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A Review on Novel Drug Delivery Systems in the Treatment of Osteoarthritis

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ABSTRACT: Osteoarthritis (OA) is a degenerative joint disorder marked by cartilage degradation, pain, and inflammation, leading to reduced mobility and quality of life. Conventional treatments such as NSAIDs and corticosteroids often provide limited relief due to poor bioavailability and systemic side effects. Recent advances in novel drug delivery systems offer promising alternatives to overcome these challenges. Techniques including nanoparticles, liposomes, hydrogels, microneedles, and intra-articular formulations enable targeted and sustained drug release directly at the affected site, enhancing therapeutic efficacy while minimizing adverse effects. These systems improve drug stability, prolong residence time, and ensure controlled delivery of anti-inflammatory and disease-modifying agents. Among them, nanoparticle- and hydrogel-based systems have shown remarkable potential in preclinical studies. Overall, integrating such innovative delivery technologies could revolutionize osteoarthritis management by improving treatment outcomes, reducing dosing frequency, and enhancing patient compliance.

KEYWORDS: Novel drug delivery system, Osteoarthritis, Gene drug delivery, Liposomes, Nanoparticles

I. INTRODUCTION

The degeneration of articular cartilage, inflammation of the synovial membrane, and structural alterations in the subchondral bone are the hallmarks of osteoarthritis (OA), a chronic degenerative joint disease. The majority of people affected by this ailment are middle-aged and older, and it severely lowers their quality of life and functioning capacities. The frequency and burden of OA are increasing due to the world's aging population, which presents difficulties for both people and public health systems. Numerous intricate processes, such as oxidative stress, subchondral bone changes, inflammatory reactions, and cartilage degradation, are involved in the pathophysiology of OA. One important characteristic is the gradual loss of cartilage, which is caused by ADAMTS family enzymes and matrix metalloproteinases (MMPs), especially MMP-13 and ADAMTS-5.[1,2]

Pro-inflammatory mediators like interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) stimulate MMP and ADAMTS expression via the NF-κB and MAPK signaling pathways, further exacerbating cartilage degradation. Chronic inflammation of the synovial membrane is central to the progression of OA. Reactive oxygen species (ROS) overproduction also has a negative impact on mitochondrial function and initiates inflammatory pathways by speeding up chondrocyte death and matrix disintegration. Atypical mechanical loads and inflammatory agents alter bone remodeling processes, aggravating joint diseases. OA also causes subchondral bone calcification, osteophyte formation, and joint space reduction.[3]

The Drug Delivery System (DDS) has improved drug stability, targeting effectiveness and sustained release capabilities, leading to significant progress in the treatment of OA. Novel drug delivery systems (NDDSs) have been shown in recent studies to be able to handle the problems of rapid drug clearance and poor targeting that are linked to traditional treatment methods.[4]

II. BASIC UNDERSTANDING OF VARIOUS NDDS

Polymer Microspheres

Spherical particles having a diameter of one micrometer are known as microspheres, and they are especially useful in drug delivery applications. These tiny spheres, which are usually between 1 and 250 µm in size, are formulated by mixing the drug in polymeric materials. Physical embedding or surface adsorption is used to load drugs into microspheres; the durability of the polymer matrix permits a regulated and prolonged release. Furthermore, these particles can selectively attach to particular receptors on target cells or tissues by adding targeting ligands, such as antibodies, receptors, or glycosyl groups, onto the microsphere surfaces. This makes active targeting in therapeutic applications possible.[5]

Hydrogel

A hydrogel, which is made up of water-soluble polymers that form a cross-linked network with both hydrophilic and hydrophobic components, is a gel in which water acts as the dispersing medium. While hydrophobic residues swell in water to facilitate cross-linking, hydrophilic residues bond with water molecules. Through surface changes and targeted ligands, hydrogels can be customized for targeted drug administration, bioactive molecule localization, and therapeutic agent transport to certain tissues or cells. This focused strategy lessens harm to healthy tissues while increasing treatment efficacy.[6]

Nanoparticles

Solid colloidal formations with sizes ranging from 1 to 1000 nanometers are called nanoparticles. They can produce drug-loaded nanoparticles by encasing medicinal substances in polymeric matrices or containing them in solution. These nanoparticles' surfaces can be altered by adding particular ligands or antibodies that identify and attach to target cell receptors. The localized concentration of therapeutic drugs at particular places is improved by this targeted interaction, which increases the uptake of nanoparticles by targeted cells.[7]

