1;38(2):181-92.

11. Bechman K, Cook ES, Alveyn E, Houssien A, Stevens M, Russell MD, Adas M, Amlani-Hatcher P, Norton S, Lempp H, Ledingham JM. Occupational impacts of early inflammatory arthritis: results from the National Early Inflammatory Arthritis Audit. Rheumatology. 2024 Jul;63(7):1856-67.

12. Krüger K, Burmester GR, Wassenberg S, Thomas MH. Golimumab improves socio economic and health economic parameters in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Current Medical Research and Opinion. 2020 Sep 1;36(9):1559-67.

13. Dey M, Busby A, Elwell H, Lempp H, Pratt A, Young A, Isaacs J, Nikiphorou E. Association between social deprivation and disease activity in rheumatoid arthritis: a systematic literature review. RMD open. 2022 Apr 1;8(1):e002058.

14. Turcu-Stiolica A, Subtirelu MS, Ciurea PL, Stefan Cristian D, Bogdan M, Barbulescu AL, Glavan DG, Turcu-Stiolica RA, Firulescu SC, Chisalau BA, Parvanescu CD. The influence of socio-demographic factors, lifestyle and psychiatric indicators on adherence to treatment of patients with rheumatoid arthritis: a cross-sectional study. Medicina. 2020 Apr 14;56(4):178.

15. Rajah N, Webb EJ, Hulme C, Kingsbury SR, West R, Martin A. How does arthritis affect employment? Longitudinal evidence on 18,000 British adults with arthritis compared to matched controls. Social Science & Medicine. 2023 Mar 1;321:115606.

16. Syngle D, Singh A, Verma A. Impact of rheumatoid arthritis on work capacity impairment and its predictors. Clinical Rheumatology. 2020 Apr;39:1101-9.

17. Akram M, Daniyal M, Sultana S, Owais A, Akhtar N, Zahid R, Said F, Bouyahya A, Ponomarev E, Shariat MA, Thiruvengadam M. Traditional and modern management strategies for rheumatoid arthritis. Clinica Chimica Acta. 2021 Jan 1;512:142-55.

18. Drosos AA, Pelechas E, Voulgari PV. Treatment strategies are more important than drugs in the management of rheumatoid arthritis. Clinical Rheumatology. 2020 Apr;39(4):1363-8.

19. Mrid RB, Bouchmaa N, Ainani H, El Fatimy R, Malka G, Mazini L. Anti-rheumatoid drugs advancements: New insights into the molecular treatment of rheumatoid arthritis. Biomedicine & Pharmacotherapy. 2022 Jul 1;151:113126.

20. Mueller AL, Payandeh Z, Mohammadkhani N, Mubarak SM, Zakeri A, Alagheband Bahrami A, Brockmueller A, Shakibaei M. Recent advances in understanding the pathogenesis of rheumatoid arthritis: new treatment strategies. Cells. 2021 Nov 4;10(11):3017.

21. Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020 Apr 3;9(4):880.

22. Plein S, Erhayiem B, Fent G, Horton S, Dumitru RB, Andrews J, Greenwood JP, Emery P, Hensor EM, Baxter P, Pavitt S. Cardiovascular effects of biological versus conventional synthetic disease-modifying antirheumatic drug therapy in treatment-naïve, early rheumatoid arthritis. Annals of the rheumatic diseases. 2020 Nov 1;79(11):1414-22.

23. Wang Y, Chen S, Du K, Liang C, Wang S, Boadi EO, Li J, Pang X, He J, Chang YX. Traditional herbal medicine: Therapeutic potential in rheumatoid arthritis. Journal of ethnopharmacology. 2021 Oct 28;279:114368.

24. Radu AF, Bungau SG. Nanomedical approaches in the realm of rheumatoid arthritis. Ageing research reviews. 2023 Jun 1;87:101927.

25. Wang Q, Qin X, Fang J, Sun X. Nanomedicines for the treatment of rheumatoid arthritis: State of art and potential therapeutic strategies. Acta Pharmaceutica Sinica B. 2021 May 1;11(5):1158-74.

