Novel Drug Delivery Technologies For The Treatment Of Rheumatoid Arthritis
J Patel, B Jigar, H Shah, D Patel

Abstract
Rheumatoid Arthritis is a chronic autoimmune disease and a major cause of disability. Current treatment of arthritis involves administration of drugs mainly by oral and parenteral route. Frequent dosing often leads to patient non compliance. Accounting this problem, drug delivery technologies should be developed which reduces frequency of dosing along with sustained release of medicament. Various drug delivery systems are documented like albumin-based drug delivery systems, bio-reductive drug delivery systems, microspheres, nanoparticles, liposomes etc. Conventional drugs like indomethacin, magestrol acetate, methotrexate and cannabidiol have been modified into extended release formulations, nano crystal oral suspensions, topical gel and transdermal patch respectively. Targeting αγβ3 integrin has been shown to enhance drug delivery. Drugs delivered by intra-nasal route significantly reduce disease severity in experimental collagen induced arthritis model. This review reports a comprehensive overview of newly developed drug delivery technologies as therapeutic targets of rheumatoid arthritis which may potentially reduce adverse extra-articular side effects.

INTRODUCTION
Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown etiology, characterized by joint synovial inflammation and progressive cartilage & bone destruction resulting in gradual immobility (1). It was first found in early Native American population several thousand years ago but might have appeared in Europe after 17th century (2). Recent research has produced exciting information about pathogenesis of RA. It is suggestive that activated synovial fibroblast plays a major role in both initiating and driving RA in addition to macrophages and T cells (3). In RA there is significant difference between the superficial synovial fibroblast lining and deeper synovial fibroblast lining. Synovial fibroblast differs morphologically and biologically from normal synovial tissue. These morphological and biological changes of synovial fibroblast results from specific changes in transcriptional genes and intracellular signaling cascade. The transcription factor NF-kB is activated in RA and appears to be important for progression of disease as well as in mediating inflammation (4–6).

Various inducers and targets of NF-kB serves as a potential target for treating RA (4–6). (Table 1).

Figure 1
Table 1: Various targets and effects of NF-kB

Many mediators have been postulated for provoking inflammation in RA such as Tumor Necrosis Factor alpha (TNF-α), Interleukins (IL-1, IL-6, IL-8, IL-15), fibroblast growth factor and platelet derived growth factor. As a result of inflammation the synovium thickens, the cartilage and the underlying bone begin to disintegrate and evidence of joint
destruction occurs. The role of cytokines in pathogenesis of RA has been established since a large number of cytokines are expressed in a rheumatoid synovium, and thus prove to be potential therapeutic target \( (9) \). RA is initiated by an unknown antigen(s) like Epstein Barr Virus, bacterial cell wall product, endogenous collagen or immunoglobulin within synovium in the genetically programmed host. These antigen triggers immune response activating monocytes and lymphocytes. Monokines stimulate synovial cells proliferation which in turn synthesizes several enzymes and product of arachidonate metabolism capable of destroying normal articular joints \( (10) \). Apart from auto immune theory, other hypothesis have also been postulated which is characterized by alteration in micro vascular anatomy and function which occur during the hypoxic state which is characteristic of RA. Increase in metabolic need in synovial tissue is usually accomplished with microcirculatory alteration which results in initiation of inflammatory process \( (11) \). Moreover generation of oxygen free radicals have also been suggested in the pathogenesis of RA \( (12) \). Recent research suggest that calcifying nanoparticles (also known as Nanobacteria) are present in synovial fluid of arthritic patients and these calcifying nanoparticles are responsible for provocation of inflammation which ultimately leads to bone and joint destruction resulting in arthritis \( (13) \).

**TREATMENT**

Since RA is a progressive and incurable disease; treatment involves frequent administration of drugs. Drugs used in treatment of rheumatoid arthritis are mainly classified as first line agents and second line agents. First line agents mainly involve non steroidal anti-inflammatory drugs (NSAIDs) and steroids such as glucocorticoids. Second line agents mainly include disease modifying anti-rheumatic drugs such as chloroquine, gold salts, penicillamine, cyclosporine, and several biological agents like TNF-\( \alpha \) and interleukin-1 inhibitors \( (14, 15) \). First line agents are used for suppression of pain manifested in arthritis; however these agents do not prevent further destruction of joints. In contrast to first line agents, second line agents do not relieve pain but are more effective in prevention of joint destruction.

