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NOVEL DRUG DELIVERY SYSTEMS FOR EFFECTIVE DELIVERY OF DRUGS IN THE MANAGEMENT OF RHEUMATOID ARTHRITIS

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ABSTRACT: Chronic joint inflammation is a hallmark of the systemic inflammatory illness known as rheumatoid arthritis (RA), which eventually causes severe disability and early death. RA may impact any joint in the body. However, it mostly impacts the wrist and knee joints' proximal interphalangeal, metacarpophalangeal and metatarsophalangeal joints. Around 1% of people worldwide are affected by it and women are 2-3 times more likely to be affected than males. Preclinical RA, genetic influences and environmental influences all have a role in the etiology of the illness. Since there is no recognized therapy for RA, achieving the lowest disease activity and, if possible, recovery remains the key goals of care. This review summarizes the research on the many RA therapy options, their mechanisms of action, side effects and novel drug delivery systems currently being used for non-steroidal anti-inflammatory drugs (NSAIDs). These delivery methods are discovered to be non-toxic, physiologically selective, compatible with cells and tissues and safe even at larger doses. The current study compares and contrasts numerous unique drug delivery methods that have been investigated for using anti-rheumatic medications, as well as the benefits of using these novel methods over traditional drug delivery methods. This will reduce the need for high doses and frequent dosing as well as the toxic side effects of the drugs, making medications safer for patients. To make these potential medication delivery methods commercially marketable, additional in-depth studies are urgently required.

INTRODUCTION: An inflammatory condition known as rheumatoid arthritis (RA) causes persistent joint inflammation that ultimately causes serious disability and early death. Chronic synovial membrane inflammation brought on by RA advances to extra-articular disease symptoms, including periarticular bone erosion, articular cartilage degradation, and irreversible abnormalities. Aging is among the main risk factors for the development of RA.

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According to estimates, RA affects 1% of people worldwide, and women are 2-3 times more likely than males to have the disease. India has a prevalence of RA between 0.28% and 0.7%, comparable to that of affluent countries. RA can affect people of any age, although it is most common in those between the ages of 30 and 50 [1].

RA may impact any joint in the body. However, it mostly impacts the wrist and knee joints' proximal interphalangeal, metacarpophalangeal, and metatarsophalangeal joints. The wrist is the area of RA most frequently afflicted. It has also been noted that there are some variances in the predominance of swelling and soreness, with swelling more common in tiny joints like the metacarpophalangeal joints and discomfort more common in major joints like the elbow, shoulder, and knee [2].

Pathogenesis of RA: Although the exact cause of RA's pathogenesis is unknown, it has been suggested that a number of inflammatory mediators, including tumor necrosis factor (TNF), C reactive protein (CRP), CD40 L, interleukins (IL-18 and IL-20), monocyte chemoattractant protein-1 (MCP-1), receptor activator of nuclear factor-B ligand (RANKL) fractalkine, matrix metalloproteinase-9 (MMP-9) and Preclinical RA, genetic factors, and environmental variables can be used to categorize the several well-known components that are involved in the pathogenesis of RA [3].

Environmental Factors: Recent investigations have shown the link between various environmental variables and an increased risk of RA. Smoking and drinking alcohol are the two most prevalent risk factors. Long-term smoking is linked to an increased chance of having seropositive RA. High salt consumption, autoimmune thyroid disease (AITD), atopic dermatitis (AD), schizophrenia, smoking, and endometriosis are more variables that raise the likelihood of getting RA [4].

Genetic Factors: The relationship between genetic makeup and a variety of environmental variables affects how RA develops. Major Histocompatibility Complex (MHC) genes were found to significantly impact the etiology of the illness by molecular biology investigations. One of the most significant genetic associations in MHC for RA has been shown to be the HLA-DRB1 gene, where certain alleles within the DRB1*04 and *01 clusters encode shared-epitope regions inside the DRB1 molecule. PADI, CTLA4, PTPN22, CCRS6, CSF2, B3GNT2, PDE2A-ARAP1, ANXA3, ARID5B, CD83, PLD4, and PTPN2 are additional genetic factors in RA etiology [5].