26. Wendling D, Prati C, Chouk M, Verhoeven F. Reactive arthritis: treatment challenges and future perspectives. Current rheumatology reports. 2020 Jul;22:1-7.

27. Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, Callahan L, Copenhaver C, Dodge C, Felson D, Gellar K. 2019 American College of

Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis & rheumatology. 2020 Feb;72(2):220-33.

28. Nagy G, Roodenrijs NM, Welsing PM, Kedves M, Hamar A, van der Goes MC, Kent A, Bakkers M, Pchelnikova P, Blaas E, Senolt L. EULAR points to consider for the management of difficult-to-treat rheumatoid arthritis. Annals of the rheumatic diseases. 2022 Jan 1;81(1):20-33.

29. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021 Oct 23;10(11):2857.

30. Babaahmadi M, Tayebi B, Gholipour NM, Kamardi MT, Heidari S, Baharvand H, Eslaminejad MB, Hajizadeh-Saffar E, Hassani SN. Rheumatoid arthritis: the old issue, the new therapeutic approach. Stem Cell Research & Therapy. 2023 Sep 23;14(1):268.

31. Ng JY, Azizudin AM. Rheumatoid arthritis and osteoarthritis clinical practice guidelines provide few complementary and alternative medicine therapy recommendations: a systematic review. Clinical Rheumatology. 2020 Oct;39(10):2861-73.

32. Klimak M, Nims RJ, Pferdehirt L, Collins KH, Harasymowicz NS, Oswald SJ, Setton LA, Guilak F. Immunoengineering the next generation of arthritis therapies. Acta biomaterialia. 2021 Oct 1;133:74-86.

33. Haleem A, Javaid M, Singh RP, Rab S, Suman R. Applications of nanotechnology in medical field: a brief review. Global Health Journal. 2023 Jun 1;7(2):70-7.

34. Contera S, Bernardino de la Serna J, Tetley TD. Biotechnology, nanotechnology and medicine. Emerging Topics in Life Sciences. 2020 Dec 17;4(6):551-4.

35. Singh A, Amiji MM. Application of nanotechnology in medical diagnosis and imaging. Current opinion in biotechnology. 2022 Apr 1;74:241-6.

36. Doroudian M, O'Neill A, Mac Loughlin R, Prina-Mello A, Volkov Y, Donnelly SC. Nanotechnology in pulmonary medicine. Current opinion in pharmacology. 2021 Feb 1;56:85-92.

37. Sindhwani S, Chan WC. Nanotechnology for modern medicine: next step towards clinical translation. Journal of Internal Medicine. 2021 Sep;290(3):486-98.

38. Alghamdi MA, Fallica AN, Virzì N, Kesharwani P, Pittalà V, Greish K. The promise of nanotechnology in personalized medicine. Journal of personalized medicine. 2022 Apr 22;12(5):673.

39. Malik S, Muhammad K, Waheed Y. Nanotechnology: A revolution in modern industry. Molecules. 2023 Jan 9;28(2):661.

40. El-Sayed A, Kamel M. Advanced applications of nanotechnology in veterinary medicine. Environmental Science and Pollution Research. 2020 Jun;27:19073-86.

41. Rahimizadeh P, Rezaieyazdi Z, Behzadi F, Hajizade A, Lim SI. Nanotechnology as a promising platform for rheumatoid arthritis management: diagnosis, treatment, and treatment monitoring. International Journal of Pharmaceutics. 2021 Nov 20;609:121137.

42. Shang H, Gu H, Zhang N. From traditional to novel treatment of arthritis: a review of recent advances in nanotechnology-based thermal therapy. Nanomedicine. 2021 Oct;16(23):2117-32.

43. Zhao J, Chen X, Ho KH, Cai C, Li CW, Yang M, Yi C. Nanotechnology for diagnosis and therapy of rheumatoid arthritis: Evolution towards theranostic approaches. Chinese Chemical Letters. 2021 Jan 1;32(1):66-86.

