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OVERVIEW OF TOPICAL DRUG DELIVERY IN ARTHRITIS

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ABSTRACT

Inflammatory diseases such as rheumatoid arthritis, osteoarthritis, tendinitis, and gout remain a global health concern, requiring effective and safer therapeutic strategies. Non-steroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen are widely used for pain and inflammation management due to their potent inhibition of COX-1 and COX-2 enzymes, thereby reducing prostaglandin synthesis. However, oral administration of flurbiprofen is often limited by gastrointestinal, cardiovascular, and renal adverse effects resulting from systemic exposure and first-pass metabolism. To overcome these drawbacks, topical drug delivery has emerged as a promising alternative that enables site-specific delivery, minimizes systemic toxicity, and enhances patient compliance. Despite its advantages, the major challenge in topical flurbiprofen delivery is its limited skin permeability due to poor aqueous solubility and moderate lipophilicity. Recent advancements in nanocarrier-based systems such as nano emulsions, liposomes, glycerosomes, ufasomes, and nanostructured lipid carriers (NLCs) have significantly improved dermal drug penetration, retention, and sustained release. These vesicular and lipid- based systems enhance therapeutic efficacy by improving solubility, facilitating controlled release, and maintaining stability. Studies have demonstrated superior anti-inflammatory effects and enhanced permeation profiles for nanocarrier-based flurbiprofen formulations compared to conventional gels. Nonetheless, challenges including nanoparticle stability, large-scale production, and cost-effectiveness persist. Future research should focus on optimizing formulation parameters and conducting clinical evaluations to ensure safety, efficacy, and commercial feasibility of these advanced topical systems.

Keyword: Flurbiprofen Topical Drug Delivery Nanostructured Lipid Carriers (Nlcs) Nano Emulsion Liposomes Glycerosomes Ufasomes Anti-Inflammatory Drugs; Rheumatoid Arthritis.

1. INTRODUCTION

The treatment of acute and chronic inflammatory diseases, including rheumatoid arthritis, osteoarthritis, tendinitis, and muscle sprains, is a major public health issue worldwide [1]. Non-steroidal anti- inflammatory drugs (NSAIDs) constitute the basis of pharmacological treatment for these diseases, offering symptomatic relief from pain and inflammation [2]. Flurbiprofen, a 2-arylpropionic acid (profen) NSAID, is an extremely potent agent with activity at inhibiting cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes, thus lowering the production of prostaglandins, the primary mediators of pain and inflammation [3].

Although oral flurbiprofen has very good bioavailability and efficacy, its application is tainted by a well-documented side effect profile of systemic adverse effects [4]. Being a non-selective inhibitor of COX, it inhibits the constitutive enzyme COX-1, which is crucial in the integrity of the gastric mucosa and renal perfusion [5]. This results in a high rate of dose-related GI intolerance such as dyspepsia, gastritis, ulceration, and possibly serious bleeding [6]. In addition, systemic NSAIDs carry cardiovascular and renal side effects, especially in the elderly and comorbid patient [7]. These constraints have generated interest in finding alternate routes of delivery that maximize therapeutic effects with minimal systemic toxicity [8].

Topical drug delivery presents itself as a logical and patient-friendly option to this dilemma.[9] The main aim of topical flurbiprofen therapy is to attain high local levels at the pathologic site whether it is muscles, joints, or tendons with low systemic levels of the drug. This site specific delivery provides a number of attractive benefits [10].

Minimization of Systemic Adverse Events: By avoiding the gastrointestinal tract and minimizing first-pass metabolism, topical delivery greatly reduces the incidence of GI ulcers and other systemic side effects [11)Increased Patient Compliance: Topical preparations are usually non-invasive, gentle to apply, and not painful, resulting in improved compliance, particularly for long-term chronic therapies[12].Avoidance of First-Pass Metabolism: The drug does not undergo pre-systemic elimination by the liver and therefore can be of special advantage for highly extracted drugs from the liver[13].Termination of Therapy Therapy can be easily terminated in the event of an adverse reaction by simply removing the formulation[14].In spite of these benefits, the skin is not a passive membrane but a very effective barrier, largely because of the outermost stratum corneum[15]. Successful topical delivery of flurbiprofen is obstructed by its inherent physicochemical nature [16]. With a log P value pointing towards moderate lipophilicity and fairly poor aqueous solubility,[17] flurbiprofen tends to show suboptimum permeability through the skin, resulting in poor bioavailability from conventional formulations [18].