Preclinical RA: It has been shown that there is an elevated level of disease-related biomarkers in preclinical RA (the stage before the onset of arthritis), including auto-antibodies. IgM-Rheumatoid factor, RA33, Sa, p68, calpastatin, and perinuclear factor are a few of the several disease-specific auto-antibodies. An essential part of the pathophysiology of RA is played by rheumatoid factor (RF). According to the American Rheumatism Association, the presence of RF is considered serological criteria for diagnosing RA [6].

Treatment OF RA: The cause of RA is unknown. The major focus of treatment is still to reduce disease activity as much as feasible, promote healing if at all possible, prevent joint damage, and enhance quality of life and physical function. Non-steroidal anti-inflammatory medicines (NSAIDs), corticosteroids, disease-modifying anti-rheumatic drugs (DMARDs) and biologicals are some of the therapeutic options for RA. Other treatments for RA include radioisotopes, antisense oligodeoxynucleotides, boron neutron capture synovectomy and enzymes (superoxide dismutase) [7].

Biologics: Biologics (more recent DMARDs) created by genetic engineering stop the overproduction of inflammatory cytokines in the joints of RA patients. IL-1 receptor antagonist (Anakinra), anti-IL-6 receptor antibody (Tocilizumab), anti-CD20 antibody that depletes B cells (rituximab), T cell signaling inhibitor (Abatacept), TNF-receptor fusion protein (etanercept), anti-TNF PEGylated antigen-binding fragment (certolizumab pegol) and anti-TNF monoclonal antibodies are some of the biologics (adalimumab, infliximab and golimumab). Patients receiving biological therapy are more vulnerable to bacterial and fungal illnesses like TB because the biologics impair the immune response [8].

Corticosteroids: Asthma, RA, inflammatory bowel disease (IBD) and other autoimmune illnesses are all commonly treated with corticosteroids, especially glucocorticoids. They function by binding with cytosolic glucocorticoid receptors and inhibiting the transcription of inflammatory genes, which reduces the synthesis of cell adhesion molecules, pro-inflammatory cytokines and chemokines and other important mediators of inflammation. Long-term usage of corticosteroids is linked to a variety of adverse effects, including pancreatitis, moderate hirsutism, osteoporosis, myopathy and osteonecrosis. In individuals who are refractory to NSAIDs and DMARDs, a modest dosage of glucocorticoids may be used, or selective glucocorticoid receptor agonists may be given [9].

Disease-modifying Antirheumatic Drugs: A family of medications called disease-modifying antirheumatic medicines (DMARDs) is used to treat RA. These medications have a sluggish onset of action and might take weeks or months to have any pharmacological impact. DMARDs lack a standardized mode of action, and each drug's adverse effects are unique. The use of DMARDs is linked to a number of adverse effects, including myelosuppression, stomatitis, liver dysfunction, and malfunction of the digestive system [10].

Non-steroidal Anti-inflammatory Drugs: Because they have both analgesic and anti-inflammatory effects, non-steroidal anti-inflammatory medicines (NSAIDs) are the most regularly used medications for the treatment of arthritic conditions. These work by preventing the cyclooxygenase (COX) enzyme from participating in the process of turning arachidonic acid into prostaglandins. The majority of NSAIDs are non-selective COX inhibitors, which means they block both COX-1 and COX-2. However, worries regarding the negative consequences of this class of medications have been on the rise. Acute renal ischemia brought on by vasoconstriction brought on by prostaglandin inhibition, changes in blood pressure, and increased bleeding brought on by platelet inhibition are some of the negative consequences. According to reports, non-selective NSAIDs can lead to major upper gastrointestinal (GI) problems such as perforation, blockage and hemorrhage because they are ulcerogenic. NSAIDs are still commonly used medications to treat RA despite their elevated cardiovascular risks, including myocardial infarction and strokes [11].

