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"Cubosomes For Rheumatoid Arthritis: Enhancing Anti-Inflammatory Drug Delivery"

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Abstract:

Inflammation is a type of defence mechanism employed by the immune system that hinders infection advancement and supports the effective elimination of a variety of external invasions. Self-assembled nanostructures, particularly cubosomes are gaining increased utility and popularity as a medication transport mechanism under circumstances like arthritis. These cubosomes serve as highly adaptable carriers with encouraging theranostic capabilities and can be delivered through oral, topical, intravenous, ocular, and transdermal routes. Recently valuable research has contributed to enhancing the effectiveness, analysis, target specificity, and regulation of drug release profiles for delivery of anti-inflammatory bioactive. However, the clinical transition has been sluggish and also necessitates substantial display. This review highlights the late developments with challenges in the progress as well as appeal of cubosomes in case of different inflammatory pathways on rheumatoid arthritis while also addressing the obstacles encountered in transforming it into a viable nanotechnological solution.

Keywords: Target specificity, Nanotechnology, Bioactives, Inflammatory pathways.

INTRODUCTION

Rheumatoid arthritis (RA) is an enduring aggravating autoimmune state that mostly affects the joints resulting in synovial inflammation, cartilage damage, and bone deterio- ration. The precise cause is not fully understood, but genetic, environmental, and immu- nological factors influence the advancement of the disease. The condition is marked by pain, swelling, stiffness, and increasing disability. Rheumatoid arthritis is linked to numerous comorbidities such as pulmonary disease and rheumatoid nodules and can negatively affect quality of life. Current treatments for RA include conventional, small molecule, and biological medications. However, these treatments often have limited effectiveness because of poor absorption, fast metabolism, and side effects like toxic- it and safety issues. To overcome these problems, new drug delivery systems are being researched.

The inflammation consists of sequence of events that can be triggered by various stim- uli including disease-causing agent, free radical damage, ischemia, and antigen-antibody interactions [3]. Thus, inflammation represents the body's reaction to tissue injury. The inflammatory processes are usually triggered within minutes or hours, and during the acute phase, the body works to return the damaged and inflamed tissue to its normal function. Conversely, unlimited or chronic inflammation can lead to conditions linked to persistent inflammation, like rheumatoid arthritis as well as cardiovascular disease, which are typically characterized by a slow onset and extended progression over time.

The FDA has authorized pharmaceuticals known as pain relievers. They can be applied to lessen pain, inflammation, also fever. One of the examples of NSAID is aspirin which is useful for soreness, period pain, degenerative joint disease, fever, gouty arthri- tis, and severe headache. In positive post-traumatic stress disorder, they are also used as opioid-sparing medications.

NSAID FUNCTIONS

NSAIDs relieve pain and inflammation by inhibiting the cyclooxygenase (COX) enzymes, which convert arachidonic acid into eicosanoids—compounds like prostaglan- dins and thromboxanes that mediate pain, fever, vasodilation, and platelet function. There are two COX isoenzymes: COX-1, which supports normal physiological func- tions such as gastric mucosal protection and renal blood flow; and COX-2, which is induced during inflammatory responses [8]. While most NSAIDs non-selectively inhibit both COX-1 and COX-2, this inhibition can lead to side effects like gastric irritation, though NSAIDs aim to reduce inflammation while preserving essential protective func- tions. They are typically administered orally, and recommended dosages are provided in Table 1.

Advanced cubosomal formulations: revolutionizing anti-inflammatory treatments Cubosomes can serve for the transport of anti-inflammatory medications to inflamed areas. The unique internal structure of cubosomes allows for sustained release of the medication, which can decrease the frequency of administration and enhance patient adherence.

Table 1 NSAIDs taxonomy [5, 6]

Classification	Drug Name	Common Brand Names	Maximum OTC dose	Primary uses
Salicylates	Aspirin	Bayer, Ecotrin	4000 mg/day (325–650 mg every 4–6 h)	Pain, fever, inflamma- tion, blood thinner
Propionic Acid Derivatives	Ibuprofen	Advil, Motrin, Brufen	1200 mg/day (200–400 mg every 4–6 h)	Pain, fever, inflammation
	Naproxen	Aleve, Naprosyn	660 mg/day (220 mg every 8–12 h)	Longer-lasting pain relief, arthritis
Acetic Acid Derivatives	Diclofenac	Voltaren, Voveran	75 mg/day (25–50 mg twice daily)	Arthritis, pain relief
Enolic Acid (Oxicams)	Piroxicam	Feldene, Dolonex	Rx only (not usually OTC	Chronic pain, arthritis
Fenamates	Mefenamic Acid	Ponstel, Meftal	1500 mg/day (500 mg every 8 h)	Menstrual pain, inflammation
Selective COX-2 Inhibitors	Celecoxib	Celebrex	Rx only	Arthritis, inflammation

MECHANISM OF CUBOSOMES FORMATION

Cellular membranes are complex assemblies of lipids and proteins. Non-lamellar phases demonstrating significant membrane curvature are considered to have crucial functions in fusion, fission, transport and membrane remodelling processes. Drug delivery systems are tools that transport a therapeutic agent to a specific site within the body. Controlled drug release is intentionally formulated to attain an efficient concentration, thereby reducing harmful side effects while improving therapeutic benefits.