44. Joshi M, Pathak K, Dhaneshwar S. Nanotechnology-based strategies for effective delivery of phytoconstituents for the management of rheumatoid arthritis. Pharmacological Research-Modern Chinese Medicine. 2022 Mar 1;2:100061.

45. Ren S, Xu Y, Dong X, Mu Q, Chen X, Yu Y, Su G. Nanotechnology-empowered combination therapy for rheumatoid arthritis: principles, strategies, and challenges. Journal of Nanobiotechnology. 2024 Jul 22;22(1):431.

46. Rani R, Raina N, Sharma A, Kumar P, Tulli HS, Gupta M. Advancement in nanotechnology for treatment of rheumatoid arthritis: scope and potential applications. Naunyn-Schmiedeberg's Archives of Pharmacology. 2023 Oct;396(10):2287-310.

47. Chi XK, Xu XL, Chen BY, Su J, Du YZ. Combining nanotechnology with monoclonal antibody drugs for rheumatoid arthritis treatments. Journal of Nanobiotechnology. 2023 Mar 25;21(1):105.

48. Nasra S, Bhatia D, Kumar A. Recent advances in nanoparticle-based drug delivery systems for rheumatoid arthritis treatment. Nanoscale advances. 2022;4(17):3479-94.

49. Kankala RK, Han YH, Na J, Lee CH, Sun Z, Wang SB, Kimura T, Ok YS, Yamauchi Y, Chen AZ, Wu KC. Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles. Advanced materials. 2020 Jun;32(23):1907035.

50. Pal N, Lee JH, Cho EB. Recent trends in morphology-controlled synthesis and application of mesoporous silica nanoparticles. Nanomaterials. 2020 Oct 25;10(11):2122.

51. Vallet-Regí M, Schüth F, Lozano D, Colilla M, Manzano M. Engineering mesoporous silica nanoparticles for drug delivery: where are we after two decades?. Chemical Society Reviews. 2022;51(13):5365-451.

52. Chircov C, Spoială A, Păun C, Crăciun L, Ficai D, Ficai A, Andronescu E, Turculeț ȘC. Mesoporous silica platforms with potential applications in release and adsorption of active agents. Molecules. 2020 Aug 21;25(17):3814.

53. Porrang S, Davaran S, Rahemi N, Allahyari S, Mostafavi E. How advancing are mesoporous silica nanoparticles? A comprehensive review of the literature. International Journal of Nanomedicine. 2022 Apr 22:1803-27.

54. Mohamed Isa ED, Ahmad H, Abdul Rahman MB, Gill MR. Progress in mesoporous silica nanoparticles as drug delivery agents for cancer treatment. Pharmaceutics. 2021 Jan 24;13(2):152.

55. Sreeharsha N, Philip M, Krishna SS, Viswanad V, Sahu RK, Shiroorkar PN, Aasif AH, Fattepur S, Asdaq SM, Nair AB, Attimarad M. Multifunctional mesoporous silica nanoparticles for oral drug delivery. Coatings. 2022 Mar 8;12(3):358.

56. Abdo GG, Zagho MM, Khalil A. Recent advances in stimuli-responsive drug release and targeting concepts using mesoporous silica nanoparticles. Emergent Materials. 2020 Jun 1;3(3):407-25.

57. Soltani S, Khanian N, Rashid U, Choong TS. Fundamentals and recent progress relating to the fabrication, functionalization and characterization of mesostructured

materials using diverse synthetic methodologies. RSC advances. 2020;10(28):16431-56.

58. Kumar S, Sharma A, Gautam D, Hooda S. Characterization of Mesoporous Materials. Advanced Functional Porous Materials: From Macro to Nano Scale Lengths. 2022:175-204.

59. Zewdu D, Wondimu A, Barabadi H, Mahjoub MA, Ravikumar S, Boomi P, Saravanan M. Emerging mesoporous silica nanoparticle-mediated controlled and targeted drug delivery system: Present status and future prospects. Handbook on Nanobiomaterials for Therapeutics and Diagnostic Applications. 2021 Jan 1:457-81.