Novel Drug Delivery Systems in RA Management: The traditional drug administration methods have benefits and drawbacks, including limited solubility and permeability, poor bioavailability, GI enzyme degradation, first-pass metabolism, food interactions, high dosage requirements, and related drug toxicity. Numerous studies have been conducted to address these drawbacks, which has resulted in the development of innovative drug delivery methods (NDDS). These cutting-edge systems have target-specific efficacy, are needed in lower dosages, have less hazardous side effects, high solubility and permeability, and improve bioavailability [12].

Back when RA was first being treated medically, NSAIDs and analgesics were the go-to treatments. As the illness worsens, they lose a lot of their effectiveness, necessitating the use of an intra-articular (i-a) steroid depot to relieve pain and inflammation. DMARDs such salazopyrine and chloroquine, as well as immunosuppressive medications like methotrexate (MTX) and azathioprine, were used after these. Other agents, with the exception of MTX, are linked to a variety of adverse effects. Leflunomide and tacrolimus, two more recent second-line drugs, have been reported to lessen the proliferation of activated CD4 T cells, an important factor in the pathogenesis of RA. Novel biologics, including infliximab, adalimumab and anakinra were created and authorized as a result of increased knowledge regarding the function of inflammatory mediators in RA. I-a drug administration is a significant advancement in the treatment of RA because it ensures regulated drug release over a longer time period and delivers the medication directly to the afflicted spot. Injections of medications contained in NDDS such as liposomes, nanoparticles, and microparticles have enhanced mean residence duration and reduced I-a drug clearance [13].

Direct Chemotherapeutic Dual Drug Delivery: Son and colleagues created viscous emulsions comprising MTX-loaded hyaluronic acid (Met-HA), dexamethasone-loaded microcapsules (Dex-M), and Dex-M distributed inside of Met-HA, and then injected these formulations into articular joints to create drug depots. When Met-HA and Dex-M were injected together, it was shown that the rate of RA repair was quicker than when they were injected separately. Thus, it was determined that using two drugs at once had a long-lasting synergistic impact that improved RA healing [14].

Emulgels: Nimesulide emulsion was incorporated into an Aloe vera gel basis to create the nimesulide-Aloe vera transemulgel (NAE), which was then subjected to *in-vitro* testing and *in-vivo* anti-inflammatory evaluation. The produced emulgels were assessed for stability, pH, viscosity, *in-vitro* permeation and skin irritation.

They conducted *in-vivo* anti-inflammatory investigations in Wistar rats using the carrageenan-induced hind paw oedema technique. With no skin

irritation following topical emulgel application, this nimesulide permeation from NAE compared to commercial nimesulide gel (CNG) at 30 min showed that NAE had superior drug release. Additionally, the authors carried out stability experiments to show the formulation's integrity. The prepared NAE's percentage edema inhibition after 240 minutes was 67.4%, which was greater than the CNG's 59.6%. By examining these findings, the scientists argued that Aloe vera gel might serve as an efficient gel foundation for the creation of nimesulideemul gel, which has a substantially higher anti-inflammatory impact and a high drug loading capacity of 86.4% compared to CNG's 70.5% [15].

Folate-conjugated Albumin Nanoparticles: Folic acid-etoricoxib-bovine serum albumin nanoparticles (F-ETX-NPs) were created by Bilthariya *et al*. They demonstrated increased bioavailability and a stronger retention potential of the nanoparticles towards activated macrophage cells. The technique may thus be a useful therapeutic alternative to reduce medication dosage and improve biocompatibility, it was determined [16].

Folate Coupled Dendrimer: Intending to deliver the medication to specific locations to alleviate inflammation and examine its biodistribution pattern in arthritic rats, Chandrasekar prepared folate-targeted polyethylene glycol (PEG) conjugates of anionic G3.5 poly (amido amine) (PAMAM) dendrimer. Scientists created indomethacin-loaded folate-PEG-PAMAM conjugates by a carbodiimide-mediated coupling process in this work. Folate-PEG conjugation boosted the drug loading efficiency 10- to 20-fold, and it was discovered that the drug release *in-vitro* was regulated. Due to noticeably lower absorption of the conjugates by the stomach, authors found little adverse effects associated with the stomach. The total drug targeting efficiency (T(e)) for the folate-PEG conjugate was determined to be 3.44 in comparison to the natural dendrimer (Te-1.72). The authors concluded that folate-PEG-PAMAM conjugates could be the best option for the effective, side-effect-free administration of antiarthritic medications to inflammation [17].

Hydrogels in Combination with Microspheres: For intra-articular administration, Qi *et al*. created fine chitosan thermosensitive hydrogels in conjunction with alginate microspheres to prove the hydrogels' anti-inflammatory potential. The authors created the microspheres using a modified emulsification technique or gelation and they were then disseminated as injectable thermosensitive hydrogels made of chitosan and -glycerophosphate. In this study, it was shown that as compared to pure chitosan hydrogels and medication solution, the mixed hydrogels showed greater anti-inflammatory activity in experimentally induced RA rabbits. The scientists concluded that mixed hydrogels could prove to be a successful method of drug delivery and a crucial technological foundation for intraarticular administration of DFNa for enhanced therapeutic impact [18].

Hydrogel-loaded Aspasomal Delivery: Ascorbyl palmitate was added to MTX aspasomes by Ghosh *et al*. as an antioxidant. Hydrogel was then added to it for *in-vivo* and *in-vitro* tests. The formulation demonstrated a greater reduction in SGOT, SGPT, Il, TNF, rat paw diameter, panus development, inflammation, bone resorption, and cartilage degradation than free MTX. The findings therefore pointed to this formulation as a non-invasive substitute with good drug loading and penetration rates as well as a superior rate of illness recovery than free medication [19].

Lipid-based Vesicular Nanocargoes: Because of their adaptability and capacity to hold several drugs, lipid nano-vesicular carriers, including ethosomes, liposomes and niosomes are some of the most recent developments in the treatment of RA. They have had notable effects in RA treatment, allowing for dosage reduction and improved drug localisation via active and passive drug targeting [20].

Lipogelosome: Using lipogelosome formulations (L1J1) containing diclofenac sodium, Turker*et al*. evaluated their capacity to reduce inflammation (DFNa). Authors found that the L1J1 formulation had a more potent anti-inflammatory effect than a topically applied commercial medication after a single dose intraarticular injection (VE-CP). In the opened joints, researchers conducted bio-distribution and histological examinations, and they found that L1J1-treated joints performed

considerably worse than contralateral control joints for inflammatory alterations in the synovium [21].

Magnetic-targeted Chemophotothermal Treatment: For magnetically targeted chemo-photothermal therapy and *in-vivo* multimodal imaging of RA, Kim *et al*. created MTX-loaded, arginine-glycine-aspartic acid-conjugated poly (lactic-co-glycolic) acid (PLGA) half-shell gold (Au)/iron (Fe/gold (Au) nanoparticles. After receiving repeated NIR radiation as well as an external magnetic field, these nanoparticles demonstrated greater therapeutic benefits. The dosage of MTX utilized in this study was also much lower than that of free MTX therapy-just 0.05% [22].

Microemulsion: Tenoxicam (TNX) formulations based on microemulsion were created by Goindi *et al*. for topical administration at the impacted areas of inflammation. The microemulsion-based formulations were created utilizing Captex 300/oleic acid as the oil, n-butanol/ethanol as the co-surfactant and Tween 80 as the surfactant. Comparing the drug's microemulsion formulations to its traditional cream and suspension, TNX demonstrated considerably greater mean cumulative percent permeation values. The created TNX formulations' *in-vivo* anti-arthritic and anti-inflammatory effects were evaluated using a variety of inflammatory models, including the air pouch model, xylene-induced ear edema, cotton pellet granuloma, and carrageenan-induced inflammation. Compared to traditional topical dose forms, microemulsion formulations were shown to be more effective in controlling inflammation and comparable to oral formulations. According to the findings, TNX may be effectively delivered topically to treat various inflammatory disorders using the created microemulsion formulations [23].