This review seeks, therefore, to give a critical and overall appraisal of the scientific progress made in the development

and formulation of topical delivery systems of flurbiprofen [19]. It will systematically examine the path from basic conventional preparations to advanced nanotechnological strategies and assess their capacity to overcome the barrier of the skin, their capacity to improve drug penetration and retention, and consequently, enhance clinical outcomes[20,21]. Through integration of the most recent available data, this paper aims to recognize present challenges and future opportunities and form a sound basis for the development of novel, high-efficiency topical preparations of flurbiprofen [22].

TYPES OF RHUMATOID ATHARITIS

1. Osteoarthritis

The most current type of arthritis is osteoarthritis, which is brought on by the slow deterioration of cartilage, the towel that protects the ends of bones in joints. Bones start to rub against one another when the cartilage deteriorates, performing in discomfort, edema, and dropped mobility(23).

2. Rheumatoid arthritis

Rheumatoid arthritis(RA) substantially affects the joints. In discrepancy to osteoarthritis, which is caused by wear and tear and gash, RA happens when the body's own apkins particularly the synovium, which lines the joints are inaptly attacked by the vulnerable system. Inflammation, discomfort, edema and eventually common degeneration result from this(24,25).

3. Gout

A form of seditious arthritis known as gout is brought on by an accumulation of uric acid in the blood, which causes sharp chargers to develop in the joints and produce abrupt, excruciating pain. Because of its literal link to rich diets and alcohol, it's constantly appertained to as the complaint of lords" and is famed for its severe flare ups(26,27).

4. Psoriatic Arthritis

The habitual autoimmune condition known as psoriatic arthritis(PsA) results in inflammation of the joints and entheses, which are the places where ligaments and tendons connect to bone. People with psoriasis, a skin complaint that results in red, scaled patches, are constantly affected. common symptoms, still, can appear in some persons either before or after egregious skin changes(28,29).

Pathogenesis

RA is caused by a combination of immunologic, environmental, and inheritable variables that intrude with the vulnerable system's normal operation. Figure 1 illustrates the citrullination process, a post- translational change of the amino acid arginine into citrulline(30). The vulnerable cells identify this as a foreign antigen and produce anticitrullinated peptide antibodies, also known asanti-cyclic citrullinated peptide(anti-CCP) bus- antibodies(31). Proteins that contain citrulline, like vimentin, filaggrin, and type II collagen, are linked as foreign antigens. The antigen- presenting cells admit these antigens and transport them to the lymph bumps, where the T- cell receptor and class II MHC- Peptide(major histocompatibility complex) interact to spark antigen CD4 T cells, which latterly separate into T coadjutor 1(TH1) and T coadjutor 17 cells(TH17)(32). T H1 secretes Lymphotoxin B and Interferon- gamma TNF- nascence, which stimulate B cells and macrophages. After that, B- cells develop into tube cells. bus- antibodies similar as anticitrullinated peptide antibodies,anti-CCP antibodies, and rheumatoid factor(anti-IgM antibodies) are buried by these tube cells(33). bus antibodies and T- cells enter the bloodstream and trip to the joints. Immune complexes are created when rheumatoid factor combines with the Fc region of modified IgG antibodies. Citrullinated proteins are the target ofanti-CCP. Original towel is now destroyed by this active medium(34,35). These T- cells and bus- antibodies enter into rotation reaching to joints. Rheumatoid factor forms a complex with Fc portion of altered IgG antibodies forming vulnerable complexes(36). Anti-CCP targets citrullinated proteins. Now, this actuated system destroys original towel(37). T- effector cells beget synovial inflammation and angiogenesis to deliver further seditious cells to the joints by stimulating synovial macrophages and fibroblasts to release proinflammatory intercessors(similar as TNF- nascence, IL- 1, and IL- 6(38)). On the face of T- cells, seditious cytokines raise the product of receptor activator of nuclear factor κ B(RANK) ligand(RANKL), which activates osteoclasts. Bone is destroyed by these actuated osteoclasts. The breakdown of cartilage is eased by the matrix metalloproteases that synovial cells release(39). The overall pathophysiology causes inflammation, bone loss, and cartilage declination. Figure 2 illustrates the distinction between RA and normal joints. Inflammation of the synovium or synovium membrane, cartilage thinning, ongoing bone corrosion, and a drop in synovial fluid are each present in RA joints(40).

