

Review Article



Vesicular systems in Treatment of Rheumatoid Arthritis

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ABSTRACT

Rheumatoid Arthritis is a chronic systemic, inflammatory disease that if untreated, results in joint destruction and disability, affecting the quality of life. Various diagnostic indicators are used to ascertain the presence of the chronic disorder. Current treatment strategies offer various side effects and decreased action at the target site. The therapeutic possibilities in the management of rheumatoid arthritis have changed with the advent of vesicular systems that can be used to target the inflammatory cascade seen in rheumatoid arthritis. Vesicular drug delivery has brought about breakthrough in improving the therapeutic efficacy of the drugs by controlling and sustaining the action while minimizing the side effects. The focus of this review is to explore the potential of various novel vesicular systems in targeting drug action, improving the bioavailability and in reducing the systemic side-effects of anti-rheumatic drugs.

Keywords: Carriers, rheumatoid arthritis, liposomes, side-effects, targeting, vesicles.

INTRODUCTION

Rheumatoid Arthritis (RA) is a systemic inflammatory disease that largely affects the synovial joints, which are lined with a specialized tissue called synovium and is characterized by chronic, progressive inflammation and gradual joint destruction. Activated macrophages are responsible for production of inflammatory cytokines that results in progressive inflammation, joint swelling, bone erosion and cartilage damage. This ultimately results in chronic pain, swelling, stiffness and functional impairment. RA is usually symmetrical and typically affects the small joints of the hands and the feet and can affect the whole body, including heart, lungs and eyes.^{1,2,3} The main aim of drug therapy in RA is to alleviate pain associated with inflammation and to slow down the disease progression by further prevention of joint destruction.⁴ Combination of symptom modifying anti-rheumatic drugs along with disease modifying anti-rheumatoid drugs are used in treatment strategy of early rheumatoid arthritis where symptom modifying drugs suppresses immediate pain on joint inflammation providing sufficient time for slow acting disease modifying drugs to prevent disease progression.

RA is a chronic disease and therefore is associated with long term drug administration and may result in gastro intestinal side effects, nephrotoxicity, hepatic toxicity, loss of bone mineral density, increased risk of fractures etc.² In addition most of the available therapies for RA do not have tissue specificity. Therefore high systemic doses of the therapeutic agent are to be given in order to achieve effective drug concentration in affected joint tissues, which may in turn lead to significant adverse systemic and extra-articular side effects. However, reducing the drug doses may attenuate toxicity but also

results in reduced therapeutic efficacy⁵. Accounting these problems, drug delivery technologies should be developed which reduces drug dosing frequency along with sustained or controlled release of medicament as well as reduced systemic side-effects. Various drug delivery technologies are documented like albumin based drug delivery systems, bio reductive drug delivery systems; lipid based drug delivery systems, nanocrystal oral suspensions etc.⁶

Over a few decades the vesicular systems has gained tremendous growth in achieving controlled and targeted drug delivery and have been greatly investigated for achieving targeted action in rheumatoid arthritis. In addition they have also helped in greatly enhancing the bioavailability of medications especially in case of poorly soluble medications.⁷ The original bio distribution of substances can be greatly modified by entrapping them in sub-microscopic drug carriers such as liposomes, transferosomes, niosomes, polymeric nanoparticles, serum proteins, immunoglobulin's, microspheres, erythrocytes, reverse micelles, monoclonal antibodies and pharmacosomes. The vesicular carrier systems are developed such as to hold the molecule effectively and then navigate them towards the targeted site without affecting the physiological conditions of the body.

RHEUMATOID ARTHRITIS

Clinical Indicators for RA

The exact cause of RA is unknown and is characterized by persistent joint synovial tissue inflammation.

