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Microsponge Drug Delivery Systems: Advancing Methotrexate Delivery for Rheumatoid Arthritis Management

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Rheumatoid arthritis, Methotrexate, Microsponge drug delivery system, Controlled drug release, Targeted drug delivery, Inflammatory mediators

Abstract

An estimated 23 million individuals worldwide suffer with rheumatoid arthritis, a debilitating inflammatory illness with a prevalence incidence of 0.5–1%. This chronic illness mostly affects synovial joints, causing inflammation, joint degeneration, and bone erosion. Patients suffer from a very low quality of life, and the condition has a significant socioeconomic impact. The pathophysiology of RA is caused by a complicated interaction between genetic and environmental variables that disrupt the control of the immune system. TNF-α, IL-6, and IL-1β are important inflammatory mediators that cause bone resorption and joint degeneration as the illness progresses. Microsponge drug delivery systems have been developed as a promising strategy to improve the therapeutic efficacy of methotrexate, which is a cornerstone in RA treatment. These systems offer controlled release, improved bioavailability, and targeted delivery to inflamed joints while minimizing systemic toxicity. Microsponge drug delivery systems can be formulated as topical gels, creams, patches, or injectable hydrogels, which allows for a variety of administration routes. Microsponge drug delivery systems are known for offering benefits of delivering methotrexate drugs by sustaining its release, providing reduced dosing, stability in the drug itself, and causing less side effect. Some challenges of microsponge drug delivery systems include a complicated manufacturing process, scalability issues, and regulatory problems that hamper its application in the clinic. In order to prove the safety and effectiveness of microsponge drug delivery systems, future research will concentrate on refining their composition, developing scalable production methods, and conducting extensive clinical studies. Innovation will keep developing, and by enhancing patient adherence, therapeutic results, and the quality of life for patients suffering from rheumatoid arthritis, microsponge drug delivery systems have the potential to completely transform the way this chronic illness is treated.

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1. Introduction

About 23 million individuals worldwide suffer with rheumatoid arthritis (RA), a chronic inflammatory disease that causes inflammation, joint deterioration, and bone erosion. Its incidence ranges from 0.5% to 1%. The condition primarily targets synovial joints, causing pain, deformities, and reduced quality of life, with significant socio-economic implications. Early diagnosis is crucial for better treatment outcomes [1].

The synovial fluid, which lubricates the joints, is housed within the synovial membrane, a thin tissue layer surrounding the joints. This membrane, along with fibrous capsules and ligaments, helps nourish the joint through its rich microcirculation. Inflammation in RA is triggered by a combination of environmental factors (e.g., obesity, alcohol, smoking, infections) and genetic predispositions, leading to immune system dysregulation [2]. RA progresses through phases,

starting with the Pre-RA phase, characterized by changes in T- and B-cell regulation and autoantibody production. In established RA, CD4+ T-helper cells are activated by antigen-presenting cells., promoting inflammation through cytokines and autoantibodies. Cytokines like TNF-α, IL-6, and IL-1β contribute to bone resorption and joint damage. As the disease progresses, osteoclast differentiation and synovial thickening accelerate, leading to cartilage and bone destruction, increased synovial fluid, joint hypertrophy, and dysfunction [3]. Joint inflammation, discomfort, and increasing destruction are hallmarks of RA, a chronic autoimmune disease. Although there isn't a cure, the aim of treatment is to control symptoms, lower inflammation, and delay the course of the illness. NSAIDs, corticosteroids, and disease-modifying antirheumatic medications (DMARDs) are the most often utilized treatments. Although they don't stop the underlying illness process, NSAIDs and corticosteroids mainly lessen pain and inflammation. These drugs have serious adverse effects, especially when taken for an extended period of time, including immunosuppression, cardiovascular risks, and gastrointestinal problems, even if they may help reduce symptoms [4].