**FIRST LINE AGENTS**

**NON STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs)**

NSAIDs, as a first line agents, offer little protection against tissue degeneration. NSAIDs like Ibuprofen, Diclofenac etc acts non selectively by inhibiting both Cyclooxygenase enzyme (COX 1 and COX 2) which is responsible for synthesis of prostanoids from its precursor Arachidonic acid. COX 1 enzyme is constitutively present in cells whereas COX 2 is inducible form and is generated at sites of inflammation. It is reported that NSAIDs provides pain relief by reducing prostaglandin, bradykinins and oxygen radicals \( (16) \). Non selective COX inhibitors produces side effects on long term use and to overcome this problem, selective COX 2 inhibitors were developed. COX 2 inhibitors decreases COX 2 mRNA levels and modulate local and systemic cytokine production in order to reduce inflammation and bone erosion \( (17) \). Celebrex® (Celecoxib, Figure 1) is a selective COX 2 inhibitor, used in relieving arthritic pain and available in Capsules formulation manufactured by Pfizer Pharmaceutical, USA \( (18) \).

**CORTICOSTEROIDS**

Corticosteroids have been widely used for suppressing pain and inflammation in arthritis since many years. Corticosteroids acts by inhibiting induction of COX enzyme. Moreover, corticosteroids also inhibits release of collagenase and lysosomal enzyme by reducing macrophage phagocytosis and IL-1 secretion \( (19) \). Glucocorticoids are immunosuppressant and acts by limiting clonal proliferation of Th cells, through decreasing transcription of many cytokine genes \( (20) \). Administering steroids to children suffering from arthritis is a matter of concern in terms of palatability. Various steroidal preparations are available in market such as Pediapred (Medeva Pharmaceuticals, Rochester, NY), Prelone (Muro Pharmaceuticals, Tewksbury, MA), prednisone oral solution, prednisone...
intensol, and prednisone 10-mg tablet crushed in 10 mL of cherry syrup (21).

SECOND LINE AGENTS
DISEASE-MODIFYING ANTI-RHEUMATIC DRUGS (DMARDs)

Various drugs of different categories are used as DMARDs such as gold, chloroquine, sulfasalazine, methotrexate, Azathioprine, d-penicillamine, cyclophosphamide, Leflunomide etc. Most of the DMARDs are immunosuppressant drugs which are reported to retard joint degeneration in about two third of patients (22). Each DMARD acts by different mechanism. Sulfasalazine acts by scavenging toxic oxygen metabolites produced by neutrophils as well as by inhibiting translocation of NF-kB resulting into inhibition of transcription of various chemokines (23). Penicillamine modify rheumatoid disease partly by decreasing IL-1 generation and partly by an effect on collagen synthesis. Azathioprine is an immunosuppressant that inhibits clonal proliferation in the induction phase of immune response and thereby depresses both cell mediated and antibody mediated immune reactions. Leflunomide has a relatively specific inhibitory effect on activated T cells. Leflunomide retards proliferation of activated T cells in addition to inhibiting adhesion and migration of inflammatory cells. Leflunomide give rise to a metabolite that inhibits de novo pyrimidine synthesis by inhibiting dihydroorotic acid dehydrogenase. Leflunomide has been reported to have clinical improvement in arthritic patients (24).

BIOLOGICAL AGENTS

The anti-cytokines agents are biological prepartions that target the action of tumour necrosis factor-α, an important mediator of the rheumatoid inflammation and inhibit its effects. TNF-α is thought to stimulate release of many tissue degradative enzymes such as matrix metalloproteinases from synoviocytes. TNF-α produces its effects through two types of membrane bound receptors (TNFRs), type I and type II. The extracellular portions of these receptors can be cleaved to become soluble TNFRs in sera. TNFRs have been shown to suppress inflammatory action of TNF-α. Enbrel (Etanercept, Figure 2) is a sTNFR having significant effect in reducing pain and joint destruction (25).

Remicade [[TM ]] (Infliximab, Figure 3) is a chimeric monoclonal antibody against TNF-α which reduces both joint pain and swelling (26).

Orencia® (Abatacept, Figure 4) is a biological agent indicated in methotrexate inadequate patients (27). Though biological agents are nowadays widely used in treating arthritis, they are also associated with local and systemic complications (28).
Apart from the above mentioned therapy, viscosupplementation is an effective treatment for OA of the knee with beneficial effects in pain, function and patient global assessment along with fewer adverse effects. Fermatron [[TM]] (Hyaluronic acid) is a viscosupplement marketed by Biomet Europe for the treating arthritic patient (29).