According to American College of Rheumatology (ACR) Criteria for classification of RA, require 4 of the following 7 conditions to be present:



- Morning Stiffness in and around joints lasting \geq 1 hour (present \geq 6 weeks)
- Physician documented arthritis involving \geq 3 joint areas simultaneously (present \geq 6 weeks)
- Arthritis of the proximal interphalangeal, metacarpophalangeal, or wrist joints (present \geq 6 weeks)
- Symmetrical involvement of joint areas (present \geq 6 weeks)
- Rheumatoid nodules
- Positive serum rheumatoid factor

- Radiographic evidence of erosions or periarticular osteopenia in hand or wrist joints

The most important diagnostic indicators for RA are Rheumatoid factor (RF), Erythrocytic Sedimentation Rate (ESR), which are used as markers of acute phase response, indicating inflammation while Tumor necrosis factor – α (TNF- α), Interleukin-6 (IL-6) and C- Reactive protein (CRP) contribute to other significant inflammatory markers⁸ as shown in table 1. In addition to these biochemical markers radiographic imaging of the hands and the feet with persistent synovitis can also be used as a measure.

Table 1: Diagnostic indicators in RA, their method of estimation and clinical use

Diagnostic Indicators	Method	Clinical Use
Rheumatoid factor (RF)	Latex fixation / Immuno turbidimetry	Most widely used test to assist the diagnosis and determining prognosis of RA ; detects primarily IgM RF
Rheumatoid factor (IgM)	ELISA	May be used in place of latex fixation/ agglutination method , especially if another RF isotype is to be tested
Rheumatoid factor (IgA)	ELISA	Provides added specificity when used in combination with other RF or anti-CCP assays
Rheumatoid factor (IgG)	ELISA	Provides added specificity when used in combination with other RF or anti-CCP assays
Anti-Cyclic Citrullinated Peptide (anti-CCP)	ELISA	Assist in diagnosis and determining prognosis of RA – more specific than RF
Rheumatoid arthritis, Diagnostic Panel RF Anti-CCP	Latex fixation / immunoturbidimetry ELISA	Provide additional diagnostic and prognostic value relative to either assay alone
Erythrocyte Sedimentation Rate (ESR)	Modified wester green	Assess disease activity
C-Reactive protein (CRP)	Chemiluminescent Immunoassay	Assess disease activity

Current treatment strategies in rheumatoid arthritis

Historically rheumatoid arthritis has been treated with a combination of anti-inflammatory drugs and immunosuppressant's. Available treatment options for RA aims at symptomatic pain relief with non-steroidal anti-inflammatory drugs (NSAID's) on one hand, and slowing down disease progression and aiming for remission with disease modifying anti rheumatic drugs (DMARDs) and corticosteroids on the other hand. All of the drugs in use have several potentially life threatening, consequences due to non-specific targeting, often in combination with impaired immune function.^{9,10} NSAIDs acts by cyclic oxygenase (COX) inhibition, which results in inhibition of prostaglandin synthesis thereby reducing pain and inflammation. DMARDs have the potential to reduce or prevent joint damage. NSAIDs are used as adjuncts to DMARDs, which helps in relieving pain and inflammation while giving sufficient time for the slow acting DMARDs to modify the disease progression. Shortcomings of DMARDs such as slow onset of action, partial remission, substantial toxicity and tendency to lose effectiveness with time led

to use of biological response modifiers (BRMs) which are designed to modulate a specific aspect of the underlying autoimmune process while avoiding generalized immunosuppression.¹¹ The drugs commonly used in rheumatoid arthritis are given in table 2.^{11,12}

Table 2: Drugs commonly used in Rheumatoid Arthritis

NSAIDs	Corticosteroids	DMARDs	BRMs
Aspirin	Prednisolone	Methotrexate	Infliximab
Indomethacin	Blood plasma or Serum derived	Sulfasalazine	Itanercept
Diclofenac		Azathioprine	Adalimumab
Ibuprofen		Tacrolimus	Anakinra
Naproxen		Leflunomide	
Ketoprofen		Auranofin	
Etodolac			
Meloxicam			
Piroxicam			
Celecoxib			
Rofecoxib			
Etorcoxib			
Valdecoxib			
Lumiracoxib			



Vesicular Drug delivery in Rheumatoid Arthritis

The vesicular systems are highly ordered assemblies of one or several concentric lipid bilayers which are formed when certain amphiphilic building blocks are confronted with water. These vesicles are formed from a diverse range of amphiphilic building blocks. The biological origin of these vesicles was first reported by Bingham in 1965, and was given the name 'Bingham Bodies'.¹³