By altering the immune system's reaction, traditional DMARDs, such methotrexate (MTX), decrease the course of the illness. Although they have limitations, such as a delayed beginning of action and other toxicities, they can be useful in managing RA. By focusing on certain inflammatory pathways, biologic DMARDs (bDMARDs), such as interleukin-6 (IL-6) and tumor necrosis factor (TNF) inhibitors, have completely changed the way RA is treated. These biologics work well to achieve remission and avoid joint injury [5]. However, their long-term use can be complicated by immunogenicity, leading to reduced effectiveness and increased side effects, such as injection site reactions, infections, and potential malignancies. For patients with moderate-to-severe RA, combinations of conventional DMARDs and bDMARDs or Janus kinase (JAK) inhibitors are often employed. JAK inhibitors are oral agents that target intracellular signaling pathways involved in inflammation, offering a different mechanism of action compared to traditional biologics. Despite these advances, current treatments mainly focus on extracellular factors, prompting research into intracellular kinase inhibitors to offer more precise and effective disease control. These inhibitors hold promise for reducing disease activity, improving patient outcomes, and minimizing systemic side effects associated with traditional treatments. MTX is a primary treatment for RA, helping to reduce inflammation and control disease progression. However, challenges such as poor bioavailability, side effects, and patient adherence have driven research into improved delivery systems. Oral MTX has limited gastrointestinal absorption and undergoes extensive liver metabolism, necessitating higher doses and increasing side effects [5]. New delivery methods are being developed to improve bioavailability, including enhanced solubility formulations, nanoparticles for targeted delivery, and microneedle patches for transdermal administration. These innovations bypass the gastrointestinal system, reducing systemic side effects. Efforts to minimize side effects like liver toxicity and gastrointestinal discomfort focus on localized delivery systems that target inflamed joints. Sustained-release formulations are also being explored to prevent sharp peaks in drug levels. Combination therapies with biologic or synthetic DMARDs may enhance MTX's effects and improve patient adherence, making treatment more efficient and patient-friendly [6].

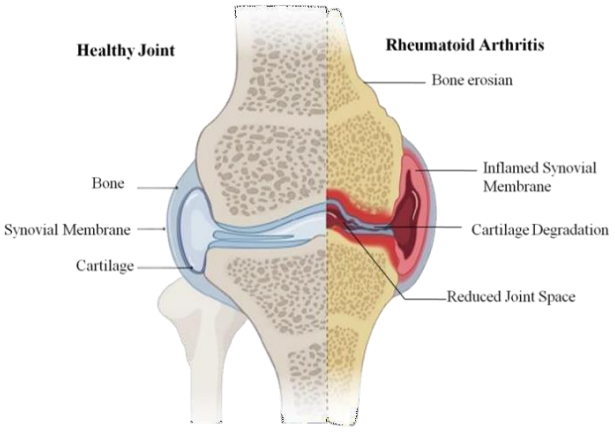

Figure 1: Inflammation in RA

MDDS represent an innovative approach to treating RA by enhancing the targeted delivery of therapeutics, improving bioavailability, and minimizing side effects [7]. These systems consist of small, porous spheres that can encapsulate drugs, allowing for controlled and sustained release over an extended period. Microspheres' porous nature offers a lot of surface area for drug loading and enables the encapsulation of various types of medications, including both conventional and biologic DMARDs, such as MTX. The primary benefit of MDDS in RA treatment is its ability to reduce the frequency of dosing while maintaining therapeutic efficacy. By using microspheres, drugs can be delivered more efficiently, ensuring that a steady, direct release of a regulated dosage of the medication occurs at the site of inflammation. This not only increases the medicine's bioavailability but also lessens the possibility of negative side effects that are frequently connected to conventional therapeutic formulations by lowering drug level variations. The low bioavailability of oral drugs, which is mostly caused by substantial first-pass metabolism in the liver and drug degradation in the gastrointestinal system, is one of the difficulties in treating RA. Microsponge systems can overcome these limitations by offering alternative routes of administration, such as topical or transdermal delivery [8]. These systems can also be used to target the drug specifically to the inflamed joints, which can help in reducing systemic side effects, such as gastrointestinal discomfort or liver toxicity, that are common with conventional treatments like oral MTX.

1. Microsponge drug delivery systems

MDDS are sophisticated formulations intended to improve the administration of and effectiveness of medications by improving their controlled release, bioavailability, and targeting specific sites. These systems consist of microparticles, typically ranging in size from 10 to 25 micrometers, made from polymers that encapsulate active drug ingredients [9]. The core idea is to enable sustained or controlled drug release over a period of time, lowering the requirement for frequent dosage while minimizing side effects. In the context of RA, microsponge systems offer several potential benefits. One of the key challenges in treating RA is achieving efficient drug delivery to the inflamed joints, where the disease activity is most prominent. Traditional drug administration methods, such as oral tablets or injections, may not be able to target the disease site effectively, leading to suboptimal therapeutic outcomes. Microsponge-based systems, however, can be made to deliver medications to the afflicted regions in a regulated way [10].