Drugs in RA are mainly administered by three routes i.e
Oral, Parenteral and Transdermal (topical). Apart from these routes intranasal route has also been described by many researchers for delivery of drugs to treat rheumatoid arthritis. The purpose of this review article is to highlight new drug delivery technologies which envisage better patient compliance in terms of less frequent dosing with increased drug efficacy while minimizing extrasynovial toxicity and producing sustained or persistent effects of drugs.

**ORAL DELIVERY**

Oral route is the most conventional and preferred route of drug administration. Most of the drugs used in treatment of RA are administered by oral route. Since the therapy involves frequent administration of drug, chances of patient noncompliance increase drastically. NSAIDs inhibit both COX-I and COX-II enzymes, and thereby results in reduction of pain and inflammation, but also leads to several side effects such as gastric bleeding, impairment of renal blood flow, renal necrosis, nephrotic syndrome, and hepatic injury (13). Oral administration of corticosteroids also produce many systemic side effects like bone loss, increased susceptibility to infection, osteoporosis, peptic ulcers and buffalo hump (36). Various approaches have been tried to overcome the cited drawbacks of orally administered drugs in RA. Since oral indomethacin produces several dose related side effects which are associated with long term administration, its use becomes limited. To overcome this problem, Indomethacin Extended release formulation was developed by pelletization and coating based on principle of micro porous membrane drug delivery using soluble salts (37). Another innovative approach for oral drug delivery involves use of oral pulsatile drug delivery system which involves liberation of drugs following a programmable lag phase from the time of administration (38). Megestrol acetate, a progestogen has been used to treat RA induced cachexia, a condition characterized by loss of > 5 % of an individual’s body weight over 2-6 months. The megestrol antagonizes metabolic effects of catabolic cytokines. Since bioavailability of megestrol directly affects its efficacy, the formulation was modified to enhance its pharmacokinetic. Megestrol acetate nano crystal oral suspension has been developed and is under review by US FDA for treatment of cachexia (39). Martha et al have reviewed safety and efficacy profiles of four different dosages of orally administered type II collagen (CII) to treat RA (40). Positive effects were observed with CII at the lowest dosage tested and no side effects were associated with this agent. NSAIDs nowadays are combined with other drugs such as misoprotol and this combination is reported to have beneficial action rather than using NSAIDs alone. Arthrotec® (Diclofenac Sodium and Misoprotol) is example of such combination marketed in U.K by Pharmacia Company. Arthrotec provides good protection against gastric erosion and is proved to be efficacious in arthritis (41). Amongst NSAIDs, oxaprozin offers several advantages in arthritis. Daypro® (oxaprozin) is a NSAID, manufactured by G.D.Searle & Co and marketed in U.S. (42).

**PARENTERAL DELIVERY**

Parenteral products are unique among dosage forms of drugs because they are injected through the skin or mucous membranes into internal body compartments (43). Inspite of advantages of parenteral drug administration in RA, this route is seldomly used due to higher incidences of patient noncompliance and rapid clearance rate of drug which ultimately compels frequent administration of drug. Moreover because self medication is not possible, it limits use of this route in treatment of RA. Intra-articular administration of corticosteroids has been recommended in order to diminish complications of oral administration and has been proved to produce symptomatic relief in joint inflammation (44). Nanoparticles encapsulating anti-arthritic drugs offer advantages of both targeted as well as sustained drug delivery. Higaki et al studied the therapeutic activity of poly (D, L-lactic/glycolic acid) nanoparticles encapsulating betamethasone sodium phosphate to produce slow release and target delivery after intravenous administration of these nanoparticles (45). Poly (D,L-lactic/glycolic acid) nanoparticles encapsulating triptolide have been reported to produce anti-inflammatory effect in adjuvant induced arthritis in rats (46). Self administered injectables are available which are easy to use and provide convenient drug delivery devices that treats RA. Humira® pen (Figure 5) is an auto injection device developed for subcutaneous administration of monoclonal antibody adalimumab which offers advantage over intravenous injection since it is easy to use (47).
Lipid Microspheres are excellent carriers for drug delivery owing to their high stability and safety. It has been shown that lipid microspheres get accumulated well in inflammatory lesions of patients with RA \( (48) \). Microspheres encapsulating fragile drugs not only increases patient comfort and compliance but also releases drug from the encapsulating device at a controlled rate for longer period of time lasting for days to genes, plasmid DNA and therapeutic proteins \( (49) \). The role of parenterally administered liposomes in treating RA has also been established. One of the novel approach to treat RA involves use of prednisolone phosphate containing TRX-20 Liposomes, which inhibits cytokines and chemokines production in human fibroblast-like synovial cells \( (50) \). Leopold F reported that intra-articular administration of super oxide dismutase was found to be effective in treatment of osteoarthritis \( (51) \). The role of Rituximab (Mabthera, Figure 6) in the treatment of arthritis has been established. Rituximab is a monoclonal antibody to CD20 protein of B cells resulting in depletion of B cells \( (52) \).