Microneedle Transdermal Patch: In order to effectively transport the formulation to deeper skin layers, Amodwala *et al*. created a fast-dissolving microneedle transdermal patch for meloxicam. In order to offer a patient-friendly approach to the care of arthritis, the formulation was designed to avoid poor patient compliance with meloxicam due to gastrointestinal problems produced by its oral administration. The formulation was shown to have a 2.58-fold better permeability compared to plain drug solution, an increased transdermal flow of 1.60 g/cm^2/h and a 63.37% drug deposition within the skin. Compared to its already marketed and authorized oral tablet, the new formulation showed comparable anti-inflammatory effectiveness in rats. The stability, effectiveness, and safety of the microneedle patch, which promoted the use of the formulation transdermally, were successfully verified by the authors [24].

Microspheres: Pectin-based colon-specific microspheres (multiparticulate delivery system) were created by Ramasamy *et al*. using an emulsion dehydration process. Eudragit S100 was applied to the microspheres using the solvent evaporation technique. The authors examined the influence of variables including emulsifier, stirring time/speed, and polymer on surface morphology, size, in-vitro release, entrapment effectiveness, and in-vivo performance. Studies conducted *in-vivo* revealed that medication at a steady therapeutic dose for 24 hr had a strong anti-inflammatory impact. Based on their research, the scientists concluded that eudragit-coated pectin microspheres might be useful for aceclofenac administration to the colon in the chronopharmacological therapy of RA [25].

To increase the duration of the dosage form in the knee joint, Tuncay *et al*. created DFNa-loaded microspheres utilizing a natural biodegradable polymer for intra-articular injection. Two acceptable formulations were chosen for *in-vivo* tests after the authors evaluated the generated DFNa microsphere formulations for *in-vitro* parameters, including yield value, particle size, surface morphology, encapsulation effectiveness, and *in-vitro* drug release. Technetium-99m-labeled polyclonal human immunogammaglobulin (99 mTc-HIG) was employed as a radio-pharmaceutical to show *in-vivo* arthritic lesions utilizing gamma scintigraphy. To find the best formulation, researchers injected DFNa-loaded radio-labeled microspheres into the articular cavity of rabbit knee joints after inducing arthritis. Later, they used gamma scintigrams to gauge the microspheres' residence duration in the knee joints [26].

To implement aceclofenac chronotherapy for RA, Sanka*et al*. created and improved pH-triggered

delayed-release colon-targeted microspheres. The created formulation was tested for delayed *in-vivo* response and anti-arthritic effectiveness in rats before being optimized using a 3-factor, 3-level Box-Behnken design (BBD) for a few selected variables. The microspheres were found to have an encapsulation efficiency of 85.06% and a particle size of 117.36 μm, respectively. Anti-arthritic activity was seen in arthritic rats induced with Freund's adjuvant through *in-vivo* testing, but delayed anti-inflammatory activity was seen in rats induced with carrageenan. The authors concluded that the aceclofenac microspheres, with their improved formulation, are a potential option for a chronotherapeutic effect in RA morning symptoms [27].

Nanoparticles: To test the anti-inflammatory efficacy on rats with adjuvant-induced arthritis (AA), Nagai *et al*. developed a unique topical formulation (nanogel ointment) comprising ketoprofen (KET) solid nanoparticles of 83 nm mean particle size. Comparing KET nanogel ointment to gel ointment containing KET microparticles with a 7.7 μm particle size, the *in-vitro* skin penetration experiment revealed significantly greater penetration coefficient and penetration rate for KET nanogel ointment. Additionally, it was shown that rats receiving KET nanogel ointment had larger areas under the KET concentration-time curve and an apparent absorption rate constant for rat skin than rats receiving KET microgel ointment in an *in-vivo* percutaneous absorption experiment [28].