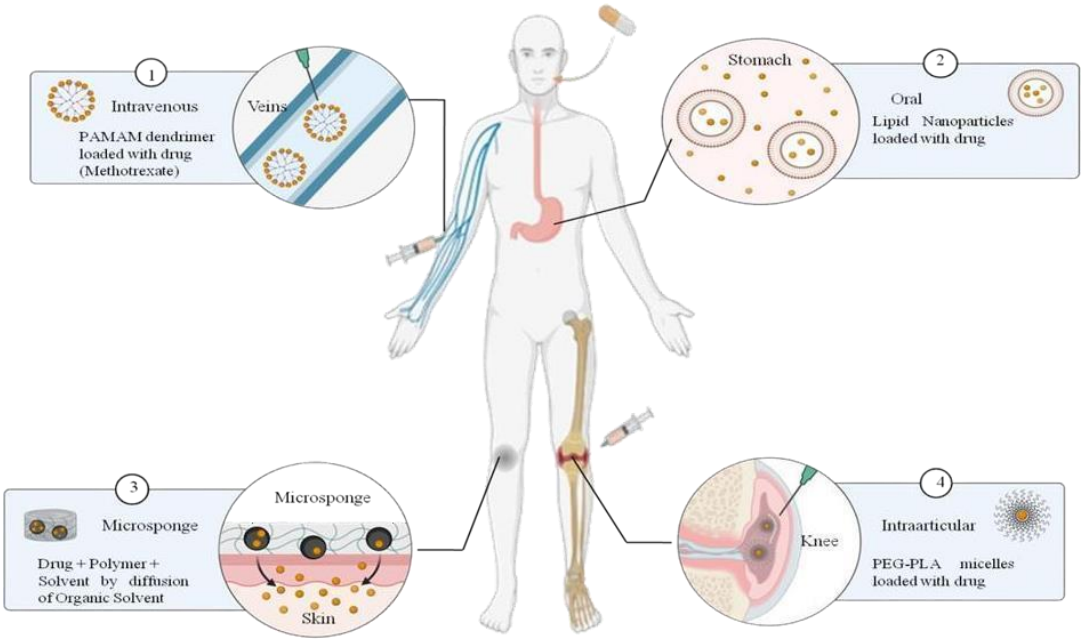

Figure 2: Drug Delivery in RA

For example, using microsponge systems to deliver NSAIDs or DMARDs could provide sustained pain relief and inflammation control in RA patients. Topical formulations that are administered directly to the skin over the afflicted joints, such lotions or gels, can include the microsponge carriers [11]. These systems offer several advantages over conventional formulations, including reduced systemic absorption, which lowers the risk of side effects, and the ability to provide localized treatment at the joint level. Microsponge systems also allow for the incorporation of multiple active ingredients, enabling combination therapies. For RA, this could mean combining NSAIDs with biologic agents or corticosteroids in a single topical treatment. These systems can also improve patient adherence by reducing the frequency of dosing and simplifying treatment regimens [12].

2.1. Types of MDDS for management of RA

DDS are a promising approach for the management of RA as they can improve localized drug delivery, reduce systemic side effects, and enhance patient adherence to treatment. There are several types of microsponge systems that have been developed or are being explored for RA management. These systems can be categorized based on their release mechanisms, the type of drugs they deliver, and the formulation approaches [13].

2.1.1. Polymeric Microsponge Systems

When it comes to medication delivery, polymeric microsponge systems are the most often utilized. These systems are made from polymers like ethylcellulose, poly(methyl methacrylate) (PMMA), and polyvinyl alcohol, which form a microporous structure that can encapsulate drugs. In RA management, polymeric microsponge systems can be used to deliver corticosteroids, NSAIDs, or DMARDs to inflamed joints, providing controlled release. These microsponge systems can be designed for topical application, ensuring that the drugs are concentrated at the site of inflammation, thus minimizing systemic side effects [14].

2.1.2. Microsponge Systems for Topical Application

Topical drug delivery is particularly advantageous for RA management because it allows for direct administration of drugs to inflamed joints, minimizing the risk of gastrointestinal or systemic side effects. Microsponge systems in gels, creams, or ointments can be applied directly to the skin over the affected joints. Drugs such as NSAIDs (e.g., diclofenac), corticosteroids (e.g., hydrocortisone), or even biologics can be delivered locally through these formulations. By controlling the release of the drug over an extended period, these systems ensure sustained therapeutic effects, reducing the frequency of applications [8].

2.1.3 Nanoparticle-Loaded Microsponge Systems

For more targeted delivery, microsponge systems can be combined with nanoparticles. This combination allows for a synergistic approach to treatment by improving drug stability, bioavailability, and release rate. Nanoparticles can enhance the penetration of the microsponge into deeper tissue layers and deliver drugs more effectively to the inflamed synovial tissues in RA patients. These systems can be loaded with DMARDs or biologic agents to improve the efficacy of RA treatment while reducing side effects associated with oral or systemic administration [15].