Lipid vesicles are widely used in immunology, membrane biology, and diagnostic techniques and most recently in genetic engineering, vesicles play a major role in biologic membrane modeling as well as in transportation and targeting of active agents. Studies have reported that encapsulation of drug in vesicular structure can prolong the existence of the drug in systemic circulation, and can also reduce toxicity, if selective uptake can be achieved.¹⁴ Various other advantages of vesicular systems involve:

- Improved bioavailability especially in case of poorly soluble drugs.
- Incorporation of both hydrophilic and lipophilic drugs
- Delayed elimination of rapidly metabolizable drugs and thus function as sustained release systems.
- Reduced cost of therapy
- Solves the problems associated with drug insolubility, instability and rapid drug degradation

Designing the drug in the form of vesicular system has brought a tremendous makeover of the old pre-existing drugs and thus improved their therapeutic efficacies by controlling and sustaining the actions while minimizing the side-effects. A number of vesicular systems like liposomes, niosomes, transferosomes, pharmacosomes, colloidosomes, ufasomes, ethosomes, herbosomes, cubosomes etc. have been developed over past few years. With the advent of every new system, the newer ones have proved to be more advantageous than the older ones. Research works are being done on upcoming phospholipid mediated drug delivery systems like aquasomes, cryptosomes, emulsomes, discosomes, genosomes, proteasomes etc.

From the last few decades the micro particulate lipoidal carriers have been extensively investigated for their specificity due to targeted action of drugs to a particular tissue, cell or intracellular sites, the control over release kinetics, the protection of the active ingredient, minimization of side-effects or a combination of the above.¹⁵ More over the lipoidal formulations are used to modify absorption and the release of active ingredients by improving the bioavailability, minimizing the first pass metabolism, protection from internal environment, stimulating lymphatic transport of active ingredients, interacting with enterocyte based transport processes, sustained and controlled release etc.¹⁶

Vesicular drug delivery systems have shown applicability in targeting drug delivery in the uptake and transport of

active ingredients to the tissue or organ through biological membranes.¹⁷ Drugs encapsulated in vesicular structures are predicted to achieve specific uptake, tissue specific distribution, decreased interaction with the blood components and reduction in toxicities.¹⁶ *In vivo* experiments on isolated perfused rat liver using small, unilamellar vesicles composed of dipalmitoyl phosphatidyl choline, cholesterol, dipalmitoyl phosphatidyl glycerol and digalactosyldiacyl glycerol showed site specific uptake of vesicles by hepatic asialoglycoprotein receptor¹⁸. Doxorubicin, a broad spectrum antibiotic and anti-tumor agent showing dose-dependent irreversible cardio-toxic effect, when administered by doxorubicin encapsulated in niosomes to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma¹⁹. The drugs used in Rheumatoid arthritis ranging from the NSAID's to DMARD's, including the modern biologics, have reported to be potentially life threatening as a result of non-specific targeting, often in combination with impaired immune function and gastro-intestinal intolerances and cardiovascular complications. Vesicular carrier systems have been widely investigated for eliminating the complications associated with anti-rheumatoid drugs as well as for improved therapeutic efficacy. Various vesicular systems were experimented for targeting drug delivery in rheumatoid arthritis and are explained under following heads.

Table 3: Therapeutic application of liposomes in RA

Drug	Formulation	Route of administration	Advantage over conventional form
Ketoprofen ²¹	Gel	Topical	Deeper penetration into skin layers and hence better drug release. Enhanced retention of drug molecule.
Methotrexate ²²	Emulsion	Parenteral	Limited side effects.
Diclofenac ²³	Suspension	Oral	Reduced gastro-intestinal side effects.