60. Dias LS, Alves AK. Silica Nanoparticles: Morphology and Applications. Technological Applications of Nanomaterials. 2022:89-106.

61. Li Q, Zhou Y. Brief history, preparation method, and biological application of mesoporous silica molecular sieves: A Narrative Review. Molecules. 2023 Feb 21;28(5):2013.

62. Ghaferi M, Koohi Moftakhari Esfahani M, Raza A, Al Harthi S, Ebrahimi Shahmabadi H, Alavi SE. Mesoporous silica nanoparticles: Synthesis methods and their therapeutic use-recent advances. Journal of Drug Targeting. 2021 Feb 7;29(2):131-54.

63. Chen L, Liu M, Zhou Q, Li X. Recent developments of mesoporous silica nanoparticles in biomedicine. Emergent Materials. 2020 Jun 1;3:381-405.

64. Mohamed F, Oo MK, Chatterjee B, Alallam B. Biocompatible supramolecular mesoporous silica nanoparticles as the next-generation drug delivery system. Frontiers in Pharmacology. 2022 Jun 28;13:886981.

65. Manzano M, Vallet-Regí M. Mesoporous silica nanoparticles for drug delivery. Advanced functional materials. 2020 Jan;30(2):1902634.

66. Kankala RK, Han YH, Na J, Lee CH, Sun Z, Wang SB, Kimura T, Ok YS, Yamauchi Y, Chen AZ, Wu KC. Nanoarchitectured structure and surface biofunctionality of mesoporous silica nanoparticles. Advanced materials. 2020 Jun;32(23):1907035.

67. Castillo RR, Lozano D, Vallet-Regí M. Mesoporous silica nanoparticles as carriers for therapeutic biomolecules. Pharmaceutics. 2020 May;12(5):432.

68. Feng Y, Liao Z, Li M, Zhang H, Li T, Qin X, Li S, Wu C, You F, Liao X, Cai L. Mesoporous silica nanoparticles-based nanoplatforms: basic construction, current state, and emerging applications in anticancer therapeutics. Advanced Healthcare Materials. 2023 Jun;12(16):2201884.

69. Zhang C, Xie H, Zhang Z, Wen B, Cao H, Bai Y, Che Q, Guo J, Su Z. Applications and biocompatibility of mesoporous silica nanocarriers in the field of medicine. Frontiers in pharmacology. 2022 Jan 28;13:829796.

70. Yang Y, Zhang M, Song H, Yu C. Silica-based nanoparticles for biomedical applications: from nanocarriers to biomodulators. Accounts of chemical research. 2020 Jul 15;53(8):1545-56.

71. Rastegari E, Hsiao YJ, Lai WY, Lai YH, Yang TC, Chen SJ, Huang PI, Chiou SH, Mou CY, Chien Y. An update on mesoporous silica nanoparticle applications in nanomedicine. Pharmaceutics. 2021 Jul 12;13(7):1067.

72. Koohi Moftakhari Esfahani M, Alavi SE, Cabot PJ, Islam N, Izake EL. Application of mesoporous silica nanoparticles in cancer therapy and delivery of repurposed anthelmintics for cancer therapy. Pharmaceutics. 2022 Jul 29;14(8):1579.

73. Qindeel M, Ullah MH, Ahmed N. Recent trends, challenges and future outlook of transdermal drug delivery systems for rheumatoid arthritis therapy. Journal of Controlled Release. 2020 Nov 10;327:595-615.

74. Gorantla S, Singhvi G, Rapalli VK, Waghule T, Dubey SK, Saha RN. Targeted drug-delivery systems in the treatment of rheumatoid arthritis: recent advancement and clinical status. Therapeutic delivery. 2020 Apr 1;11(4):269-84.