2.1.4. Multidrug-Loaded Microsponge Systems

Multidrug-loaded microsponge systems allow for the combination of multiple active pharmaceutical ingredients (APIs) in a single formulation. For example, a single microsponge-based system can contain a combination of NSAIDs, corticosteroids, and DMARDs. This approach is beneficial in RA management because it addresses different aspects of the disease simultaneously. NSAIDs help with pain and inflammation, corticosteroids reduce flare-ups, and DMARDs slow down disease progression. These medications may be released from the microsponge system at varying speeds, offering a thorough method of treating RA symptoms [16].

2.1.5. Microsponge Systems for Oral Delivery

Although topical delivery is preferred for localized RA treatment, oral delivery remains an important route for drugs like MTX or other systemic DMARDs. Oral microsponge delivery systems are made to increase the drug's bioavailability and regulate its release. By guaranteeing a gradual release of the medication, these systems might lessen the gastrointestinal adverse effects of MTX or other oral DMARDs, which lowers dosage frequency and enhances patient compliance [8].

2.1.6. Thermosensitive Microsponge Systems

Drugs are released by thermosensitive microsponge systems in reaction to temperature variations. These systems can be applied as a gel that transforms into a solid form upon application to the skin, improving the adherence of the formulation to the affected area. The body's temperature can cause these systems to release

drugs or by the heat generated during joint inflammation. These systems are particularly useful for RA management, as they can provide continuous, gradual, controlled delivery of the medication to meet patients' therapeutic needs [17].

Table 1: Various MTX-loaded microsponge formulations, carriers, drug delivery systems, and applications

S. No.	Formulation	Carrier/Polymer	Drug Delivery System	Application	References
1.	Microsponge Gel	Ethylcellulose, Carbopol 940	Topical Gel	Localized treatment of rheumatoid arthritis; reduces systemic side effects.	[18]
2.	Microsponge Cream	Eudragit RS100	Topical Cream	Enhanced skin penetration for managing arthritis pain and inflammation.	[19]
3.	Microsponge Tablets	Polyvinyl alcohol (PVA)	Oral Tablet	Controlled oral release to maintain therapeutic drug levels.	[20]
4.	Microsponge Hydrogel	Chitosan	Injectable Hydrogel	Sustained release for intra-articular administration.	[21]
5.	Microsponge Patch	Hydroxypropyl methylcellulose (HPMC)	Transdermal Patch	Non-invasive delivery for prolonged therapeutic effects.	[22]
6.	Microsponge Capsules	Gelatin, Eudragit S100	Oral Capsule	Targeted drug release in the gastrointestinal tract to improve bioavailability.	[23]
7.	Microsponge Lotion	Polylactic acid (PLA)	Topical Lotion	Easy application for localized arthritis management.	[24]
8.	Microsponge Nanoparticles	Polycaprolactone (PCL)	Injectable Nanoparticles	Targeted drug delivery to inflamed joints.	[25]
9.	Microsponge Film	Sodium alginate, HPMC	Buccal Film	Sustained release for mucosal administration.	[26]
10.	Microsponge Powder	Ethylcellulose	Dry Powder	Direct application to affected areas; enhanced drug retention.	[27]
11.	Microsponge Spray	Polyvinylpyrrolidone (PVP)	Aerosol Spray	Non-invasive delivery for inflamed skin.	[28]
12.	Microsponge Ophthalmic Gel	Carbopol 934, Eudragit RS100	Ophthalmic Gel	Treatment of inflammatory eye conditions in rheumatoid arthritis.	[29]
13.	Microsponge Emulsion	Polyglycolic acid (PGA)	Topical Emulsion	Enhanced skin penetration and hydration.	[30]