Liposomes

Liposomes have been emerged as most practically useful carriers for *in vivo drug* delivery and targeted drug action. Liposomes are simple microscopic vesicles with closed bilayered lipid structures enclosing an aqueous media, where in both water and lipid soluble drugs can be successfully incorporated. The lipid soluble or the lipophilic drug may be successfully entrapped within the bilayered phospholipid membrane whereas water soluble or hydrophilic drugs get incorporated in the central aqueous core of the vesicles. Liposomes can be used to reduce toxicity and to increase stability of entrapped drug via encapsulation (e.g. Amphotericin B, Taxol). It also helps in reducing exposure of sensitive tissues to toxic drugs as well as to alter the pharmacokinetic and pharmacodynamics property of drugs by reducing their elimination and increased circulation life time.²⁰ Some of

the liposomal formulations explored for delivering drugs in arthritic conditions are given table 3.

Niosomes

Now a days tremendous research works are being done on overcoming the barrier properties of skin and niosomes have proved to be the most convincing carrier system for transdermal drug delivery. Niosomes are novel drug delivery systems, in which, medication is incorporated within a vesicular carrier composed of a bilayer of non-ionic surface active agent and hence the name niosome. They are very small microscopic lamellar structures whose size usually lies in the nanometric range. Although structurally similar to liposomes, niosomes offer several advantages over them. In addition to transdermal drug delivery they are widely used for targeted drug delivery as well as for immunological applications.^{24, 25} Although the NSAIDs used in rheumatoid arthritis helps in reducing pain and inflammation against the body's immune system, they also exhibit certain side effects like narrow therapeutic index, short biologic half-life etc. They also help in reducing dosing frequency and therefore better patient compliance. Niosomes possesses a hydrophobic and hydrophilic infra-structure and can be used for accommodating a wide range of drugs with different solubilities. Niosomes are biodegradable, biocompatible and non –immunogenic to the body and can be used for incorporating hydrophilic, lipophilic as well as amphiphilic drugs. They can also be widely used as depot formulations showing controlled and sustained drug release action.²⁶⁻²⁹

Niosomes are widely been utilized for enhanced therapeutic efficacy of anti-neoplastic drugs like doxorubicin hydrochloride, methotrexate, bleomycin etc. and have demonstrated high tumoral efficacy. Anti-inflammatory agents Diclofenac, Nimesulide, Flurbiprofen etc. have showed increased anti-inflammatory action than that of the plain drug. Transdermal delivery of ketoprofen niosomes with span 60 have been investigated for increased bioavailability and therapeutic effect.^{30, 31} Topical meloxicam niosomal gels containing non-ionic surfactants showed better pharmacological activity than plain meloxicam gel and thus offers greater potential than conventional systems.³²

Pharmacosomes

The development of pharmacosomes offers a significant advance over conventional vesicular systems providing protective and controlled drug delivery of various drugs. Pharmacosomes are lipid vesicular systems which are amphiphilic in nature, possessing phospholipid complexes to improve bioavailability of poorly water soluble as well as poorly lipophilic drugs. These are particulate dispersions in which colloidal dispersions of drugs are bounded to phospholipids by means of covalent, electrostatic or by hydrogen bonds. Drugs containing active hydrogen atom ($-\text{COOH}$, $-\text{OH}$, $-\text{NH}_2$) can be esterified to lipid with or without spacer chains and may exist as ultrafine micellar or hexagonal aggregates

depending upon their chemical structure. Pharmacosomes have been widely prepared for various NSAID's, proteins, cardiovascular and antineoplastic agents having improved pharmacokinetic and pharmacodynamic properties^{33,34}.

L.M Raikhman *et al.* discussed pharmacosomes as building materials characterized by high selectivity (acting on target cells) and are capable of delivering various biologically active substances including biopolymers (nucleic acid and proteins)³⁵. A. Semalty *et al.* optimized formulation and evaluation of aceclofenac pharmacosomes and found the drug content was 91.8%w/w for aceclofenac phospholipid complex (1:1) and 89.03% (w/w) for aceclofenac phospholipid complex (2:1). Solubility of aceclofenac pharmacosomes was found to be higher than aceclofenac³⁶. A.Semalty *et al.* also studied the development of diclofenac pharmacosomes and evaluated for drug's solubility, *in vitro* dissolution study, drug content, surface morphology, crystallinity and phase transition behavior. Diclofenac pharmacosomes showed better water solubility and enhanced entrapment efficiency³⁷. A.Semalty *et al* also conducted investigations on development and characterization of aspirin-phospholipid complex in (1:1 molar ratio) for improved drug delivery and found to enhance bioavailability of aspirin and also reduced gastro intestinal toxicity of aspirin³⁸.