In a different study, Nagai *et al*. developed an IMC nanogel ointment that included solid Indomethacin (IMC) nanoparticles and conducted a pharmacokinetic analysis. Using ingredients including Carbopol 934, methylcellulose, and 2-hydroxypropyl cyclodextrin, Bead Smash 12 was utilized to make the IMC nanogel ointment. The produced nanoparticles were found to have an average particle size of 173 nm. Comparing IMC nanogel ointment to IMC microgel ointment, it was found that the latter showed less of an increase in paw edema on the hind foot of AA rats (rats with adjuvant-induced arthritis). Additionally, the IMC nanogel ointment had a much higher IMC buildup than the IMC microgel ointment. The plasma concentration of IMC was the same for both gel formulations, though [29]. Nagai *et al.* created an ibuprofen (IBU) nanogel formulation for topical administration to demonstrate their anti-inflammatory effectiveness in AA rats. Gel-based formulations were made using the bead mill process using additives like Carbopol 934, 2-hydroxypropyl-cyclodextrin and methyl-cellulose. The IBU particle size was determined to be 208 nm in the IBU nanogel formulation. After treating AA rats with IBU nanogel formulation, authors noticed a substantial decrease in the inflammation of the hind paws and a noticeable inhibitory response to inflammation compared to IBU microgel formulation, which had particles of an average size of 85.4μm. Additionally, scientists claimed that as compared to IBU microgel formulation, IBU nanogel formulation gave exceptionally considerable permeability and accumulation in the skin. After giving AA rats 0.30 g of the synthesized 5% IBU nanogel once daily for 42 days, the authors noted no gastrointestinal lesions. The scientists concluded from their data analysis that topically applied IBU nanoparticles exhibited effective treatment with no negative patient side effects [30].

Nano-structured Lipid Carriers (NLCs) Mediated Delivery: Colloidal lipid carriers called nano-structured lipid carriers (NLCs) have demonstrated improved drug absorption through skin. They have been demonstrated to outperform the drawbacks of solid lipid nanoparticles, such as gelation, drug leakage caused by lipid polymorphism, and poor drug loading capacity. It has been found that NLCs made using physiological and biological lipids have a reduced level of systemic cytotoxicity [31].

NSAIDs-Carbonic Anhydrase Inhibitors (CAIs) Hybrids: To treat RA, Bua *et al*. reported the synthesis of a number of hybrid compounds including 6- and 7-substituted coumarins (carbonic anhydrase inhibitors) that were derived from commonly prescribed NSAIDs (indomethacin, sulindac, ketoprofen, ibuprofen, diclofenac, ketorolac, *etc*.). Most of the compounds had KI values in the low nanomolar or subnanomolar ranges and were efficient at inhibiting RA over-expressed hCA IX and XII. Using an *in-vivo* RA model, paw-pressure and incapacitance tests were used to examine the antihyperalgesic effects of such drugs. The 7-coumarin hybrid with ibuprofen

showed the most effective and consistent anti-hyperalgesic activity up to 60 minutes after all the investigated compounds were administered [32].