14.	Microsponge Injectable Solution	Polyethylene glycol (PEG)	Injectable Solution	Intravenous sustained release for systemic treatment.	[31]
15.	Microsponge Lipid Suspension	Liposomes	Injectable Lipid Suspension	Targeted delivery to inflamed joints.	[32]
16.	Microsponge Injectable Beads	Chitosan, Gelatin	Injectable Beads	Slow-release intra-articular therapy.	[33]
17.	Microsponge Inhaler Formulation	Ethylcellulose, PVP	Dry Powder Inhaler	For pulmonary delivery in associated arthritis conditions.	[34]
18.	Microsponge Oral Suspension	Hydroxypropyl cellulose	Oral Suspension	Patient-friendly delivery for pediatric or elderly patients.	[35]
19.	Microsponge Nanogel	Polyethylene oxide (PEO)	Nanogel	Nano-sized hydrogel for deep joint penetration.	[36]
20.	Microsponge Transdermal Cream	Poloxamer	Transdermal Cream	Prolonged drug effect for arthritis management.	[37]
21.	Microsponge Coated Beads	Alginate, PLA	Coated Beads	Dual-layered drug release for precise dosing.	[38]
22.	Microsponge Loaded Plaster	Gelatin, HPMC	Medicated Plaster	Continuous drug release via dermal contact.	[39]
23.	Microsponge Oral Thin Film	PVP, Gelatin	Oral Thin Film	Fast-dissolving delivery system.	[40]
24.	Microsponge Ophthalmic Suspension	Carbopol 940	Ophthalmic Suspension	Long-lasting relief for inflammatory eye symptoms.	[41]
25.	Microsponge-loaded Liposomes	Lecithin	Liposomal Suspension	Improved drug encapsulation and release.	[42]
26.	Microsponge Sustained-Release Tablet	Hydroxypropyl methylcellulose (HPMC)	Sustained-Release Tablet	Consistent therapeutic drug levels over time.	[43]
27.	Microsponge Foam Formulation	Poloxamer	Topical Foam	Easy application and absorption for joint pain.	[44]
28.	Microsponge Microcapsules	Poly(lactic-co-glycolic acid) (PLGA)	Microcapsules	Precision-controlled drug delivery.	[45]
29.	Microsponge Nanoparticle Suspension	PEG, PLA	Injectable Suspension	Advanced drug targeting for localized treatment.	[46]

2. Advantages of MDDS in MTX Delivery

3.1. Controlled and Sustained Release

MDDS provide a significant advantage in the controlled and sustained release of MTX, especially for managing chronic conditions like RA. This controlled release is crucial in maintaining stable drug levels in the body, which is essential for optimal therapeutic outcomes while minimizing side effects. Traditional MTX delivery methods, such as oral

tablets, often result in fluctuating drug concentrations, with peaks that can cause toxic side effects and troughs that may not be therapeutically effective. In order to solve these problems, MDDS releases the medication gradually over a long period of time, guaranteeing that the body can access it at constant amounts [47]. The sustained release feature of MDDS reduces the frequency of drug administration, which improves patient adherence to treatment regimens. MTX, when administered orally, often requires weekly doses, which can be difficult for patients to maintain, especially for those with memory issues or those who experience side effects. With MDDS, the drug can be released gradually, reducing the need for frequent dosing and simplifying the treatment schedule. This helps patients stay on track with their medication, ultimately improving treatment compliance and disease control [48]. The sustained release of MTX from MDDS ensures that the drug is available at the target site such as the inflamed joints in RA over an extended period. This localized delivery can enhance the therapeutic effect at the site of inflammation while minimizing systemic side effects. By avoiding large, rapid doses that would otherwise be required in conventional delivery systems, MDDS can reduce the risk of gastrointestinal discomfort, liver toxicity, and myelosuppression, common side effects associated with high doses of MTX [49].

The controlled release offered by MDDS also helps prevent the peaks and troughs in drug concentration that are common with oral MTX. Traditional MTX treatments often result in high initial concentrations that can lead to toxicity, followed by lower concentrations that may not effectively control disease progression. By releasing MTX at a controlled rate, MDDS provide a more consistent and predictable therapeutic response, allowing for more precise disease management [50]. This approach minimizes the risk of side effects while ensuring that therapeutic levels are maintained over time. The controlled and sustained release of MTX via MDDS enhances the drug's effectiveness, reduces the risk of adverse effects, and improves patient adherence to treatment regimens [51]. This makes MDDS an invaluable tool in the management of chronic conditions like RA, where long-term, consistent treatment is essential for improving patient outcomes and quality of life [52].

3.2. Reduced Side Effects

MDDS offer a significant advantage in reducing the side effects commonly associated with MTX treatment for RA. One of the primary challenges with conventional MTX therapies, such as oral tablets, is the occurrence of severe side effects due to the high initial drug concentrations in the bloodstream. These side effects, including gastrointestinal discomfort, liver toxicity, and myelosuppression, are often a result of fluctuating drug levels caused by the rapid absorption and subsequent systemic distribution of the drug [53]. MDDS address this problem by providing a controlled and sustained release of MTX over time, it reduces the possibility of adverse effects and aids in maintaining more stable blood medication concentrations. By ensuring that MTX is released gradually, MDDS avoid the peaks in drug levels that can lead to toxicity. In traditional delivery methods, the body absorbs a significant amount of MTX quickly, leading to higher-than-necessary drug concentrations in the bloodstream [54]. These peaks can contribute to unwant side effects, including nausea, vomiting, liver damage, and bone marrow suppression. With MDDS, MTX is released slowly, allowing for a steady and controlled dosage that reduces the risk of such adverse reactions. The consistent release means the body is exposed to therapeutic levels of the drug over a longer period, rather than being overwhelmed by sudden high doses [55].