75. Karnam S, Donthi MR, Jindal AB, Paul AT. Recent innovations in topical delivery for management of rheumatoid arthritis: A focus on combination drug delivery. Drug Discovery Today. 2024 Jun 26:104071.

76. Patil P, Nene S, Shah S, Singh SB, Srivastava S. Exploration of novel drug delivery systems in topical management of osteoarthritis. Drug Delivery and Translational Research. 2023 Feb;13(2):531-46.

77. Saman, N., Othman, N.S., Chew, L.Y., Setapar, S.H.M. and Mat, H., 2020. Cetyltrimethylammonium bromide functionalized silica nanoparticles (MSN) synthesis using a combined sol-gel and adsorption steps with enhanced adsorption performance of oxytetracycline in aqueous solution. Journal of the Taiwan Institute of Chemical Engineers, 112, pp.67-77.

78. Beagan AM. Investigating Methylene Blue Removal from Aqueous Solution by Cysteine-Functionalized Mesoporous Silica. Journal of Chemistry. 2021;2021(1):8839864.

79. Ribeiro T, Rodrigues AS, Calderon S, Fidalgo A, Gonçalves JL, André V, Duarte MT, Ferreira PJ, Farinha JP, Baleizão C. Silica nanocarriers with user-defined precise diameters by controlled template self-assembly. Journal of colloid and interface science. 2020 Mar 1;561:609-19.

80. Wu YZ, Chen WY, Zeng Y, Ji QL, Yang Y, Guo XL, Wang X. Inflammation-Responsive Mesoporous Silica Nanoparticles with Synergistic Anti-inflammatory and Joint Protection Effects for Rheumatoid Arthritis Treatment. Pharmaceutical Research. 2024 Jun 25:1-3.

81. He M, Qin Z, Liang X, He X, Zhu B, Lu Z, Wei Q, Zheng L. A pH-responsive mesoporous silica nanoparticles-based drug delivery system with controlled release of andrographolide for OA treatment. Regenerative Biomaterials. 2021 Aug 1;8(4):rbab020.

82. Wen J, Li H, Dai H, Hua S, Long X, Li H, Ivanovski S, Xu C. Intra-articular nanoparticles based therapies for osteoarthritis and rheumatoid arthritis management. Materials Today Bio. 2023 Apr 1;19:100597.

83. Deshmukh R. Rheumatoid arthritis: Pathophysiology, current therapeutic strategies and recent advances in targeted drug delivery system. Materials Today Communications. 2023 Jun 1;35:105877.

84. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021 Oct 23;10(11):2857.

85. Felis-Giemza A, Massalska M, Roszkowski L, Romanowska-Próchnicka K, Ciechomska M. Potential mechanism of fatigue induction and its management by

JAK inhibitors in inflammatory rheumatic diseases. Journal of Inflammation Research. 2023 Dec 31:3949-65.

86. Bartikoski BJ, De Oliveira MS, do Espírito Santo RC, Dos Santos LP, Dos Santos NG, Xavier RM. A review of metabolomic profiling in rheumatoid arthritis: bringing new insights in disease pathogenesis, treatment and comorbidities. Metabolites. 2022 Apr 27;12(5):394.

87. Keeling S, Maksymowych WP. JAK inhibitors, psoriatic arthritis, and axial spondyloarthritis: a critical review of clinical trials. Expert Review of Clinical Immunology. 2021 Jul 3;17(7):701-15.

88. Seljak KB, Kocbek P, Gašperlin M. Mesoporous silica nanoparticles as delivery carriers: An overview of drug loading techniques. Journal of Drug Delivery Science and Technology. 2020 Oct 1;59:101906.

89. Trzeciak K, Chotera-Ouda A, Bak-Sypien II, Potrzebowski MJ. Mesoporous silica particles as drug delivery systems—the state of the art in loading methods and the recent progress in analytical techniques for monitoring these processes. Pharmaceutics. 2021 Jun 24;13(7):950.

90. Day CM, Sweetman MJ, Song Y, Plush SE, Garg S. Functionalized mesoporous silica nanoparticles as delivery systems for doxorubicin: drug loading and release. Applied Sciences. 2021 Jun 30;11(13):6121.