Liposome

Liposomes are spherical vesicles that range in size from 1 nm to 10 µm and are formed from lipid bilayers composed primarily of natural lipid molecules, such as cholesterol and phospholipids. They can accommodate lipophilic pharmaceuticals within the lipid bilayer and encapsulate hydrophilic medications in their internal watery environment. Targeted delivery is improved by developments in liposome administration methods, delivery locations, and particle size customization. Furthermore, because of their affinity for particular target cells, the addition of particular recognition molecules to liposomal structures enables selective targeting.[8]

Bionic Delivery Materials

Utilizing natural biomaterials to produce nanoscale carriers for targeted medication administration through the body's natural routes, bionic delivery materials represent a novel advancement in drug delivery systems.[9]The main focus is on cell membrane bionic delivery systems that are mostly made from mammalian cells, such as extracellular vesicles, red blood cells, platelets, white blood cells, and immune cells. To improve medication delivery precision, these methods take advantage of these cells' inherent abilities to evade immune responses and achieve homologous targeting.Red blood cell membrane-based biomimetic nanocarriers, for instance, can prolong the duration of a drug's circulation within the body.[10]

III. NDDS IN OSTEOARTHRITIS

The use of NDDSs for the intra-articular (IA) way of delivering several medication classes for osteoarthritis will be covered in this part.

(i) Polymer Microsphere Delivery System

Polymer microsphere delivery systems aid in drug administration, primarily used in osteoarthritis treatment for NSAIDs, glucocorticoids, anti-inflammatory cytokines, antioxidants and gene therapy advancements.

NSAIDs

NSAIDs are commonly used in managing arthritis, but they can cause side effects like gastrointestinal discomfort. Polymer microsphere systems can help mitigate these side effects. A study by Yurtdaş-Kırımlıoğlu et al. developed a polyphosphazene-based ibuprofen microsphere system, which showed improved analgesic and anti-inflammatory effects.[11] Another study used chitosan microspheres for diclofenac sodium delivery, showing superior anti-inflammatory properties. These findings could lead to new intra-articular drug delivery systems.

Delivery of Anti-Inflammatory Cytokines

In chondrocytes, anti-inflammatory cytokines such as IL-4, IL-10, and IL-13 can reduce inflammation and encourage protective metabolic responses. They prevent chondrocyte death, proteoglycan breakdown, and matrix metalloproteinases. Effective therapeutic doses can be complicated by the quick metabolic breakdown of traditional cytokine injections. Park et al. created bioresponsive microspheres, which provide a cytokine release mechanism that is sustained.[12] These microspheres cross-link anti-inflammatory cytokines using a gelatin solution in an oil-in-water emulsion, extending their half-life and lowering clearance during periods of decreased disease activity. Co-culturing these microspheres with arthritic chondrocytes can lower inflammation by as much as 80%. This on-demand administration method may help repair wounds and stop inflammation-induced cartilage degradation.[13]

(ii) Hydrogel Delivery Systems

Research on the use of hydrogels to treat osteoarthritis has mostly focused on developing anti-inflammatory drugs, antioxidants, gene treatments, stem cell applications, and multipurpose delivery systems. Significant advancements in this area over the last five years are described in the section that follows.[14]

Anti-Inflammatory Drugs

In order to reduce the systemic toxicity of traditional anti-inflammatory medications, hydrogel delivery devices have been developed. In order to protect articular cartilage, Wang et al. developed a single-component hydrogel made of polycitric acid ester that scavenges reactive oxygen species (ROS), alters the inflammatory milieu, and lowers MMP-13 expression.[15]

Antioxidants

Hydrogels have been created by researchers to lessen oxidative stress in OA, a disorder that damages chondrocytes and synovial cells. Chitosan nanoparticles, hydroxytyrosol, and a thermosensitive hydrogel are combined in an injectable system, and chondrocytes are shielded from inflammatory damage by a dynamically cross-linked hydrogel.[16]

Gene Drugs

Small interfering RNA and microRNA can suppress pro-inflammatory genes in joint cavities, reducing inflammation. Hydrogels enhance gene drug stability, as demonstrated by Yu et al.’s hydrogel delivery of genetically modified stem cells and Garcia et al.’s encapsulation of anti-ADAMTS5 gapmers, reducing joint degeneration and enhancing anti-inflammatory effects.[17]

(iii) Liposome Delivery System

Liposome administration methods have been increasingly popular in the treatment of OA in recent years. In addition to the development of multifunctional liposomes, these systems mainly aid in the delivery of antioxidants, gene treatments, and anti-inflammatory drugs.[18]