MDDS can be tailored to target certain bodily parts, like the joints affected by RA. By delivering MTX directly to the inflamed joints, MDDS can concentrate the drug where it is needed most, while minimizing systemic exposure. This localized delivery helps reduce the impact of the drug on other organs and tissues, thereby lowering the likelihood of side effects outside of the target area. The reduced side effects also extend to the long-term management of RA [56]. As MTX is known for its potential for liver toxicity with prolonged use, the gradual release from MDDS can help mitigate this risk. Lower peak concentrations of the drug can reduce

ditional delivery systems, preventing both sub-therapeutic levels and the high peaks that can lead to toxicity. Another key factor in improving bioavailability is the potential for targeted delivery. In order to maximize the drug's concentration at the site of action and minimize systemic exposure, MDDS can be made to target the medication to certain regions, such as RA patients' swollen joints. This focused strategy not only increases medication efficacy but also lowers the possibility of adverse effects, resulting in safer and more effective therapy [62].

3.4. Localized Delivery

One of the main benefits of MDDS in MTX therapy, especially for the treatment of RA, is localized delivery. Therapeutic efficacy is increased and systemic adverse effects are reduced when the medication can be delivered directly to the site of inflammation, such as RA-affected joints. The synovial joints are the main target of RA, which results in persistent inflammation, discomfort, and damage [63]. Conventional drug delivery techniques, such oral or intravenous routes, disperse the medication throughout the body, increasing systemic exposure. As is typical with MTX therapy, this may lead to adverse consequences such myelosuppression, liver damage, and gastrointestinal distress. However, localized administration by MDDS aims to reduce needless systemic exposure and lower the risk of side effects by delivering MTX directly to the inflammatory joints, where it is most required [64].

MDDS can be engineered to release MTX gradually at the site of inflammation, maintaining therapeutic drug concentrations in the joint while minimizing the impact on other tissues. The microsponge particles act as carriers that are either absorbed by the synovial membrane or can be administered directly to the joint, offering precise control over the drug's release. This localized release enhances the drug's effectiveness in controlling inflammation and slowing disease progression in RA, while ensuring that the MTX remains active at the targeted site over an extended period [65].

3. Challenges and Future Perspectives

4.1. Formulation Optimization

Formulation optimization is a critical aspect of developing effective MDDS for MTX delivery in the management of RA. While MDDS has demonstrated significant potential in overcoming issues like bioavailability, sustained release, and reduced side effects, the process of creating an optimal formulation remains challenging. Several factors must be addressed to achieve a stable, effective, and safe system. One of the primary concerns in formulation optimization is achieving the appropriate drug loading [66]. MTX must be efficiently encapsulated within the microsponge matrix, ensuring that a sufficient dose is delivered over an extended period. This requires careful control of the microsponge's structural properties, including its porosity, surface area, and particle size. The ideal formulation should be able to load a therapeutically effective amount of MTX while maintaining a controlled release profile. Overloading the microsponge could lead to an initial burst release, which might cause side effects or toxicity, while underloading could result in suboptimal therapeutic effects [67].

Making sure the MTX is stable within the microsponge formulation presents another difficulty. The powerful medication MTX may be susceptible to changes in light, humidity, and temperature. In order to maintain the drug's stability until it is delivered, the microsponge matrix must shield it from deterioration during transportation and storage. Slow and steady MTX release from the microsponge is necessary to produce long-lasting therapeutic benefits without giving the body too much medication at once. Another important factor to take into account is how the medicine and the excipients used in the formulation interact. Excipients, such as polymers, surfactants, and stabilizers, play an essential role in determining the microsponge's release characteristics and ensuring the stability of the drug [68]. The choice of excipients must be compatible with MTX and not interfere with its bioavailability or therapeutic action. Moreover, excipients should not cause adverse reactions, as patient safety is a top priority. Particle size and surface charge also impact the pharmacokinetics of the MDDS. The size of the microsponge particles must be optimized for efficient drug absorption, particularly for targeted delivery to inflamed joints. Smaller particles may improve tissue penetration and targeting, but they must be balanced with their ability to be retained at the site of action for prolonged periods [69]. The method of administering the MDDS whether through oral, transdermal, or injectable routes adds another layer of complexity to formulation optimization. Each route of administration has its own set of challenges and requirements, such as solubility for oral delivery, skin permeability for transdermal delivery, and injection site reactions for injectable forms. The formulation must be tailored to the delivery route to ensure patient compliance and comfort [70].

4.2. Manufacturing Complexity

Manufacturing complexity is one of the significant challenges in developing MDDS for MTX delivery in RA management. While MDDS offers numerous advantages, such as controlled release, reduced side effects, and improved bioavailability, the process of scaling up production while maintaining product consistency, quality, and cost-effectiveness is intricate. One of the primary challenges in manufacturing MDDS is the development of the

microsponge matrix itself [71]. The microsponge particles must be precisely engineered to encapsulate MTX in a way that ensures its stability, controlled release, and targeted delivery to inflamed joints. The creation of such matrices typically involves complex techniques such as emulsion solvent evaporation, suspension polymerization, or coacervation, each with its own set of requirements. These techniques require careful optimization of parameters like solvent concentration, temperature, and stirring speed, as even slight variations can lead to differences in particle size, porosity, and release characteristics[72]. Maintaining uniformity in the size, shape, and surface characteristics of microsponge particles is also challenging. The particle size plays a crucial role in determining the rate of drug release, as well as the ability of the microspheres to penetrate tissues effectively. Inconsistent particle sizes can lead to erratic drug release profiles, making it difficult to predict and control the therapeutic effects. Large-scale manufacturing processes must account for batch-to-batch consistency, as variations in particle size distribution can affect both the efficacy and safety of the final product. The selection of excipients is another critical factor in the manufacturing process. Excipients such as polymers, stabilizers, and surfactants are necessary to ensure the stability and performance of the drug delivery system. However, the interaction between MTX and excipients must be carefully considered [73]. Some excipients may cause degradation of the drug, affect its bioavailability, or result in undesirable interactions with the body. The manufacturing process must ensure that excipients do not interfere with the sustained release properties of the MDDS. Manufacturing MDDS also requires precise control over drug loading and release kinetics. The amount of MTX encapsulated within the microsponge matrix must be optimized to achieve a therapeutically effective dose while preventing an initial burst release, which could lead to adverse effects [74].

This requires a careful balance of factors such as polymer concentration, particle size, and drug-excipient ratio. Overloading the microsponge with MTX can lead to poor release control, while therapeutic effects. Scaling up production of MDDS can also introduce challenges in terms of quality control. Each step in the manufacturing process must be closely monitored to underloading may result in suboptimal ensure the microsponge particles maintain their desired characteristics [74]. The production of MDDS for pharmaceutical use must comply with Good Manufacturing Practices (GMP), which involve stringent quality assurance protocols to ensure the safety, consistency, and efficacy of the final product. This requires significant investment in specialized equipment, trained personnel, and testing procedures. Finally, the cost of manufacturing MDDS can be higher compared to traditional drug delivery systems. The complexity of the formulation, the need for specialized equipment, and the stringent quality control processes all contribute to increased production costs. This could limit the widespread adoption of MDDS-based treatments unless cost-effective manufacturing techniques are developed [71].

4.3. Long-Term Safety and Efficacy

When creating MDDS for MTX distribution in RA treatment, long-term safety and effectiveness are essential factors to take into account. While MDDS offers numerous advantages such as controlled release and reduced side effects, ensuring their long-term safety and sustained therapeutic effects remains a complex challenge that must be thoroughly evaluated. One primary concern is the potential for chronic toxicity due to the prolonged release of MTX from the microsponge system [75]. MTX, although effective in managing RA, can have serious long-term side effects such as liver toxicity, gastrointestinal discomfort, and myelosuppression. While MDDS aims to minimize these adverse effects by providing a sustained release profile, there is still the risk of cumulative toxicity over time. If the drug is released at a constant rate over extended periods, there is the potential for drug accumulation in tissues, which could lead to unanticipated toxic effects, particularly in patients with impaired organ function. Thus, long-term safety studies are needed to evaluate how MTX behaves in the body over months or years, as well as to assess any potential interactions alongside other drugs frequently used to treat RA [76].

The release kinetics of MDDS must be carefully controlled to avoid an initial drug burst. A rapid release of MTX at the beginning of therapy could cause acute toxicity or exacerbate side effects. Although MDDS are designed to provide sustained and controlled release, there is a possibility that environmental factors or changes in the patient's body could affect the release rate over time. For instance, changes in pH, temperature, or the composition of synovial fluid in the joints could influence how the microsponge releases MTX. Therefore, thorough testing is necessary to ensure that the drug is released in a consistent manner throughout the treatment period, even in the long term [77]. Another challenge

is assessing the long-term therapeutic efficacy of MDDS-based treatments. Over time, patients with RA may develop a tolerance or resistance to MTX, leading to diminished effectiveness. While MDDS can improve drug delivery efficiency and reduce peak drug concentrations in the bloodstream, ensuring that these systems continue to deliver the desired therapeutic effects throughout the course of treatment is essential. Long-term clinical trials and follow-up studies are necessary to monitor the sustained effectiveness of MTX delivered via MDDS, particularly in terms of disease control, joint function, and pain management [78]. The biocompatibility of the microsponge carrier itself is another important consideration. While the microsponge system may be designed to be inert and non-toxic, prolonged exposure to the body's tissues raises concerns about any potential immune responses or chronic inflammation caused by the drug delivery system. Studies must assess whether the microsponge particles could accumulate in the body over time, potentially leading to adverse effects such as granuloma formation or immune system activation. The degradation products of the microsponge materials need to be evaluated for potential toxicity [79].

4.4. Patient Compliance

Patient compliance is one of the most critical factors influencing the effectiveness of RA treatment, particularly in the case of MTX therapy. MDDS offer significant improvements in patient adherence to treatment by addressing common challenges related to conventional drug regimens. However, there are still several factors to consider when optimizing patient compliance with MDDS-based MTX therapies. The capacity of MDDS to deliver a regulated and continuous release of MTX over a long period of time is one of its main benefits. Traditional MTX treatments, especially oral formulations, often require patients to take the medication on a frequent, typically weekly, basis [80]. This can lead to issues with adherence, especially if patients experience side effects like gastrointestinal discomfort or fatigue, which are common with MTX. Moreover, patients may forget or neglect to take their medication on schedule, leading to suboptimal drug levels and reduced efficacy. MDDS, on the other hand, can improve patient compliance by offering less frequent dosing. By utilizing controlled release, MDDS allows for more predictable drug delivery with fewer doses, potentially reducing the treatment burden on patients. For example, MTX delivered via MDDS may be formulated for weekly, bi-weekly, or even monthly dosing. This reduction in dosing frequency could make it easier for patients to manage their treatment and improve long-term adherence [81].

Another factor that influences patient compliance is the method of drug administration. Some people may find oral MTX difficult to tolerate, particularly those who experience gastrointestinal issues or other side effects. In these cases, MDDS systems could offer alternative methods of administration, such as transdermal patches or injectable formulations, which may be less irritating and easier to administer. This shift in the mode of delivery can significantly enhance patient comfort and willingness to adhere to the treatment plan. MDDS formulations could be designed to reduce the frequency of healthcare visits [82]. This is especially relevant in the case of biologic therapies or injectables, which typically require frequent clinic visits for administration. MDDS systems that allow for self-administration at home, with longer intervals between doses, could decrease the burden on both patients and healthcare providers. By reducing the frequency of visits, patient convenience improves, potentially leading to better compliance. Despite these advantages, challenges in patient compliance still exist. Some patients may not fully understand the benefits of using MDDS-based therapies, or they may have concerns about new drug delivery technologies [83]. Education plays a crucial role in improving compliance. Healthcare professionals are responsible for making sure patients are aware of the advantages, appropriate usage, and any adverse effects of MDDS formulations. The cost of MDDS products may be a barrier for some patients. While MDDS systems can offer significant clinical benefits, they are often more expensive than traditional oral formulations. The financial burden may lead to reluctance in adopting MDDS-based treatments, particularly in settings with limited healthcare resources. Insurance coverage and cost-effectiveness analyses will be important factors in the widespread adoption of these technologies [84].

Conclusion

MDDS represent a transformative advancement in the treatment of RA, offering significant improvements over conventional MTX therapy. RA, a chronic autoimmune disease, poses challenges in management due to its progressive nature, systemic complications, and adverse effects associated with long-term drug use. MDDS provides a solution by enabling controlled drug release, targeted delivery to inflamed joints, and enhanced bioavailability. These

systems not only prolong the therapeutic effect of MTX but also reduce systemic toxicity, dosing frequency, and side effects, thereby improving patient adherence and overall quality of life. Diverse MDDS formulations, including topical gels, creams, patches, and injectable hydrogels, offer flexibility for localized and systemic applications, catering to varying patient needs. Despite their advantages, challenges such as complex manufacturing processes, scalability issues, and regulatory hurdles remain significant barriers to widespread clinical adoption. Addressing these challenges requires focused efforts in optimizing formulations, advancing cost-effective and scalable production techniques, and conducting comprehensive preclinical and clinical studies to establish safety, efficacy, and long-term outcomes. The integration of MDDS into RA treatment protocols holds the potential to revolutionize disease management, offering a more patient-centric approach that enhances therapeutic outcomes while minimizing adverse effects. Continued innovation, collaboration among researchers, and investment in translational research are essential to unlock the full potential of MDDS. As research progresses, MDDS could pave the way for a new era in RA treatment, improving the lives of millions of patients worldwide.

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Author Contributions

M.K. conceptualized the study, supervised the research, and prepared the manuscript draft. **S.A.** contributed to the literature review and critical revision of the manuscript. **S.G.** assisted in data collection, formatting, and technical editing.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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