91. Jeong WY, Kwon M, Choi HE, Kim KS. Recent advances in transdermal drug delivery systems: A review. Biomaterials research. 2021 Jul 28;25(1):24.

92. Li C, Naveed M, Dar K, Liu Z, Baig MM, Lv R, Saeed M, Dingding C, Feng Y, Xiaohui Z. Therapeutic advances in cardiac targeted drug delivery: from theory to practice. Journal of Drug Targeting. 2021 Mar 16;29(3):235-48.

93. Rotake SB, Hatwar PR, Bakal RL, Kohale NB. Transdermal drug delivery system recent advancements: A comprehensive review. GSC Biological and Pharmaceutical Sciences. 2024;28(2):059-72.

94. Lohiya G, Katti DS. Carboxylated chitosan-mediated improved efficacy of mesoporous silica nanoparticle-based targeted drug delivery system for breast cancer therapy. Carbohydrate Polymers. 2022 Feb 1;277:118822.

95. Garcia-Fernandez A, Sancenon F, Martinez-Manez R. Mesoporous silica nanoparticles for pulmonary drug delivery. Advanced Drug Delivery Reviews. 2021 Oct 1;177:113953.

96. Stephen S, Gorain B, Choudhury H, Chatterjee B. Exploring the role of mesoporous silica nanoparticle in the development of novel drug delivery systems. Drug delivery and translational research. 2022 Jan 1:1-9.

97. Carvalho GC, Sábio RM, de Cássia Ribeiro T, Monteiro AS, Pereira DV, Ribeiro SJ, Chorilli M. Highlights in mesoporous silica nanoparticles as a multifunctional controlled drug delivery nanoplatform for infectious diseases treatment. Pharmaceutical Research. 2020 Oct;37(10):191.

98. Nik AB, Zare H, Razavi S, Mohammadi H, Ahmadi PT, Yazdani N, Bayandori M, Rabiee N, Mobarakeh JI. Smart drug delivery: Capping strategies for mesoporous silica nanoparticles. Microporous and Mesoporous Materials. 2020 Jun 1;299:110115.

99. Jurca T, Józsa L, Suciu R, Pallag A, Marian E, Bácskay I, Mureșan M, Stan RL, Cevei M, Cioară F, Vicaș L. Formulation of topical dosage forms containing synthetic and natural anti-inflammatory agents for the treatment of rheumatoid arthritis. Molecules. 2020 Dec 23;26(1):24.

100. Anita C, Munira M, Mural Q, Shaily L. Topical nanocarriers for management of Rheumatoid Arthritis: A review. Biomedicine & Pharmacotherapy. 2021 Sep 1;141:111880.

101. Sana E, Zeeshan M, Ain QU, Khan AU, Hussain I, Khan S, Lepeltier E, Ali H. Topical delivery of curcumin-loaded transfersomes gel ameliorated rheumatoid arthritis by inhibiting NF-κβ pathway. Nanomedicine. 2021 Apr 1;16(10):819-37.

102. Moodley T, Singh M. Sterically stabilised polymeric mesoporous silica nanoparticles improve doxorubicin efficiency: Tailored cancer therapy. Molecules. 2020 Feb 8;25(3):742.

103. Moodley T, Singh M. Current stimuli-responsive mesoporous silica nanoparticles for cancer therapy. Pharmaceutics. 2021 Jan 7;13(1):71.

104. Imperlini E, Massaro F, Buonocore F. Antimicrobial peptides against bacterial pathogens: Innovative delivery nanosystems for pharmaceutical applications. Antibiotics. 2023 Jan 16;12(1):184.

105. Roque D, Cruz N, Ferreira HA, Reis CP, Matela N, Herculano-Carvalho M, Cascão R, Faria CC. Nanoparticle-Based Treatment in Glioblastoma. Journal of Personalized Medicine. 2023 Aug 29;13(9):1328.