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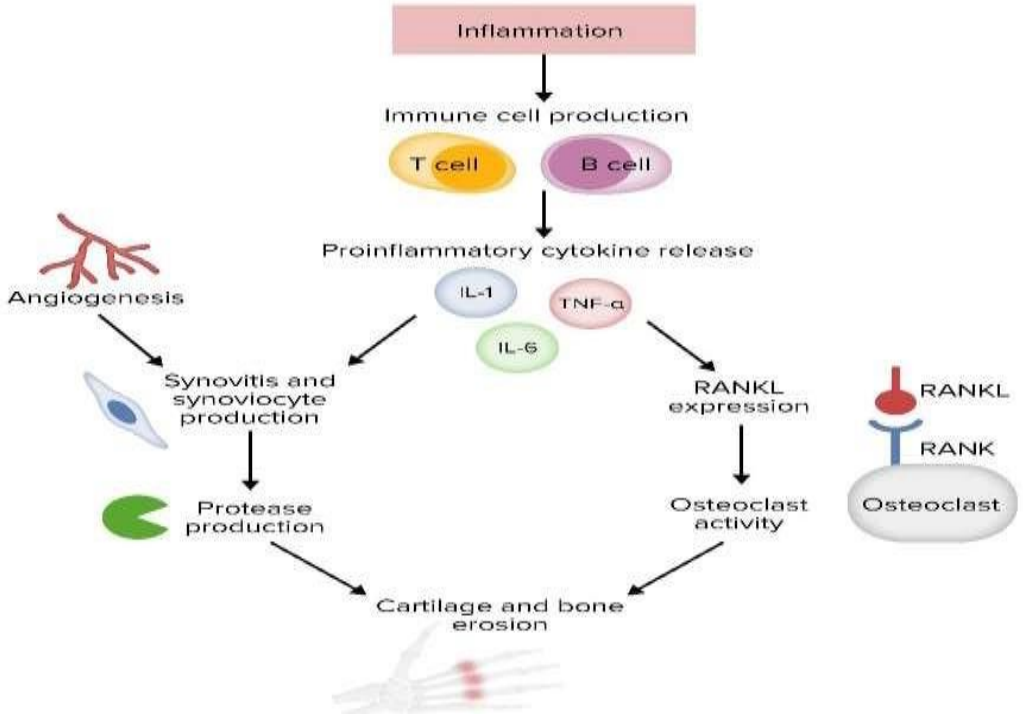

Fig 1: Pathogenesis Rheumatoid Arthritis

Diagnosis:

Identification and Evaluation One or a small number of joints may be affected by RA in its early stages. Tenosynovitis, or inflammation of the tendons, appears concurrently or even earlier [41]. Imaging using color Doppler sonography or gadolinium-enhanced magnetic resonance imaging, which show expansion of intra-articular soft tissue or hypervascularization of the synovial membrane, can identify the presence of tenosynovitis, such as at the flexor carpi ulnaris tendon, and subclinical synovial inflammation [42]. There are no diagnostic standards for RA.

2. FORMULATION OF NANOLIPID CARRIER FOR TOPICAL DRUG DELIVERY SYSTEMS

1. Nanoemulsion:

These are biphasic water-in-oil or oil-in-water dispersions that are thermodynamically stable and stabilized by an emulsifier. The dispersed phase's particle size falls between 20 and 200 nm. This system appears translucent due to the extremely small particle size[43].Drug delivery using nano emulsion serves several purposes, including preventing drug degradation, transporting hydrophilic and lipophilic molecules in one system, and enabling controlled release action[44)showed promising anti-arthritic properties with 78.76% reduction in inflammation and regulated drug release for up to 48 hours when a gel loaded with nano emulsion of two medications Methotrexate and Resveratrol was examined for transdermal use in rats[45]. Shows that a self-nano emulsifying drug delivery system loaded with Meloxicam has been developed for transdermal application to manage arthritic pain [46]. This formulation has proven to have a higher release rate, an 11.89-fold increase in drug permeation, and droplet sizes ranging from 14.41 ± 2.50 nm to 25.58 ± 2.33 nm (ultra-fine) [46].

2. Liposomes:

Liposomes are spherical, bilayered phospholipid vesicles with an aqueous core and a self-closing structure [48]. Depending on their internal structure, these phospholipid-, cholesterol-, and stabilizer- based vesicles are categorized as either unilamellar or multilamellar [49,50]. Additionally, they can produce sustained-release activity by acting as a reservoir in the stratum corneum layer. Puglia and associates [51] created a carbomer gel that included methotrexate-loaded thermally responsible flexible liposomes. These liposomes have demonstrated enhanced skin penetration and quick drug release in hot environments when compared to free methotrexate. A study conducted by Sharma et al[52]. examined the in vivo drug release profile of indomethacin-loaded liposomes made of cholesterol and dipalmitoyl- L-phosphatidylcholine and discovered that the liposomal gel had a longer-lasting anti-inflammatory impact than the gel without liposomes [53,54].

3. Glycerosomes:

Glycerosomes, which create a flexible vesicular structure with greater penetrating ability compared to liposomes, are produced when glycerol is present at a concentration of 10%–30% v/v with phospholipids and cholesterol [55]. Celecoxib and cupferron glycerosomes were prepared for topical application in a study. The results showed that the drug- loaded glycerosomes had a spherical morphology, with optimal particle size and high entrapment of approximately 89.66 ± 1.73% and 93.56 ± 2.87%. They also demonstrated significant drug release with high permeation and a notable reduction in paw edema when compared to the control group [56,57].

4. Ufasomes:

The effectiveness of transdermal administration is restricted by the skin and synovial capsule barriers. Unsaturated fatty acid addition can get around this obstacle [58]. The process takes place at basic pH ranging from 7-9, as vesicle formation of unionized fatty acid and fully ionized groups occurs at this pH [59]. These have the ability to transport medication molecules and improve the stratum corneum's penetration efficiency [60]. created a gel that contained methotrexate- loaded oleic acid vesicles (ufasomes). According to an in-vitro assessment, the gel's penetration was three to four times more than that of a normal gel [61], and a skin permeation test revealed that 50% of the dose was absorbed by the skin [62].

3. CONCLUSION

Topical delivery of flurbiprofen from plain gels to advanced nanocarriers is a paradigm shift in local therapy of inflammatory diseases. This review has comprehensively explained how sophisticated systems such as emulgels, microemulsions, ethosomes [63], and NLCs have effectively solved the major problems of skin barrier function and low drug permeability. These systems enhance drug delivery by multiple mechanisms: drug solubility improvement, penetration enhancement, reservoir effect, and sustained release [64]. The combined evidence from the literature persuasively indicates that these new formulations are superior to traditional bases in the areas of in-vitro permeation, retention in the skin, in-vivo potency, and possibility of less frequent dosing [65] Yet, the area is not trouble-free. The colloidal system stability over the long term (e.g., nanoparticle aggregation, lipid hydrolysis), the scalability of production operations [66], and cost-effectiveness against well-established generic products are still enormous challenges. Additional clinical data are also required to categorically demonstrate their superiority in human patients[67].

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