Polymeric Micelles: Through thermal ring-opening polymerization, followed by substitution reactions, Zhang *et al*. created amphiphilic polyphosphazenes (PNIPAAm/ EAB-PPPs) containing ethyl 4-aminobenzoate (EAB) and poly (N-isopropylacrylamide) (PNIPAAm) as side groups. By using a dialysis approach, the authors created polymeric micelles based on PNIPAAm/ EAB-PPPs and filled with indomethacin (IND). *In-vivo* pharmacodynamic studies using carrageenan-induced acute paw edema and complete Freunds adjuvant (CFA)-induced ankle arthritis models, as well as *in-vivo* pharmacokinetic studies using Sprague-Dawley rats, were conducted to examine the *in-vitro* IND release kinetics. By conducting an *in-vivo* pharmacodynamic study, the authors reported the sustained therapeutic efficacy of an aqueous solution of IND-loaded micelles when applied topically and the prevention of severe gastrointestinal stimulation by local delivery of IND, which frequently resulted in ulceration when given orally. Hence, authors advocated that such amphiphiliccopolymers could serve as potential injectable drug carriers for hydrophobicdrugs [33].

Prodrug Approach: Using aryl acetic acid NSAIDs and 2-hydroxychloroquine (HCQ), Poorvashree and Suneela created a brand-new business venture called dual-acting prodrugs. The authors concentrated on sluggish accumulation and onset issues of HCQ in non-targeted areas with NSAIDs as vectors. They designed their mutual ester prodrugs to lessen these issues and reduce local stomach irritation brought on by NSAIDs for the effective therapy of RA. The authors employed several animal models to assess the prodrugs' anti-inflammatory, anti-arthritic and analgesic properties. In comparison to HCQ alone and physically mixed doses of HCQ and NSAIDs, authors found that the prodrugs of HCQ with aceclofenac (HA) and licofelone (HL) boosted analgesia, normalized joint diameter/paw volume, and weight growth [34].

Solid Lipid Nanoparticles: Kaur *et al*. created and evaluated dermally/topically applied solid lipid nanoparticles loaded with diclofenac (DIF) (SLNs). According to the authors of this work, SLNs generated using a hot homogenization process based on micro emulsification had a mean size of 124 nm, a spherical shape, and a PDI of 0.294. According to the authors, the permeation flux was 6.30 g/cm^2/h, the area/total quantity penetrated was 109.99 g/cm^2 and the skin retention across mouse skin was 11.74 g/cm^2. DIF-loaded SLNs showed a substantial decrease in granuloma tissue weight, fluid volume and leukocyte count/mm3 after DIF SLN formulation administration in the mice air pouch model. Additionally, after applying the DIF SLN formulation compared to traditional cream, scientists discovered a 1.29 and 2.30 times increase in the percentage inhibition of edema in the rat paw and mice ear edema models, respectively. The authors concluded that DIF SLNs would be useful nanocarriers for successfully managing inflammation associated with arthritis [35].

Stimuli-responsive Drug Delivery System: Stimuli-responsive block copolymers may undergo rapid and significant chemical and physical changes in response to externally applied minor stimuli. Because a little alteration in their structure and function causes drug release, they are attractive candidates for both controlled drug transport and gene delivery.

A pH-responsive, non-toxic, multifunctional envelope-type mesoporous silica nanoparticle (MEMSN) system for drug administration and magnetic resonance imaging (MRI) was created by Chen *et al*. [36]. Zhang *et al*. created gold nanorods for drug delivery that are pH- and near-infrared (NIR) light dual-stimuli sensitive [37]. Li and Zhang created amphiphilic block copolypeptoids with poly (N-ethyl glycine) as the hydrophilic segment and poly [N-propargyl glycine)-r-(N-decyl glycine)] as the hydrophobic segment.

These molecules combined to form redox-responsive core-crosslinked micelles (CCLMs) in water with diazide that contains disulfide. When the cue decrease in the solution was applied, these CCLMs broke down into smaller aggregates or unimers (e.g. 1,4-dithiothreitol) [38]. As a reduction-responsive micellar system for intracellular drug administration, Ding *et al*. created biocompatible disulfide-linked block copolymers of poly (benzyloxycarbonyl - L- lysine) and methoxylpoly

(ethylene glycol). The micelles showed great compatibility with cells, tissues, and the hematological system, making them a possible drug delivery mechanism [39]. In order to transport an imaging agent and painkillers, Lima and Reis created temperature-responsive gold nanoparticles and PEGylated PLGA nanospheres with MTX. Compared to free MTX, the nanospheres demonstrated pH- and temperature-dependent drug release, greater macrophage and monocyte viability, and decreased TNF-α, IL-1 and IL-6. The findings indicated that these multifunctional nanospheres could have interesting theranostic uses in detecting and managing RA [40].