Anti-Inflammatory Drugs

Anti-inflammatory drugs such as NSAIDs and glucocorticoids are frequently used to treat osteoarthritis (OA), which is largely caused by low-grade inflammation. These drugs do, however, have serious systemic adverse effects. Systems for delivering liposomes can lessen these adverse effects while guaranteeing sustained release in the joint cavity. [19]To extend medication retention duration, exhibit low cytotoxicity, and shield miRNA from degradation, researchers have employed cationic liposomes loaded with clonixin and microRNA-140. In a rat model of OA, this has resulted in a notable decrease in synovial inflammation. Polyethylene glycol has also been added to liposomes to improve medication efficacy at the OA site.[20]

Antioxidant Delivery

One of the main causes of osteoarthritis is oxidative stress, which damages chondrocyte and synovial cells. ROS levels in the joint cavity can be reduced by antioxidants such as glycyrrhizin and astaxanthin. It was discovered that a liposomal formulation containing astaxanthin reduced inflammation and tissue damage by removing excess ROS and NO. [21]Additionally, this work demonstrated that liposomal nanoparticles can aid in cartilage tissue healing, offering fresh perspectives on the function of astaxanthin in OA.[22]

Cytokine Delivery

The development of articular cartilage, maintenance of homeostasis, and cartilage repair all depend on transforming growth factor beta (TGF-β). Stable cytokine concentrations are challenging to maintain with traditional injection techniques due to their short half-life and proteolytic breakdown. Continuous release provided by liposome delivery systems enables extended administration and efficient therapeutic doses.

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TGF-β1 encapsulation in liposomes also increases the stability of anti-inflammatory cytokines and extends the duration of therapeutic drug retention. However, for physiological effects and sustained release, substantial dosages are usually needed.[23]

(iv) Biomimetic Delivery Systems

Exosome Biomimetic Delivery System

In the exosome biomimetic delivery system, therapeutic drugs are packaged in exosomes, which are tiny vesicles that transport a variety of biomolecules such as proteins, lipids, mRNA, and miRNA. These vesicles can be precisely delivered to inflammatory cells in the joint cavity because of their inherent targeting capabilities and biocompatibility. Studies have demonstrated that modifying exosomes to transport microRNA-140 to chondrocytes can reduce inflammation and cartilage deterioration, hence delaying the onset of osteoarthritis. By modifying the miR-3473b/PTEN pathway, exosomes derived from bone marrow mesenchymal stem cells primed with decellularized extracellular matrix can aid in the healing of OA cartilage.[24]Furthermore, by preserving equilibrium between chondrocyte ECM synthesis and degradation, exosomes produced from embryonic mesenchymal stem cells promote joint tissue and slow the course of OA. Exosome-based NDDS dominates patent submissions in spite of regulatory obstacles and standardization issues.[25]

IV. CHANLLENGES FACED

Variability in Efficacy

Different patients have different pathogenic causes for osteoarthritis, which results in different medication responses. The flow of synovial fluid or biological barriers may make nanoparticles less effective in some situations than others. The distribution of drug delivery is also impacted by the severity of synovitis.[26]

Biocompatibility

Innovative drug delivery systems, like liposomes and nanoparticles, have shown effectiveness in preclinical animal models but face challenges in biocompatibility and safety. These systems may trigger inflammatory responses or cause toxic reactions, and may pose chronic inflammation risks.[27]

Dosage vs. Efficacy

With worries about preserving efficient medication concentrations while avoiding harmful side effects from higher drug levels, dose optimization in novel drug delivery systems continues to be a controversial topic.[28]

Clinical to Commercial

Although novel medication delivery methods are effective in the lab, it is difficult and costly to apply these results in clinical settings. The production of biomimetic materials and gene therapy vectors necessitates strict quality control and purification, which makes large-scale deployment difficult. Numerous systems don't meet industry standards, which raises manufacturing costs and causes problems with regulations. Drug approval is made more difficult by long-term safety evidence from clinical studies.[29]

V. CONCLUSION

Because of their focused distribution, prolonged release, and biocompatibility, innovative drug delivery systems hold tremendous promise for the management of obstructive pulmonary disease (OA). It is anticipated that these systems will integrate growth factors, gene treatments, antioxidants, and stem cells with an emphasis on intelligence, multifunctionality, and customisation. Biocompatibility, preparation techniques, medication release control, and the accumulation of clinical evidence are obstacles, nevertheless. Future studies should concentrate on streamlining preparation methods, improving material qualities, and using clinical trials to confirm long-term safety and effectiveness. CRISPR-loaded exosomes and 4D-printed stimuli-responsive scaffolds are examples of next-generation drug delivery methods that represent new frontiers. These systems may provide OA patients with safer and more effective treatment alternatives and accomplish full translational application in clinical practice with further technology advancements and interdisciplinary cooperation.

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