Dexamethasone crystal suspension (Supertendin®) available in 5 to 10 mg is used for treating arthritis \( (53) \). SimpleJect™ Self-Injection Device is auto-injector system is designed for self-administration of Amgen Inc.’s Kineret™ (Anakinra, Figure 7.1, 7.2) drug for rheumatoid arthritis \( (54) \).

Figure 8
Figure 5: is a biological therapy used to treat symptoms of arthritis and is available in pre-filled syringes to be administered twice a month

Figure 9
Figure 6: MabThera (Rituxan): Acts mainly by targeting B cells which plays a key role in initiating inflammatory events leading to bone and joint damage
TARGETED DELIVERY

Despite noteworthy advances that have been made over recent years in drug therapy for the management of RA, the currently used agents still have a dose limiting therapeutic index and compromised safety implications. Specific targeting of drug to the synovium or specific tissues may increase the drug efficacy with minimum extrasynovial toxicity. Targeting the inflamed synovium as a strategy for the drug delivery is therefore a major research goal.

NON SPECIFIC TARGETING STRATEGIES

A number of approaches have been employed to alter the pharmacokinetics of systemically administered compounds so as to improve their therapeutic index. The simplest of these is direct conjugation of a drug to another large molecule. Examples of such drugs currently available are the PEGylated soluble Tumour Necrosis Factor (TNF) receptor and an anti-TNF antibody, which have both shown encouraging results in the treatment of RA. Further, RA is characterized by synovial proliferation with chronic inflammatory cell infiltration and new vessel formation (55). Thus neoangiogenesis strategy seems to be successful in RA. The newly formed vessels show substantially enhanced permeability to macromolecules (56). This has been successfully exploited in the use of macromolecules to target therapeutic compounds to synovial tissue. For example: Methotrexate (MTX) has a relatively short plasma half life owing to rapid renal excretion, while conjugation to albumin prolongs its circulating half-life and improves pharmacokinetics in animal tumor and arthritis models. Also, active uptake of albumin is rapid by synovial fibroblasts (57, 58). Thus radiolabelled albumin-MTX conjugate is significantly more effective than MTX alone for both, treatment and prophylaxis of collagen induced arthritis.

Another well established strategy for the improvement of drug pharmacokinetics and tissue delivery is encapsulation in liposomes. Liposomes are vesicles consisting of a phospholipid bilayer encapsulating an aqueous core, and they can be used as vehicle for a variety of therapeutic compounds (59). Encapsulation increases retention time in the joint and enhances uptake by macrophages due to phagocytosis of non-PEGylated liposomes, and macrophage depletion has been shown after intra articular injection of clodronate-liposomes in patients with RA. Promising results have been obtained with intra-articular injection of liposomal preparations of encapsulated corticosteroids in humans with RA (60) and MTX in animal models (61). Recently, Matselaar and colleagues demonstrated that liposomal prednisolone phosphate is significantly more efficacious in reducing the cartilage damage than the same dose of the free drug in two murine arthritis models (62, 63).

SPECIFIC TARGETING APPROACHES

Vascular Endothelium is an attractive therapeutic target in RA. Therapeutic blockade of angiogenesis has been shown to be efficacious in preclinical models of arthritis. An important molecule that is expressed at low levels by normal endothelial cells but up-regulated in neoangiogenic vessels is the αγβ3 integrin, a dimeric transmembrane molecule which binds naturally occurring Arg-Gly-Asp (RGD) sequences in a number of components of the extracellular matrix, including vitronectin, fibronectin, and fibrinogen (64). Targeting of αγβ3 integrin has been shown to enhance the drug delivery. In another study, i.v injection of RGD-liposome encapsulated dexamethasone at the time of disease onset in rat adjuvant-induced arthritis was significantly more efficacious than non targeted liposomal dexamethasone or control vehicle. Promising results has been seen with the targeting of synovial macrophages. The Folic acid receptor FRβ is up-regulated on activated synovial macrophages in a rat arthritis model (65). Thus specific targeting of Liposomes has been shown to be effective in arthritis and represents an important step forward towards enhancement of efficiency of drug delivery.