Even though pharmacosomes exhibit greater shelf life and stability, they also have some limitations such as covalent bonding is required to protect the leakage of drugs, and sometimes it may undergo fusion, aggregation as well as chemical hydrolysis³⁹

Ethosomes

Ethosomes are novel vesicular systems used as non-invasive delivery carriers that enable drug to reach the deep skin layers and or the systemic circulation. Although ethosomal vesicles are conceptually sophisticated, they are characterized by simplicity in their preparation, safety and efficacy – a combination that can highly expand their application. Ethosomes are soft, malleable vesicles tailored for enhanced drug delivery of active drug moiety and are mainly composed of phospholipids, high concentration of ethanol and water. The high concentration of ethanol in ethosomes disturbs the skin lipid bilayer, such that when integrated into a vesicle membrane, it gives the vesicle the ability to permeate the stratum corneum⁴⁰.

Research works on Aceclofenac ethosomes have clearly demonstrated that the *in vivo* efficacy of Aceclofenac ethosomal gel was found to be significantly higher than marketed Aceclofenac gel and gel containing free drug. The study also suggested that aceclofenac ethosomal gel can be used for transdermal treatment of rheumatoid arthritis where chronic use is needed⁴¹. Cannabidiol ethosomes were investigated for transdermal drug delivery and was found to have improved bioavailability, increased skin permeation and improved gastro intestinal



tract degradation⁴². Diclofenac ethosomes offers selective drug delivery to described site for a prolonged period of time⁴³.

Transfersomes

Transfersomes are recently introduced specially designed, ultra deformable lipid supramolecular aggregates used for transdermal delivery of low as well as high molecular weight drugs. Transfersomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together and can therefore accommodate drug moieties with a wide range of solubilities. They offer high entrapment efficiency, up to 90% in case of lipophilic drugs and can also protect the encapsulated drug from metabolic degradation. They can act as depot formulations, releasing their contents gradually and slowly in a controlled manner and can be used for both systemic as well as topical drug delivery^{44,45}.

Research works were done on Ibuprofen, a highly potent NSAID used in Rheumatoid arthritis to formulate it into Ibuprofen transfersomes, in order to combat its limitations like low solubility, low incorporation in formulations and low skin permeations⁴⁶. Diractin (ketoprofen in transfersome gel) is a new, carrier-based formulation for local application that has shown to reduce pain comparable to oral celecoxib in patients with knee osteoarthritis⁴⁷.

CONCLUSION

Although the advent of biologics markedly increased the number of available treatment options, numerous rheumatoid arthritis patients still use, either alone or in combination, NSAID's, glucocorticoids and conventional disease modifying anti-rheumatoid drugs (DMARD's). All of these compounds are associated with severe negative side-effects resultant from non-specific organ toxicity. In some cases, the side effects necessitate the cessation of a treatment option that may be effectively altering the course of the disease. The application of drug delivery strategies as outlined herein, promises to improve patient outcome by reducing the likelihood of an adverse reaction to NSAID's, glucocorticoid's, and biologic and conventional DMARD's. These strategies can also be extended in future to facilitate diagnostic imaging and gene therapy, thereby further increasing the possibility of successfully controlling the progression of the disease in all patients suffering from rheumatoid arthritis.

Abbreviations:

RA – Rheumatoid arthritis

NSAID – Non-steroidal anti-inflammatory drug

RF – Rheumatoid factor

ESR – Erythrocytic Sedimentation Rate

ELISA – Enzyme Linked Immunosorbent Assay

Ig – Immunoglobulin

IL – Interleukin

TNF – Tumour Necrosis Factor

CRP – C – Reactive Protein

COX – Cyclo oxygenase

DMARD – Disease Modifying Anti-rheumatoid Drug

BRM – Biologic response Modifier

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