A more sophisticated version of this, known as an Innovative Drug Delivery Systems (IDDS) is the current era in the drug release arena, mainly due to their capacity to tackle the curb of conventional drug delivery systems. IDDS has several distinct advantages, including less frequent dosage, improved site specificity, fewer toxic side effects, protection against degradation (particularly in the acidic gastrointestinal environment), and enhanced bio- availability. According to research, IDDS provide a promising strategy to treating serious disorders. Several carriers have been developed over the last decade, and new ones are emerging at a rapid pace.

EXPLORING DIFFERENT ROUTES OF CUBOSOMAL DELIVERY FOR ANTI-INFLAMMATORY EFFECTS

Oral administration is a commonly accepted method of drug delivery; however, its appli- cation is restricted because of the drug's physico-chemical characteristics, such as inade- quate solubility, low permeability, instability, and swift metabolism, all of which diminish oral bioavailability. This limitation remains a notable obstacle, presenting challenges for pharmaceutical producers in creating drug delivery systems that offer enhanced phar- macokinetic profiles and therapeutic outcomes. Cubosomes are used for numer- ous poorly soluble materials and large molecular-weight compounds via the oral route. There are few instances of employing cubosomes orally to enhance their characteris- tics, for example 20(S)- protopanaxadiol (PPD), an anticancer medication formulated as cubosomes, for improved oral absorption Table 2

Table 2 Nanocarriers in anti-inflammatory drug delivery [12–15, 17]

Feature	Cubosomes	Liposomes	Niosomes	Solid lipid nano particles(SLNS)
Structure	Bicontinuous cubic phase: lipid bilayers	Spherical vesicles with one or more lipid bilayers enclosing an aqueous core	Vesicular systems built with non- ionic surfactants, less rigid structure	Solid lipid core stabi- lized by surfactants, crystalline or amor- phous structure
Drug loading	Both hydrophilic and lipophilic drugs	Both hydrophilic (aque- ous core) and lipophilic (bilayer) drugs, moderate capacity	Similar to liposomes but lower loading stability	Primarily lipophilic drugs; limited for hydrophilic drugs
Stability	Thermodynamical ly stable	Prone to fusion or leak- age on storage	Sensitive to pH	Good stability prone to Polymorphic transitions
Targeting potential	Surface modification, active targeting	Easily modified for targeting	Possible surface modification	Ligand modification possible
Release profile	Sustained release and controlled release	Often faster release	Faster and less con- trolled release	Sustained release but risk of burst effect
Therapeutic outcomes	Enhanced bioavail- ability, site-specific delivery	Good for systemic and local delivery	Suitable for topical and transdermal delivery	Topical and systemic delivery; mainly lipo- philic drugs

The oral formulation of efavirenz (EFV) using a nano-structured lipid carrier is devel- oped to enhance bioavailability and ensure a prolonged release effect. In another study, the Tween-modified cubosomes (T-cubs) incorporated with piperine were administered orally for targeting the brain parenchyma. penetration, prolonging retention time, and providing controlled release at the ocular surface. Their nanostructured architecture and bioadhesive properties allow them to bypass ocular barriers and improve drug absorption, making them an effective platform for ocular drug delivery.

TRANSDERMAL DRUG DELIVERY

In the domain of drug delivery via the skin, the highly organized outer layer, known as the epidermal barrier, acts as a major impediment to the absorption of drugs that are applied topically. Nanoparticles, due to their distinctive architecture and properties, present a favour- able option for skin-based drug delivery. Considering the adhesive characteristics of nanoparticles in connection with the outer skin layer as influenced by glycerol mono- oleate, they can be efficiently used in topical and mucosal drug applications. Newley, there have been several advancements in dermatological nanoparticles. A significant dermatological application is vaccines administered through transcutaneous immunization. However, microneedles (MNs) and nanoparticles have been effectively used together for delivering vaccines through the skin, studies have shown that using MNs enhances the penetration of the aqueous peptide mixture through the skin layers, while nanoparticles formulated with peptides demonstrated prolonged retention in the skin.