Alam*et al*. created PEGylated hyaluronic acid, 5-cholanic acid, and calcium phosphate-based pH-responsive MTX-loaded mineralized nanoparticles (MP-HANPs). Even at larger MTX doses, this formulation was proven to be safe and decreased inflammatory arthritis by a substantial amount. Thus, the MP-HANPs emerged as a viable MTX carrier for the treatment of RA [41].

Ultrasound-mediated Microbubbles: In research by Liao *et al*., the effectiveness of delivering diclofenac using ultrasonic and microbubbles (US-MBs) for adjuvant-induced RA in rats was evaluated. By injecting 100 μL into the ankle joints of male SD rats, the authors were able to cause RA. For 10 days before and after treatment, ankle width was measured using high frequency (40 MHz) US B-mode and color Doppler mode imaging. Neovascularity and synovitis were seen on the longitudinal US pictures of the arthritic model. Authors found negligible post-treatment neovascularization. Additionally, the authors revealed that group DUB had a considerably greater 10-day recovery rate than the other groups. Thus, the authors concluded that US-MBs might improve skin permeability to enhance DFNa distribution, thereby suppressing inflammation of the arthritic ankle's surrounding tissues. Following the combined therapy, color doppler imaging revealed an immediate decrease in synovial neoangiogenesis in the arthritic region[42].

CONCLUSION: A significant portion of the global population is afflicted by the highly deadly condition known as rheumatoid arthritis. There is still no permanent treatment for RA despite decades of intensive study. The present therapy choices, such as NSAIDs, corticosteroids, DMARDs, and biologics, are extremely promising, but several drawbacks also accompany them. While DMARDs take a very long time to work and are linked to side effects like liver and kidney dysfunction, biologics suppress the immune response, making patients more susceptible to bacterial and fungal infections. NSAIDs are known to cause gastric irritation. Corticosteroids cause impaired wound healing. Innovative drug delivery techniques such liposomes, microspheres, nanoparticles, dendrimers and transdermal administration show great promise. These medication delivery techniques have been demonstrated to be more effective than traditional drug administration systems. These have also successfully addressed the drawbacks of traditional drug delivery methods, such as poor bioavailability, toxicity, limited solubility and permeability, and first-pass metabolism.

The innovative drug delivery methods have high bioavailability, excellent permeability, and solubility. Low dosages of medication are used to reduce the risk of drug toxicity. The fact that they are tailored medication delivery systems is the biggest benefit of innovative drug delivery techniques. However, most of these drug delivery systems' *in-vitro* testing has occurred to date. Researchers from all around the world have been interested in regulated medication transport and gene delivery.

Delivery systems that respond to external stimuli can experience sudden, significant changes in their physical or chemical properties. They are, therefore, prospective options for controlled medication release and gene delivery. To offer medication delivery customized to the patient's demands, the stimuli-responsive drug delivery devices can be pH-, NIR-, redox-, reduction-, or temperature-responsive. These delivery methods are discovered to be non-toxic, physiologically selective, compatible with cells and tissues, and safe even at larger doses. They may be made to carry imaging agents, anti-inflammatory medicines, and theranostics for the efficient treatment of RA. Their many uses in RA vary from diagnostic to intracellular medication delivery.

By releasing drugs based on physiological changes in the body, these cutting-edge drug delivery methods can benefit society as knowledge and technology advance. This will reduce the need for high doses and frequent dosing as well as the toxic side effects of the drugs, making medications safer for patients. To make these potential medication delivery methods commercially marketable, additional in-depth studies are urgently required.

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