TOPICAL DELIVERY

Topical route allows drug to diffuse out of its vehicle onto the surface tissues of skin. Infact ease of applicability makes
this route more comfortable for the patient which results in better patient compliance. Penetration of drugs from trans-epidermal route is fairly rapid, although slower than intestinal tract absorption. There is no significant hindrance to penetration, once the drug passes through stratum corneum of epidermis of skin (68). Topical NSAIDs have been reported to have reduced incidences of systemic side effects like gastric bleeding and peptic ulcer (67). The feasibility of topical route over parenteral route in treatment of RA has been assessed. Topical methotrexate gel in poloxamer 407 polymer have been found to produce sustained and higher drug levels in muscle tissues beneath the site of administration (69). So far most of the analgesics and anti-inflammatory drugs used for the treatment of RA, are administered mainly by transdermal route. Currently anti inflammatory drugs are mainly delivered by transdermal iontophoresis. New drug application (NDA) of Alza corporation for iontophoteric fentanyl containing trandermal analgesic have been approved by US FDA (69).

Iontophoresis is a special method of applying drug to and pushing it through the skin to reach the blood vessels and surrounding deeper tissues by electric transmission. Cannabidiol which is a drug used to treat RA is associated with number of systemic side effects when administered orally, however transdermal delivery of cannabidiol using ethosomes carrier system has been designed and is found to prevent inflammation and edema (70). A significant amount of Piroxicam was retained in the skin after transdermal iontophoresis from piroxicam: Hydroxypropyl-β-cyclodextrin complex gel (71). Penetration enhancers and vehicles play an important role in penetration and absorption of drug in percutaneous drug delivery system. In vivo percutaneous absorption of Methotrexate and Edatrexate in hairless mouse skin has been established using different vehicles and penetration enhancers (72). In order to enhance skin permeability of ketoprofen, various topical formulations have been formulated; one such formulation includes topical Oleo Hydrogel Ketoprofen preparation with enhanced skin permeability (73). In order to increase penetration lipid nano/submicron emulsion can be used as a vehicle for topical delivery of drugs (74). Apart from oral, parenteral and topical drug delivery systems, several innovative drug delivery approaches in treatment of rheumatoid arthritis have been developed. Hypoxia is a common finding in RA which facilitates delivery of bioreductive drug targeting system as oxygen suppresses release of active drug. Bioreductive drug delivery involves three system viz. quinone lactonization systems, self alkylating system and redox mediated cyclisation. Quinone lactonization system involves reduction of quinine and thereby facilitates release of drug through bond cyclisation. Self alkylating system involves conversion of nucleophile into bioreductive structure to favor intramolecular cyclisation over nucleophilic attack from DNA molecules (75).

Nasal Delivery

Intranasal route of drug administration provides accurate, effective, repeatable and hygienic dosing. Moreover devices used to deliver drug through intranasal route are easy to use and are in pre-filled dose format. Drugs can be given both for local use as well as systemic use through nasal route. Extensive research has been conducted to assess the feasibility of drug delivery through intranasal route. Although it has been established that oral and parenterally administered collagen suppresses arthritis, collagen administered by intranasal route offers an additional advantage of ease of administration (76). Role of peptides derived from Heat shock protein in induction of arthritis has been established. A method of partially suppressing arthritis has been developed by inducing tolerance to peptides derived from Heat shock proteins through nasal administration of peptide analogue (77). Intranasal administration of human cartilage glycoprotein 39 has been shown to reduce sign and symptoms of arthritis in mouse model (78). Intranasal vaccination with Cholera Toxin B subunit (CTB) conjugated with type II collagen (CII) is demonstrated to be effective in collagen induced arthritis. Vaccination results in decreased production of interleukin-4 (IL-4), IL-6, and interferon-gamma (79). Intranasal delivery of an IL-10 plasmid (PG-IL-10) significantly delayed arthritis onset and reduced disease severity in experimental collagen-induced model of arthritis. Gene delivery reduced bone destruction, showed evidence of reducing joint inflammation (80).

Conclusions

Thus RA is immensely complex and very likely caused by more than one type of inciting factors. Development of various technologies to tailor various available therapies to the unique circumstances and disease processes of each individual patient will prove very challenging. However, these novel targeted drug delivery systems have proved to be a successful intervention not only in experimental arthritis but also in clinical settings where it demonstrates great promise in terms of ease of drug administration and better compliance of patients suffering from rheumatoid arthritis.
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Author Information

Jagruti Patel, PhD
Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology

Bhatt Jigar, M.Pharm
Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology

Harshit Shah, M.Pharm
Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology

Dhavel Patel, M. Pharm.
Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology