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NANOSTRUCTURED LIPID CARRIER–BASED TOPICAL GEL OF IGURATIMOD FOR THE MANAGEMENT OF RHEUMATOID ARTHRITIS: FORMULATION STRATEGIES, EVALUATION AND THERAPEUTIC PERSPECTIVES

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ABSTRACT

Rheumatoid arthritis (RA) is a long-term autoimmune disease that causes swelling in the joints, breaks down cartilage, and slowly destroys bone, leading to joint damage and trouble moving. The main treatment for RA is drugs called DMARDs, and Iguratimod is one of these that works by reducing inflammation and controlling the immune system. But taking Iguratimod by mouth for a long time can cause side effects and some people don't take it as they should. Using a cream or ointment with the drug could help treat the affected joints directly while keeping the medicine out of the rest of the body. However, Iguratimod doesn't mix well with water and doesn't easily pass through the skin, making it hard to use this way. Nanostructured lipid carriers (NLCs) are advanced nanocarriers made from lipids. They have shown great promise in improving how well drugs dissolve, stay stable, and get through the skin. When NLCs are added to topical gels, they help the drug stay on the skin longer, release slowly, and be more comfortable for patients. This review covers the disease process of rheumatoid arthritis, how the drug Iguratimod works, the problems with older treatments, and why using Iguratimod in NLC-based gels could be a better option. It also looks at how these gels are made, how they're tested, the challenges involved, and what might come next.

KEYWORDS: Rheumatoid arthritis, Iguratimod, Nanostructured lipid carriers, Topical gel, Transdermal delivery, DMARDs.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-term autoimmune disease that mainly affects the joints, causing ongoing inflammation, pain, and stiffness. Over time, it can lead to damage in the joints and make movement difficult. RA affects about 0.5 to 1 percent of people worldwide, and women are more likely to develop it than men. The constant inflammation causes the lining of the joints to thicken, which can lead to the breakdown of cartilage and bone, eventually causing joint deformities and loss of function.[1]

The treatment of rheumatoid arthritis (RA) involves several types of medicines, including NSAIDs, corticosteroids, traditional DMARDs, biologic DMARDs, and targeted synthetic DMARDs.[2] Iguratimod is a newer traditional DMARD that has drawn interest because it helps reduce inflammation and control the immune system. Still, taking it by mouth for a long time can cause stomach problems, liver damage, and other side effects.[3] This means there's a need for better ways to deliver the drug. Using medicine on the skin can help treat the affected joints directly and lower the amount of medicine in the body. But the outer layer of the skin blocks most drugs from getting through.[4] New developments in nanotechnology, especially using nanostructured lipid carriers (NLCs), have shown good results in solving this problem. Topical drug delivery systems can deliver medicine directly to inflamed joints and lower the amount of drug in the rest of the body. But the outer layer of the skin, called the stratum corneum, makes it hard for drugs to get through. New developments in nanotechnology, especially nanostructured lipid carriers (NLCs), have shown potential to help drugs pass through this barrier more easily.[5]

PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) happens when the body's immune system attacks the joints. This process involves different types of immune cells, chemicals that cause inflammation, and proteins that control cell activity. These parts work together to cause long-term swelling in the joint lining and damage to the cartilage and bone.[6] The disease starts and keeps going because both the body's first-line immune response and its more specific immune system become active. Activated T cells, B cells, macrophages, and cells in the joint lining move into the joint and form a layer of tissue that eats away at the joint over time.[7] B cells help in a few ways—not just by making antibodies like rheumatoid factor and anti-citrullinated protein

antibodies, but also by helping other cells recognize threats and releasing signals that increase inflammation.[7]

These immune and stromal cells release a mix of inflammatory signals, like tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-17 (IL-17), and granulocyte-macrophage colony-stimulating factor (GM-CSF). These signals make the nflammation worse and help bring more immune cells to the area, leading to swelling and damage in the joints. TNF-α and IL-6 are especially important in keeping the inflammation going and are key targets for treating rheumatoid arthritis.[8]

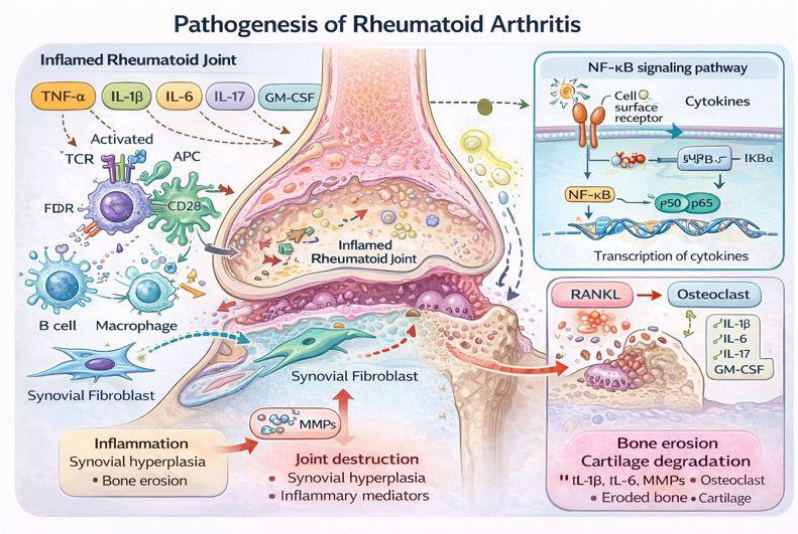

Figure 1: Pathophysiology of rheumatoid arthritis.

IGURATIMOD AS A DISEASE-MODIFYING ANTIRHEUMATIC DRUG

Pharmacological Profile

Iguratimod is a type of drug used to treat rheumatoid arthritis, approved in several Asian countries. Unlike NSAIDs, it helps slow down the disease by controlling the immune system.[9]

Mechanism of Action

Iguratimod works by affecting the immune system and reducing inflammation. It lowers the levels of certain harmful proteins, like TNF-α, IL-1β, IL-6, and IL-17, which are involved in causing and worsening long-term inflammatory and autoimmune diseases.[10] Iguratimod not only stops the body from making too many cytokines but also stops B cells from producing antibodies, which helps lower the amount of harmful autoantibodies. It also changes how T cells develop, helping the immune system get back to a normal balance. One main way it

works is by blocking a protein called NF-κB, which reduces the production of substances that cause inflammation. In addition to its effects on the immune system, Iguratimod also helps protect bones. This is important in diseases where bones can break down. The drug stops bone-eating cells from growing and working, which limits bone loss. At the same time, it helps bone-forming cells work better, which keeps bones strong and healthy.[11]

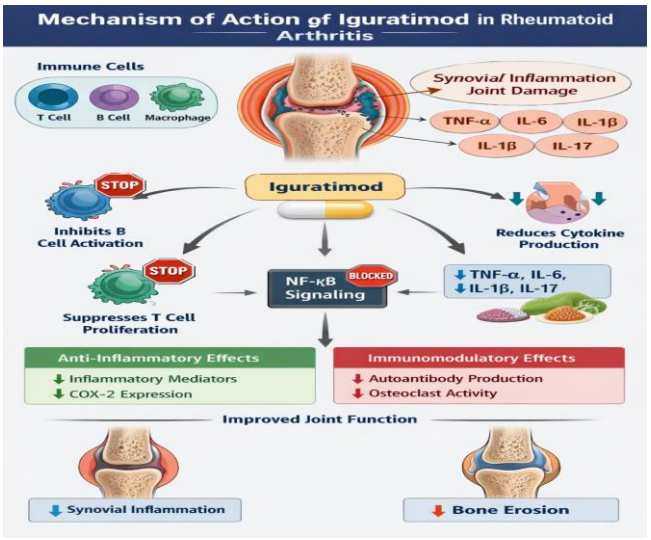

Figure 2: Mechanism of action of Iguratimod in rheumatoid arthritis.

LIMITATIONS OF ORAL IGURATIMOD THERAPY

Taking Iguratimod by mouth can cause a number of stomach-related side effects, like irritation and discomfort, and it can also harm the liver. These issues may make it hard for patients to keep taking the drug long-term and could affect how safe it is.[12] Along with these local effects, some people also have more widespread reactions, which show how tough it is to use the drug over time.[13] From a pharmacokinetic point of view, Iguratimod doesn't dissolve well in water, which means it doesn't mix well with the fluids in the stomach and intestines. This leads to poor absorption after being taken by mouth. Also, a lot of the drug gets broken down by the liver before it reaches the bloodstream, which lowers how much of the drug actually works in the body. This results in inconsistent levels of the drug in the blood.[14] All these problems make the drug less effective and show the need for better ways to deliver it.

RESEARCH GAP AND SCIENTIFIC RATIONALE

Rheumatoid arthritis (RA) is a long-term condition where the immune system attacks the joints, causing swelling, pain, and joint damage. While medicines called DMARDs are still the main treatment for RA, using them for a long time can cause side effects like liver

problems, stomach issues, and a weakened immune system. Most of the treatments applied directly to the skin for RA are based on NSAIDs, which help with pain but don't stop the disease from getting worse. Iguratimod is a type of DMARD that helps control the immune system and reduce inflammation. It also protects bones by stopping certain harmful proteins and preventing cells that break down bone from working too much. However, its use is mainly limited to oral form.[15] Even though a lot of research has been done on nanostructured lipid carriers (NLCs) for delivering NSAIDs and corticosteroids through the skin, there's still very little known about using them for DMARDs, especially Iguratimod. So far, there's no approved topical treatment based on DMARDs for rheumatoid arthritis. This shows a big missing piece in the research, pointing to the need for better local treatments that can help manage the disease without causing too much harm to the rest of the body.[16]

TOPICAL DRUG DELIVERY IN RHEUMATOID ARTHRITIS

Topical drug delivery systems offer several benefits, especially when treating conditions that affect a specific part of the body. They can deliver medicine directly to the affected area, giving more of the drug where it's needed and less to the rest of the body. This helps reduce side effects and makes treatment safer, especially for medicines used over a long time. Also, because these treatments are easy to apply and don't require injections or pills, people often find them more comfortable and are more likely to use them as directed.[17] Even though there are benefits, getting drugs to work properly through the skin is still hard. The outer layer of the skin, called the stratum corneum, acts like a strong shield that stops most medicines from getting through. This makes it tough for drugs to reach deeper parts of the skin or tissues below. It's especially hard for certain types of molecules. Because of this, regular treatments like creams and gels usually don't deliver enough medicine where it needs to go, which can make them less effective. That's why new ways to deliver drugs are needed.[18]

Table 1: Comparison of NSAID- and DMARD-Based Topical Gels.

Parameter	***NSAID-Based Topical Gels***	***DMARD-Based Topical Gels (Proposed)***
Therapeutic goal	Symptomatic relief	Disease modification
Primary mechanism	COX inhibition	Immunomodulation, cytokine suppression
Effect on disease progression	No	Potentially yes
Systemic exposure	Reduced but present	Minimal
Long-term suitability	Limited	Improved
Examples	Diclofenac, Aceclofenac	Iguratimod (proposed)

NANOSTRUCTURED LIPID CARRIERS (NLCs)

Nanostructured lipid carriers, or NLCs, are a type of second-generation nanocarrier made from a mix of solid and liquid lipids, along with stabilizing agents like surfactants.[10,11] This special mix creates a less organized structure inside, which helps fix some of the problems seen in earlier lipid-based nanoparticles. Compared to solid lipid nanoparticles, NLCs can hold more drug because their lipid core has small imperfections that let more drug molecules fit in. They're also more stable, so the drug is less likely to come out during storage. The way the lipids are arranged also helps release the drug slowly over time, making treatment more effective and keeping the drug at the right place longer.[18]

Benefits of NLCs Nanostructured lipid carriers have several advantages that make them good for applying medicine to the skin. They help dissolve drugs that don't mix well with water and improve how much drug can be packed into the formulation, leading to better performance. Their small size and oil-based makeup help the drug get through the outer layer of the skin and into deeper layers. NLCs also release the drug slowly over time, keeping the right amount of medicine in the skin for longer and reducing how often it needs to be applied. Because they use safe, body-friendly ingredients, they are gentle on the skin and safe for long-term use.[19]

NLC-BASED TOPICAL GEL FORMULATIONS

Adding NLC dispersions to gels helps make them thicker, easier to spread, and longer-lasting on the skin. Common ingredients like Carbopol and HPMC are used to make these gels. These kinds of gels help medicines get into the skin better and are more comfortable for people to use.[20]

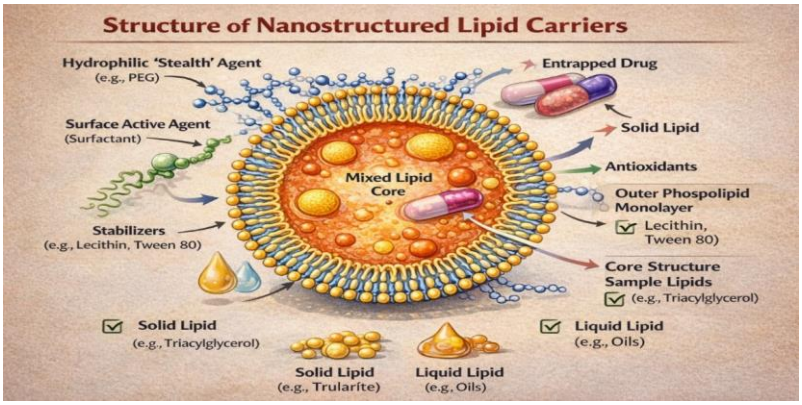

Figure 3: Structure of nanostructured lipid carriers.

FORMULATION STRATEGIES FOR IGURATIMOD-LOADED NLC GEL

Iguratimod-loaded NLCs are usually made using a hot homogenization process followed by ultrasonication. This is a common way to create stable lipid particles that are small and even in size. In this method, the drug is mixed into a melted fat, then broken up into tiny droplets in a water-based solution with the help of strong mixing. The ultrasonication step makes the particles even smaller.

Choosing the right solid and liquid lipids, along with surfactants and co-surfactants, is key to shaping the properties of NLCs, like how big the particles are, how uniform they are, how stable they stay, and how much drug they can hold. Using the right mix of these ingredients helps get the drug inside the particles and keeps the formula stable over time. After making the NLCs, the best version is usually mixed into a gel that's easy to apply on the skin. The final product is adjusted to match the skin's natural pH, which makes it gentle, comfortable, and more effective for treatment.[21]

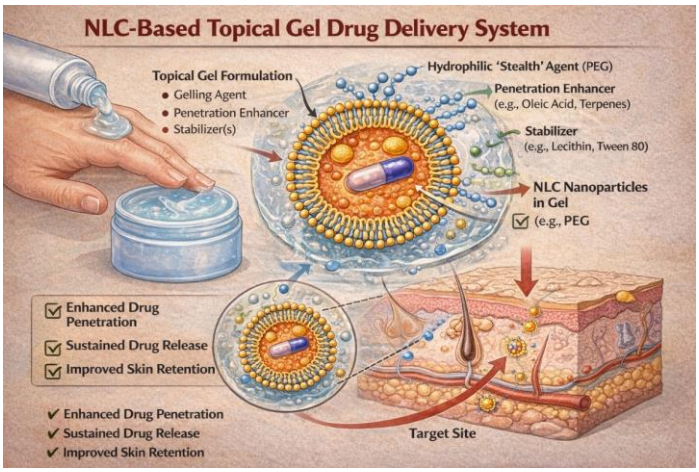

Figure 4: NLC-based topical gel drug delivery system.

CHARACTERIZATION AND EVALUATION PARAMETERS

Iguratimod-loaded nanostructured lipid carrier (NLC) gels are tested for various physical and chemical properties to make sure the formulation is good quality, stable, and works well as a treatment. Important tests include checking the size of the particles, how uniform they are, and their electrical charge. These tests help show how evenly the nanoparticles are spread out and how stable they are. The amount of drug that's trapped inside the lipid part of the gel is also checked to see how well the drug is incorporated. The gel's suitability for use on the skin is also tested by looking at its pH, thickness, and how easily it spreads, which are important for how well it works on the skin, how easy it is to apply, and how much patients like it [22] To

check how well the formulation works and how effective it could be as a treatment, researchers do lab tests to see how quickly Iguratimod is released from the NLC gel. They also test how well the drug moves through skin layers using real tissue samples. Then, they test the formulation in living animals to see if it helps with arthritis and link the results from the lab tests to what happens in real life.[23]

RECENT ADVANCES AND FUTURE PERSPECTIVES

Recent studies on nanostructured lipid carrier (NLC) gels for anti-inflammatory drugs like aceclofenac and diclofenac show better skin absorption, longer-lasting effects, and better results than older topical treatments. This suggests that NLC systems can help fix some of the problems with getting drugs through the skin and make local treatment more effective. Using an advanced delivery method for Iguratimod could be a good way to treat rheumatoid arthritis. It might help the drug get through the skin better, work more effectively, and reduce side effects that happen when taking medicine by mouth. But to make sure this works in real life, more testing is needed. Studies must show it's safe, effective, and can be used in patients.[24]

STUDIES SHOW NLC GELS WORK WELL FOR INFLAMMATION

Research shows that gels made with NLC technology can help treat inflammation. Gels with aceclofenac or diclofenac have been found to work better than regular gels. They let the medicine stay in the skin longer, release it slowly, and reduce inflammation more effectively.

Studies have shown that using NLC-based versions of ibuprofen, ketoprofen, and flurbiprofen lead to similar results, showing that lipid nanocarriers work well for topical anti-inflammatory treatments. While most of these studies look at NSAIDs, they show that NLC technology could also work for DMARDs. This is especially useful for long-term conditions like rheumatoid arthritis, where you want to reduce how much medicine gets into the bloodstream.[25]

REGULATORY AND CLINICAL CONSIDERATIONS

Topical NLC systems made with ingredients that are generally recognized as safe, like certain lipids and surfactants, are usually acceptable if they meet quality, stability, and safety standards. But for Iguratimod-loaded NLC gels to be used in patients, there need to be thorough studies on skin irritation, allergic reactions, and long-term safety, plus tests that link lab results to real-world effects. It’s also important to follow guidelines from ICH, CDSCO,

and other standards for skin products before moving forward with clinical use. Since there's little data on topical DMARDs, carefully planned trials that look at how well the treatment works, how safe it is, and what patients feel are needed for approval and use in practice.[26]

CONCLUSION

Iguratimod-loaded **nanostructured lipid carrier (NLC)–based topical gel formulations** represent a promising and innovative alternative to conventional oral therapy for the management of **rheumatoid arthritis (RA)**. By enabling **targeted and localized drug delivery**, this approach has the potential to achieve effective therapeutic concentrations at the site of inflammation while significantly **reducing systemic exposure and associated adverse effects**. Furthermore, the non-invasive nature and ease of topical application may contribute to **improved patient compliance**, particularly in long-term RA treatment.

With continued formulation optimization, comprehensive preclinical evaluation, and rigorous clinical validation, Iguratimod-loaded NLC-based topical systems may emerge as a **novel and clinically viable therapeutic strategy** for the effective and safer management of rheumatoid arthritis.[27]

CONFLICT OF INTEREST

The authors declare there were no conflict of interest.

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