TOPICAL DRUG DELIVERY

Cubosomes have emerged as a promising nanocarrier system for topical drug delivery, improving drug solubility by 30% and significantly enhancing skin penetration by 25% over conventional, regulated release, and thorough skin penetration [38]. These liquid crystalline nanoparticles offer a viable platform for delivering antimicrobial, antifun- gal, and anti-inflammatory agents to specific skin layers. Figure 1 Multiple studies have illustrated their promise in topical antimicrobial therapy, such as delivering LL-37 pep- tide for enhancing wound healing and miconazole nitrate-based cubosome hydrogels for addressing fungal infections. Moreover, cubosomes have been investigated for oph- thalmic drug delivery, such as beclomethasone dipropionate, ensuring prolonged drug release and greater ocular bioavailability. Additional applications encompass ketocon- azole-loaded cubosomes for addressing fungal skin infections, erythromycin cubosomes for treating acne, and clotrimazole cubosomal formulations for wide-ranging antifungal efficacy. The distinctive structure of cubosomes, made up of bicontinuous lipid-water domains, facilitates the incorporation of both hydrophilic and lipophilic drugs, thereby increasing therapeutic effectiveness. In addition, ex vivo and in vitro studies, such as epidermis skin irritation tests and pig skin wound infection models, validate their bio- compatibility and efficiency in treating dermatological ailments. With their capability to enhance drug stability, penetration, and retention in the skin, Table 3 cubosomes signify a groundbreaking and effective strategy for topical and ocular drug delivery systems.

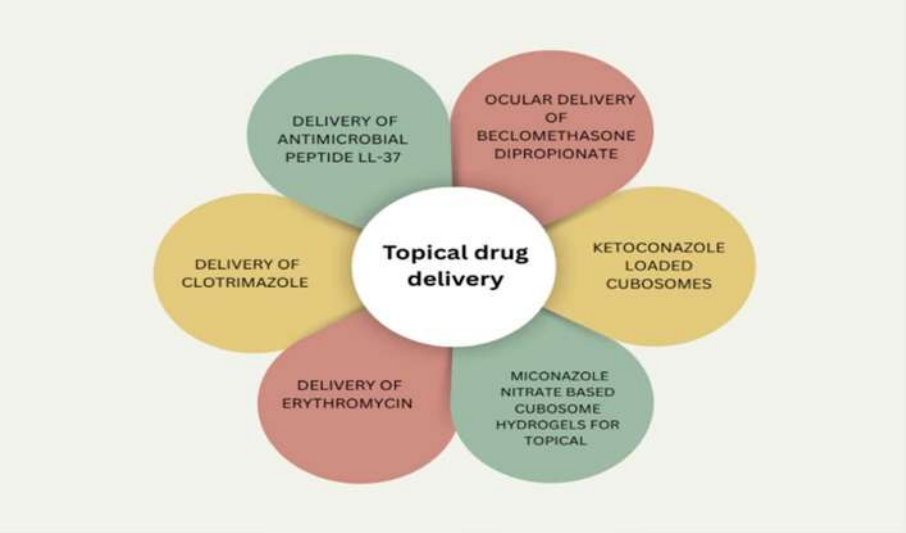

Fig. 1 Cubosome based topical drug delivery system

Table 3 Comparative analysis of cubosomal delivery routes

Delivery route	Benefits	Limitations	Refer-ence
Oral	**Enhances bioavailability;**	**Low permeability for some drugs; first- pass metabolism may limit certain APIs.**	**[13]**
Ocular	**Improved precorneal retention;**	**May cause blurred vision or discomfort; challenges in crossing corneal barriers.**	**[17, 19]**
Intranasal	**Bypasses first-pass metabolism; direct brain targeting via olfactory pathway; rapid onset**	**Limited drug loading; potential irritation to nasal mucosa.**	**[11, 25]**
Transdermal	**Sustained drug release**	**Skin irritation**	**[13, 17]**
Topical	**Localized effect; improved solubility and penetration of antimicrobial/anti-inflammatory drugs**	**May require permeation enhancers.**	**[13, 17]**

A variety of cubosomal delivery routes—oral, ocular, intranasal, transdermal, and topical—have been explored for anti-inflammatory effects, each with unique benefits and limitations. animal model 3 summarizes these routes, highlighting key advantages, drawbacks, and supporting studies to guide future research and clinical translation.

Fig. 2 Common DMARDs used in rheumatoid arthritis therapy

Conclusion

Through a comprehensive review of various drug delivery routes of cubosomes, can improve the anti-inflammatory effect on rheumatoid arthritis, and improves cancer therapy can improve the drug performance. A complete understanding of cubosomes can lead to the combination of drug delivery like cubosomes with microneedles, ulti- mately improving the therapeutic effect and patient compliance. Early detection of rheumatoid arthritis and access to advanced therapies still pose significant challenges. Although cubosomes offer novel drug delivery solutions, their incorporation into con- ventional clinical practice requires additional research, regulatory endorsement, and economical manufacturing procedures to guarantee their widespread accessibility. In conclusion, cubosomes signify a promising route for enhancing drug delivery and treatment efficacy in RA, with studies showing 1.5–2 times increased bioavailability and significantly improved anti-inflammatory effects. Continued research is directed towards overcoming existing challenges and completely actualizing their potential to enhance patient outcomes.

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