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Controlled Drug Delivery Approaches for Rheumatoid Arthritis

Amandeep Kaur and S.L. Harikumar

Amandeep Kaur and S.L. Harikumar
Rayat & Bahra Institute of Pharmacy,
Sahauran, Kharar, Mohali (Pb),
140104

For correspondence
Dr. SL Harikumar
Director-Principal
Rayat & Bahra Institute of Pharmacy
Sahauran, Kharar, Dist. Mohali,
PIN-140104
Mobile: 9888017546

ABSTRACT

A cure for rheumatoid arthritis is yet to be discovered. Although vast resources have been expended in the search for an immunological key to switch off the rheumatoid process, the most significant advances in the treatment of rheumatoid arthritis in recent times had come from gaining better understanding and skill in the safe use of existing disease modifying anti-rheumatic drugs (DMARDs). If prescribed appropriately and combined with adequate patient education and monitoring, Disease modifying anti-rheumatic drugs are safe and effective tools in the treatment of rheumatoid arthritis. The step down approach has been proposed for the treatment of patients with recent onset rheumatoid arthritis who have clinical features predictive of an adverse prognosis. More efficient 'targeting' of drugs at the site of desired action should help to minimize the adverse effects of therapy. Ultimately the most efficient way of relieving pain and stiffness will be to prevent or suppress the inflammatory disorders which give rise to the symptoms. Unfortunately this is a goal at present.

Keywords: Rheumatoid arthritis, Delivery of NSAIDs, Delivery of disease modifying anti-rheumatic drugs, DMARDs, Controlled delivery, inflammatory disease.

INTRODUCTION

Rheumatoid arthritis is a chronic disease in which various joints in the body are inflamed, leading to swelling, pain, stiffness, and the possible loss of function. Rheumatoid arthritis is characterized by persistent synovitis, systemic inflammation, and auto antibodies (particularly to rheumatoid factor and citrullinated peptide) (Afeltra *et al.,* 2001). Rheumatoid arthritis is a heterogeneous disease which may run a benign course with little or no long term loss of function, or at the other extreme, may lead to serious morbidity with rapid loss of function (Scohrn *et al.,* 2000). Rheumatoid arthritis is an autoimmune disease that causes inflammation of the joints, the tissue around the joints, as well as other organs in the body. Rheumatoid arthritis is a progressive illness that can lead to long-term joint damage, loss of function and disability. Morning stiffness is a common problem for patients with rheumatoid arthritis (Silson *et al.,* 2000).

Rheumatoid arthritis is a common inflammatory disease characterized by progressive bone and cartilage destruction, resulting in severe functional limitations, shortened lifespan, and increased mortality rates (Pharm *et al.,* 2011).
Rheumatoid arthritis management:

Causes

- Abnormal immune response
- Genetic factors
- Environmental factors

Symptoms

- Morning stiffness
- Weight loss
- Decreased appetite
- Muscle aches
- Swelling of soft tissues
- Subcutaneous noudles

Diagnosis

- Positive rheumatoid factor.
- Increase C-reactive protein
- Decrease of serum haemoglobin

DELIVERY APPROACHES

a) Delivery of Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)
b) Delivery of Disease Modifying Anti-Rheumatoid Drugs (DMARDS)
c) Delivery of Corticosteroids
d) Novel Approaches and Developments in Colon Specific Drug Delivery Systems
e) Micro and Nano-Carrier Mediated Intra-Articular Drug Delivery Systems for
f) Immunosuppressive Exosomes

Delivery of Nonsteroidal Anti-Inflammatory Drugs (NSAIDS)

Although nonsteroidal anti-inflammatory drugs are still widely used to lessen pain, they are no longer considered first-line treatment because of their limited effectiveness, inability to modify disease course in the long term, and adverse effects. The current approaches aim at decreasing Nonsteroidal anti-inflammatory drugs -related adverse effects through site-specific delivery and controlled release. For lipophilic drugs such as Nonsteroidal anti-inflammatory drugs, several groups of investigators found that lipid microspheres, lipid-based preparations with an internal oil phase surrounded by a phospholipid monolayer, offer better loading capacity compared with conventional liposomes (Christine *et al.,* 2011). Nonsteroidal anti-inflammatory drugs are usually indicated for the treatment of acute or chronic conditions of pain and inflammation. Nonsteroidal anti-inflammatory drugs are the most prescribed medications for treating conditions such as arthritis (Paola *et al.,* 2005).

Diclofenac

Controlled release tablets

Enteric coated tablets were formulated having good efficacy and tolerability. Sustain release tablets were also prepared. Tablets had better targeting profile in terms of release (Anne *et al.,* 2009). It was concluded that controlled-release formulations were as efficacious and well tolerated as sustained-release diclofenac sodium (Cheng-liu *et al.,* 2005). The present study was aimed at developing a novel sodium diclofenac formulation for colonic release. Tablets containing the drug central core were prepared by direct compression; diclofenac from a central core matrix tablet aimed for colonic drug delivery (Maria *et al.,* 2003). Fast dissolving tablets were prepared by using super disintegrant croscarmellose sodium and crospovidone. Fast disintegrating tablets were prepared successfully by direct compression method. Tablets show excellant in-vitro disintegration time and drug release profile as compared to other formulations (Amita *et al.,* 2007).

Liposomes

Liposomes had been formulated to avoid various problems in conventional dosage forms. In the preparation of liposomes, propylene glycol was added to the hydrophilic phase in order to obtain new systems able to enhance the skin delivery of diclofenac (Vyas *et al.,* 2004). The introduction of the liposome-based formulation of the Nonsteroidal anti-inflammatory drugs diclofenac had shown promising effect as a safe and convenient treatment for lameness associated with osteoarthritis (Manconi *et al.,* 2009).

Sustained Release Pellets

Diclofenac sustained release pellets coated with polymethacrylic films formulated. The objective of the present study was to evaluate three formulation parameters for the application of polymethacrylic films from aqueous dispersions in order to obtain multiparticulate sustained release of diclofenac sodium (Kramar *et al.,* 2003). Immediate-release diclofenac pellets had been formulated. Pellets had better dissolution profile and increased bioavailability of dosage forms (Bernard *et al.,* 2003).

Microcapsules

Dual coated erodible microcapsules were prepared for modified release of diclofenac sodium (Biju *et al.,* 2008). Spray-Dried Sodium Diclofenac enteric-coated microcapsules had been formulated. Microencapsulated controlled release preparations of diclofenac sodium using different proportions of ethyl cellulose as the retardant material to extend the release. Oral controlled release formulation of diclofenac sodium by microencapsulation with ethyl cellulose. All the formulations were highly stable (Sajeev *et al.,* 2002).

Microspheres

Development of sustained release diclofenac microspheres intended for use in a suspension formulation. The microspheres had a release profile that made them suitable to be formulated as a sustained release suspension (Lewis *et al.*, 2008). Microspheres of diclofenac sodium were prepared using a natural biodegradable polymer as a carrier for intraarticular administration to extend the duration period of the dosage form in the knee joint. Microspheres provided a very rapid onset of analgesic activity, a prolonged analgesic duration, and an acceptable side-effect profile. After intra-arterial administration of microspheres, at the target site this revealed good targeting efficiency. In this present study, it was aimed to prepare microsphere formulations of DS using a natural biodegradable polymer as a carrier for intraarticular administration to extend the duration period of the dosage form in the knee joint. The microspheres effectively reduced joint swelling, but lesser extent than the oral diclofenac sodium in high dose (Tunvay *et al.*, 2003).

Nanocomposites

Diclofenac sodium-loaded is magnetic nanomedicine, which consists of a magnetic core (iron) and a biocompatible polymeric shell (ethyl cellulose), was used for parenteral administration (Adeyeye *et al.*, 2004). Such nanocomposites possessed very important characteristics such as unusually high drug loading, enhanced magnetic susceptibility and prolonged drug release, indicating their potential use as nanocarriers for efficient delivery of diclofenac sodium to inflammation sites (Arias *et al.*, 2009).

Soft gel

Soft gel provided a very rapid onset of analgesic activity, a prolonged analgesic duration, and an acceptable side-effect profile in the postoperative third molar surgery pain model. In an acute pain situation, the rapid absorption of nonsteroidal anti-inflammatory drugs from a formulation like the Soft gel may positively affect the time of onset and duration of inflammatory pain compared with other commercially available nonsteroidal anti-inflammatory drug formulations (Joseph *et al.*, 2003).

Suppositories

Suppositories had been prepared by pour moulding method. Suppositories had been used for clinical purposes.Therefore long acting Suppositories would be helpful to patients. Suppositories of diclofenac have been prepared to avoid gastric irritation. Suppositories had been found to stable formulations (Ahmed *et al.*, 2000).

Topical formulations

Topical formulations of non-steroidal anti-inflammatory drugs (NSAIDs), in particular diclofenac, have become popular for treating various acute and chronic painful inflammatory conditions (Phillips *et al.*, 2000).

Pharmacosomes

Pharmacosomes of diclofenac were prepared with an equimolar ratio (1:1) of diclofenac and phosphatidylcholine in the presence of dichloromethane by the conventional solvent evaporation technique (Kavitha *et al.*, 2010). Pharmacosomes showed a high percentage of drug loading. Thus it can be concluded that the pharmacosomes of diclofenac may be of potential use for improving dissolution and for reducing the gastrointestinal toxicity of the drug (Semalty *et al.*, 2010).

Ibuprofen

Nanosuspensions

Indomethacin nanosuspensions were prepared by microfluidization. Nanosuspensions were of good efficacy and tolerability (Roland *et al.*, 2000).

Controlled release alginate beads

Controlled release alginate beads of ibuprofen had been made. In vivo data showed that the administration of ibuprofen in alginate beads prevented the gastric lesions (Arica *et al.*, 2005). Sustain release ibuprofen was at least as efficacious and at least as well tolerated as the standard formulation of the drug. It was suggested that the simplified treatment regimens possible with the sustain release preparation can be considered an advantage in clinical practice (Fernandes *et al.*, 2007).

Topical formulations

Ibuprofen-Phosphatidylcholine was an effective osteoarthritis agent with an improved gastrointestinal safety profile compared with ibuprofen in older arthritis patients, who are most susceptible to Nonsteroidal Anti-Inflammatory Drugs-induced gastro duodenal injury (Connor *et al.*, 2006). Ibuprofen-Phosphatidylcholine was similar to ibuprofen with regard to both bioavailability and efficacy to treat arthritis symptoms. Ibuprofen-phosphatidylcholine was used in arthritis. Gastrointestinal safety and analgesic efficacy was confirmed in osteoarthritic patients (Brabander *et al.*, 2000).

Microemulsion

The purpose of this study was to construct microemulsion-base hydrogel formulation for topical delivery of ibuprofen. Microemulsion-based hydrogel showed a good stability. These results indicate that the studied microemulsion-based hydrogel may be a promising vehicle for topical delivery of ibuprofen. Ibuprofen formulated as microemulsion .Cholesteryl ester was used in phospholipid microemulsions (Huabing *et al.*, 2006).

Microspheres

Sustained release ibuprofen-wax microspheres had been formulated. In this study sustained-release ibuprofen was shown to be a more effective alternative to conventional ibuprofen therapy for the treatment of arthritic diseases in general practice, offering the convenience of once-daily dosing and the associated potential benefit of improved patient compliance. The results indicate that sustain release ibuprofen was at least as efficacious and at least as well tolerated as the standard formulation of the drug. It is suggested that the simplified treatment regimens possible with the Sustain release preparation can be considered an advantage in clinical practice (Janjikhel *et al.*, 2009).

Controlled release tablets

Mini-tablets could be used to formulate sustained-release dosage forms. A novel sustained-release formulation of ibuprofen provided effective once-daily therapy in the treatment of rheumatoid arthritis and osteoarthritis and improved patient compliance (Baumgartner *et al.,* 2009).

Indomethacin

Sustain release capsules

Slow release formulations like indomethacin micro granules, Sustain release capsules prepared by the centrifugation (Crowley *et al.,* 2001). Clinical studies indicated comparable safety and efficacy profiles. The preparation of a sustained release dosage form for indomethacin was studied. Microcapsules were formulated for better stability of product. Sustained release formulations for the potent anti-inflammatory drug indomethacin were prepared by dispersing indomethacin in polysaccharide matrixes to form small microspheres (Rowe *et al.,* 2000). Polymeric nanocapsules were able to successfully carry indomethacin into the inflammatory sites and produced an increased anti-inflammatory efficacy in long-term models of inflammation, allied to an improved gastrointestinal safety (Jager *et al.,* 2005).

This formulation might represent a promising alternative for treating chronic inflammatory diseases, with reduced undesirable effects. Indomethacin sustained release microparticles showed the fastest release rate of drug. Indomethacin-loaded nanocapsules produced an increased anti-inflammatory efficacy in long-term models of inflammation, allied to an improved gastrointestinal safety. Polymeric nanocapsules were able to successfully carry indomethacin into the inflammatory sites (Emel *et al.,* 2004).

Sustain release pellets

The resultant formulations were further coated with various combinations of Eudragit RS (poorly water permeable) and Eudragit RL polymers (readily water permeable) also using the Wurster column. As expected, the total amount of drug released from the coated pellets increased as the concentration of Eudragit RL increased in the barrier coating. Pellets coated with Eudragit RL alone showed the fastest release rate of drug (Rhymer *et al.,* 2002).

Alginate-Gelatin Coacervates

Indomethacin sustained release formulations such as alginate-gelatin or pectin-gelatin coacervate had been formulated. The results of this study offer an inexpensive alternative form of sustained release. Controlled-release cellulose acetate films for local delivery of indomethacin were formulated. This study confirmed the good efficacy and tolerability of the new slow release indomethacin preparation. Cellulose acetate films may be a suitable inert material for obtaining a prolonged local release of indomethacin. As a conclusion, cellulose acetate may be a suitable inert material for obtaining a prolonged local release of various anti-inflammatory agents (Hasan *et al.,* 2009).

Liposomes

Liposomes were formulated for sustain release. The application of liposomes is the development of nonsteroidal antiinflammatory drugs that have minimal gastrointestinal side effects (Manadan *et al.,* 2006). The application of liposomes to the development of nonsteroidal antiinflammatory drugs that have minimal gastrointestinal side effects, an enhanced anti-inflammatory activity of lipo-indomethacin was found as compared with the activity recorded for plain drug. Encapsulation of indomethacin in liposomes provided protection against both gastric and intestinal ulceration (Katare *et al.,* 2005).

Microballoons

Microballoons of indomethacin are developed as a model drug, to increase its residence time in the stomach without contact with the mucosa. This multiparticulate drug delivery system showed good floating ability (Yun *et al.,* 2003). Objective of present study involves preparation and evaluation of floating microballoons of indomethacin as a model drug, to increase its residence time in the stomach without contact with the mucosa. The microballoons were prepared by the emulsion solvent diffusion technique using different ratio of acrylic polymers as carriers. Microballoons showed passable flow properties. In vitro drug studies were performed (Puebla *et al.,* 2005).

Microspheres

Biodegradable indomethacin microspheres were used for intra-articular administration in rheumatoid arthritis. Microspheres were prepared by solvent evaporation. Dissolution results showed that all formulations gave prolonged release of indomethacin (Claudia *et al.,* 2008).

Co-crystals

Indomethacin-saccharin co-crystals had been formulated. The study indicates that the improved aqueous solubility of the co crystals leads to improved bioavailability of Indomethacin. Thus, the co crystals are a viable alternative solid form that can improve the dissolution rate and bioavailability of poorly soluble drugs (Jung *et al.,* 2010).

Nanoemulsions

Nanoemulsions could be used as potential vehicles for improved transdermal delivery of indomethacin. These results suggested that nanoemulsions can be used as potential vehicles for improved transdermal delivery of indomethacin (Prasanthi *et al.,* 2009).

Suppository

An inexpensive alternative form of sustained release is indomethacin suppository in the treatment of rheumatoid arthritis with special regard to morning stiffness and pain on awakening. Both treatments were well tolerated with only a few transient and mild side-effects being reported. Indomethacin suppositories had equal therapeutic effects in the treatment of night pain and morning stiffness (Meyer *et al.,* 2006).

Dendrimers

Dendrimers promise better targeting efficiency of nonsteroidal antiinflammatory drugs with potentially reduced side effects. Dendrimers are another emerging class of biocompatible nanoparticles that promise to be effective vectors for the delivery of nonsteroidal antiinflammatory drugs because of their versatile surface functionalities. The branching structure of dendrimers can either entrap small drug molecules or their many end functional groups can be covalently attached to NSAIDs, thus increasing the solubility of these hydrophobic drugs (Alan *et al.*, 2005).

Naproxen

Sustained-Release Matrix Tablets

Sustained-Release Matrix Tablet of Naproxen was formulated. The objective of the present study was to develop once-daily sustained-release matrix tablets of naproxen, one of the most potent non-steroidal anti-inflammatory agents used in the treatment of arthritic pain. All the formulations exhibited diffusion-dominated drug release (Muhammad *et al.*, 2010). Clinical evaluation of a new controlled-release formulation of naproxen was done in osteoarthritis and rheumatoid arthritis. It was concluded that, in osteoarthritis and rheumatoid arthritis patients, once-a-day controlled-release naproxen tablets can be substituted for standard naproxen tablets without loss of efficacy or tolerability (Ryley *et al.*, 1999). A new controlled-release naproxen tablet was used in the treatment of osteoarthritis and rheumatoid arthritis. A new controlled-release tablet formulation of naproxen was suggested for use once daily for the treatment of arthritic diseases. It was concluded that, in osteoarthritis and rheumatoid arthritis patients, once-a-day controlled-release naproxen tablets can be substituted for standard naproxen tablets without loss of efficacy or tolerability. This study confirms the good efficacy and tolerability of the new slow-release indomethacin preparation. Controlled release tablets of naproxen with predictable drug release characteristics were obtained by compressing its microspheres with Eudragit (Zaghloul *et al.*, 2001).

Nanoparticles

Chitosan treated Ca-alginate microparticles of naproxen were prepared. Solid dose nanoparticulate naproxen formulations had high rates of dissolution and had a faster onset of action. Naproxen was loaded in poly-caprolactone nanoparticles as an implantable sustained release system to prolong its anti-inflammatory activity In vitro naproxen release profile was sustained and the kinetic followed the Higuchi model. In vivo release was sustained by one month.

Thus, nanoparticles showed potential to act as an implantable sustained release system for chronic inflammatory diseases use. Naproxen was loaded in poly-caprolactone nanoparticles as an implantable sustained release system to prolong its anti-inflammatory activity. Thus, nanoparticles showed potential to act as an implantable sustained release system for chronic inflammatory diseases. Nanoparticles of naproxen were prepared using eudragit.

The objective of the present study was to formulate naproxen–eudragit nanoparticles and investigate the physicochemical characteristics of the prepared nanoparticles. According of these findings, formulation was able to improve the physicochemical characteristics of the drug and possibly will increase the anti-inflammatory effects of drug following its ocular or intra-joint administration. Nanoparticles were able to improve the physicochemical characteristics of the drug and possibly will increase the anti-inflammatory effects of drug following its ocular or intra-joint administration (Zong-Zhu Piao *et al.*, 2008).

Ketoprofen

Tablets

Fast-dissolving tablets were formulated. The aim of this work was to develop a ketoprofen tablet which dissolve-rapidly in the mouth, therefore, needing not be swallowed. Results obtained showed that the increase in solubility of ketoprofen. Hence bioavailability was increased (Ahmed *et al.*, 2006).

Table. 1: Summary for the treatment of rheumatoid arthritis.

Drugs	Delivery approaches	Importance	References
NSAIDS (Nonsteroidal anti-inflammatory drugs)			
1.Diclofenac	Liposomes	Enhance skin delivery	Manconi et al, 2007
	Pellets	Increase bioavailability	Bernard et al, 2009
	Microcapsules	Better efficacy	Biju et al, 2008
	Microspheres	Good targeting efficiency	Tunvay et al, 2003
	Nanocomposites	Prolonged action	Arias et al, 2009
	Soft gels	Acceptable side-effect	Joseph et al, 2003
	Suppositories	Avoid gastric irritation	Ahmed et al, 2000
	Pharmacosomes	High drug loading	Semalty et al, 2010
2. Ibuprofen	Nanosuspensions	Decrease side-effects	Roland et al, 2000
	Microemulsions	Good stability	Huabing et al, 2006
	Microspheres	Effective therapy	Janjikhel et al, 2009
3.Indomethacin	Capsules	Better safety	Crowley et al, 2001
	Pellets	Faster release of drug	Rhymer et al, 2002
	Liposomes	Minimum side effects	Mandan et al, 2006
	Microballoons	Good floating ability	Yun et al, 2003
	Microspheres	Prolonged delivery	Claudia et al, 2008
	Nanoemulsions	Transdermal delivery	Prasanthi et al, 2009
	Suppositories	More therapeutic efficacy	Meyer et al, 2006
	Dendrimers	Improve bioavailability	Alan et al, 2005

4. Naproxen	Tablets Nanoparticles	Better safety Implantable sustain release	Ryley et al, 2003 Zang-Zhu et al, 2008
5. Ketoprofen	Tablets Microspheres Microcapsules Microsponges Nanoemulsions Transdermal patch Suppository Floating microparticles	Improve bioavailability Increase in-vitro release High drug loading Usage in dermatology Modify drug release More skin permeation Good efficacy profile Good flow property	Ahmed et al, 2006 Mathew et al, 2009 Morley et al, 2004 Comoglu et al, 2002 Beom et al, 2008 Tak et al, 2009 Uddenfel et al, 1999 Khosro et al, 2011
DMARDS (Disease modifying Anti-Rheumatic Drugs)			
1.Methotrexate	Microspheres Sustain release tablets Injections	Better targeting Good efficacy Improve safety	Chilukuri et al, 2008 Jundt et al, 2002 Crawford et al, 2005
2. Sulfasalazine	Delayed release tablets	Improved efficacy	Peppercorn et al, 2011
3. Azathioprine	Sustain release tablets	Better safety	Rodrigues et al, 2011
4. Tacrolimus	Solid dispersion	Potent suppressive activity	Gostick et al, 2010
5. Leflunomide	Sustain release Tablets Microcapsules Microspheres	More safety profile Better sustain action Rapid action of drug	Roland et al, 2010 Chon et al, 2011 Mikuls et al, 2009
6. Auranofin	Sustain release Tablets Injectables	More efficacy Produce high drug concentration at target site	Ashok et al, 2001 Kamel et al, 2004
Corticosteroids			
Prednisolone	Liposomes Microspheres Nanoparticles	Better targeting Fast release of drug Prolonged release	Singh et al, 2005
Blood plasma- or serum-derived	Immunosuppressive Exosomes	Safe therapeutic approach for arthritis	Chenjie et al, 2012

Microspheres

Microspheres were prepared by a spray-drying technique using solutions of ketoprofen and two polymers, cellulose acetate butyrate (CAB) and hydroxyl propyl methylcellulose phthalate (HPMCP), in different weight ratios. In vitro release studies were performed. The spray-drying process of solutions of ketoprofen with polymeric blends of cellulose derivatives leads to microparticles which, depending on their final formulation, can give a rapid or prolonged drug release. Albumin loaded microspheres were prepared by emulsion cross-linking method. From these results it was concluded that the developed albumin microspheres of ketoprofen is a potential delivery system for once-a-day intramuscular administration (Mathew *et al.,* 2009). Eudragit microspheres containing ketoprofen as model drug, prepared by solvent evaporation technique using acetone-liquid paraffin solvent system were examined. In vitro release was increased in microspheres (Pandit *et al.,* 2001).

Microcapsules

Microencapsulated forms of ketoprofen were formulated using polymers and polymer combinations. Suspensions of cellulose acetate phthalate were prepared and various quantities of drug, glycerin, Tween 80, span 80 and avicel were added and the resulting solution was passed through a peristaltic pump into a hardening solution. The dissolution studies of the ketoprofen demonstrated differences in drug release properties depending on composition and method of preparation. Rapid drug dissolution was seen when the formulations contained Tween 80 as a surfactant (Muhammad *et al.,* 2005). A new approach for site-specific delivery of ketoprofen was developed. Gastro-resistant microcapsules were developed. The aim of this study was to prepare and evaluate gastro resistant microcapsules containing ketoprofen. Drug loading capacity was very high for all the microcapsules prepared (Barbara *et al.,* 2009). The controlled-release preparation, however, was significantly better tolerated than the ordinary capsule form and produced improvement in all parameters (Morley *et al.,* 2004).

Topical formulations

Soya-lecithin aggregates, prepared by a technique using compressed gas, are used to formulate new dermal preparations. Results from the diffusion studies using artificial membranes were confirmed by permeation studies using excised rat skin. The novel soya-lecithin aggregates are promising candidates for new drug delivery systems in dermatology and cosmetology. Extended-release ketoprofen appears to be a good choice for the symptomatic treatment of rheumatoid arthritis and osteoarthritis. Convenient once-daily administration may help improve patients' compliance (Schumacher *et al.,* 2004). Transdermal delivery of ketoprofen was done using microemulsion formulation. A transdermal preparation containing ketoprofen was developed using O/W microemulsion system. Oleic acid was chosen as the oil phase of the microemulsion, as it showed a good solubilizing capacity and excellent skin permeation rate of the drug (Rhyleye *et al.,* 2008). Ketoprofen- Phosphatidylcholine appeared to induce significantly less GI injury and bleeding while maintaining anti-inflammatory and COX-inhibitory activity. Phosphatidylcholine (PC)-associated non-steroidal antiinflammatory drugs, which appear to have improved gastrointestinal safety and therapeutic efficacy (Kennedy *et al.,* 2004).

Microsponges

Microsponges were prepared by quasi-emulsion solvent diffusion method. All the factors studied had an influence on the physical characteristics of the Microsponges. In vitro dissolution results showed that the release rate of ketoprofen was modified in all formulations (Comoglu *et al.,* 2002).

Nanoemulsions

The nanoemulsions of this system evidenced a high degree of stability. All ketoprofen-loaded nanoemulsions enhanced the in vitro permeation rate (Beom *et al.,* 2008).

Pellets

Matrix pellets were formulated. The aim of this study was to evaluate the in-vivo behavior of matrix pellets formulated with nanocrystalline ketoprofen after oral administration. The in-vivo burst release observed for the spray dried nanocrystalline ketoprofen matrix pellets was reduced following compression of the pellets in combination with placebo wax/starch pellets (Vergote *et al.,* 2006).

Transdermal Patch

Ketoprofen patch were useful formulation that can deliver the drug in sufficient amounts to inhibit prostaglandin production in the skin and knee joint. The purpose of this study was to evaluate percutaneous penetration and pharmacological effects of ketoprofen after transdermal administration, compared to the oral route. These results indicate that the transdermal ketoprofen patch was a useful formulation that can deliver the drug in sufficient amounts to inhibit prostaglandin production in the skin and knee joint (Tak *et al.,* 2009).

Suppository

Suppository Dosage Forms of ketoprofen had been made. The suppository hardness data revealed that the theobroma oil base produced relatively brittle suppositories (Uddenfeldt *et al.,* 1999).

Floating microparticles

A sustained release system for ketoprofen designed to increase its residence time in the stomach without contact with the mucosa was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. All floating micro particle formulations showed good flow properties and pack ability (Khosro *et al.,* 2011).

Delivery of Disease Modifying Anti-Rheumatoid Drugs (DMARDS)

A disease modifying anti-rheumatic drugs may also benefit the patient by reducing the need for other medications, e.g. corticosteroids and NSAIDs, which may have a greater potential for toxicity than the disease modifying anti-rheumatic drugs (Lydia *et al.,* 2008).

NON BIOLOGIC DISEASE MODIFYING ANTI-RHEUMATIC DRUGS (DMARDS)

Methotrexate

Matrix Systems

Because of low dose, it is considered as the first line drug. Eudragit-based matrix system for transdermal delivery, sublingual and oral liquid formulations were also formulated (Chilukuri *et al.,* 2008).

Microspheres

Methotrexate encapsulated microspheres release in the joint in a slow, controlled manner following intra-articular injection. A phospholipid conjugate of methotrexate was synthesized and liposomally formulated (Jundt *et al.,* 2002).
Low dose methotrexate administered as tablet, oral solution, and subcutaneous injection to that of intramuscular injection in patients with rheumatoid arthritis (Crawford *et al.,* 2005).

Cyclosporine

Capsules

Oral formlations like capsules had improved bioavailability (Landewe *et al.,* 2003). Neoral Soft Gelatin Capsules and Neoral Oral Solution have increased bioavailability (Rojkovich *et al.,* 2009).

Micospheres

Micospheres of cyclosporine have been made. Dissolution results showed that all formulations gave prolonged release of cyclosporine. In vitro release studies were performed. The spray-drying process of solutions of cyclosporine with polymeric blends of cellulose derivatives leads to microparticles which, depending on their final formulation, can give a rapid or prolonged drug release. The results indicate that sustain release cyclosporine was at least as efficacious and at least as well tolerated as the standard formulation of the drug (Peeyush *et al.,* 2010).

Microemulsion

Microemulsion formulation of cyclosporine had been made. The purpose of this study was to construct microemulsion-base hydrogel formulation for topical delivery. Microemulsion-based hydrogel showed a good stability. These results indicate that the studied microemulsion-based hydrogel may be a promising vehicle for topical delivery (Allard *et al.,* 2002).

Sulfasalazine

Delayed release tablets

An effective disease modifying anti-rheumatic drug for the treatment of rheumatoid arthritis is Sulfasalazine. Its effectiveness overall is somewhat less than that methotrexate, but it has been shown to reduce signs and symptoms and slow radiographic damage. Delayed release tablets were formulated for rheumatoid arthritis. It is also given in conjunction with methotrexate and hydroxychloroquine as part of a regimen of "triple therapy" which has been shown to provide benefits to patients who have had inadequate responses to methotrexate alone (Peppercorn *et al.,* 2011).

Azathioprine

Oral formulations

Systemic Azathioprine is usually administered either orally or intravenously. Oral administration is the preferred route in most cases, since the intravenous preparation is an extreme irritant. Azathioprine had been proven to be beneficial in the treatment of rheumatoid arthritis but does not influence the progression of radiographic changes. Its efficacy has been found to be comparable to hydroxychloroquine, d-penicillamine and cyclosporine. In Felson's meta-analysis, Azathioprine had similar toxicity to sulphasalazine and methotrexate, but was less efficacious. Its efficacy was similar to that of anti-malarials, but it had greater toxicity, causes nausea, fatigue, hair loss, and rash.

Topical formulations

The use of a topical formulation of Azathioprine theoretically offers the benefit of increasing the therapeutic local effect without the need for an increased dosage of systemic immunosuppressive agents. It is possible that the absorption of this agent via oral mucosa may increase the systemic effect (Rodrigues *et al.,* 2011).

Tacrolimus

Solid Dispersion

An oral formulation of one of macrolide compounds namely Tacrolimus with a useful, immunosuppressive activity has been prepared as a solid dispersion. Tacrolimus is macrolide lactone antibiotic with potent immunosuppressive activity. It acts primarily on CD4+ T helper lymphocytes by inhibiting the production of lymphokines, which are required for cell growth and differentiation (Landewe *et al.,* 2003).

Tacrolimus exerts its immunosuppressive effects by the inhibition of calcineurin, leading to interference with T-cell activation. As T-cell activation plays a major role in the pathogenesis of rheumatoid arthritis, there has been an interest in the use of tacrolimus for the treatment of rheumatoid arthritis. The pharmacological properties of tacrolimus have the potential of suppressing the production of inflammatory cytokines, improvement of joint inflammation, improvement of bone and cartilage destruction, improvement of functional status and relief from arthritic pain, infectious conditions (Gostick *et al.,* 2010).

Leflunomide

Tablet

Leflunomide is one of the new drugs used in the treatment of rheumatoid arthritis. It works by suppressing the immune system because rheumatoid arthritis is caused by damage from an overacting immune system. It is available for oral administration as a tablet (Roland *et al.,* 2010).

Microcapsules

Its control release dosage form is still not available. But, microcapsules have been widely accepted as a means to achieve oral- and parenteral-controlled release drug delivery systems (Chon *et al.,* 2011). With the help of some polymeric substances such as Chitosan, polyacrylate, polymethacrylate and ethyl cellulose, sustained release formulations had been prepared. Leflunomide microcapsules and compare with conventional tablets of Leflunomide sustained action. Microcapsule formulations offer several advantages over other sustained release systems, especially matrix-type tablets, because they can be widely distributed throughout the gastrointestinal tract and produce a local high concentration of the drug at the absorption site (Rabindranath *et al.,* 2009).

Microspheres

Therefore, it may be concluded that drug-loaded microspheres are a suitable delivery system for leflunomide with a new choice of an economical, safe and more bioavailable formulation in the management of rheumatoid arthritis (Mikuls *et al.,* 2009).

Gold Compounds

Oral Formulations

An oral gold compound (Auranofin®) is also available but its efficacy is even more limited than injectable compounds (Ashok *et al.,* 2001). Although auranofin has been shown to be superior to placebo in the treatment of rheumatoid arthritis, it is less efficacious than injectable gold. Auranofin had a low incidence of serious toxicity, but the overall frequency of side effects (e.g. rash, diarrhoea) is higher with auranofin than any other disease modifying anti-rheumatic drugs (Alexandreas *et al.,* 2011). Auranofin tablet or capsule is an oral formulation of gold for the treatment of rheumatoid arthritis. Although gold compounds are no longer employed for the treatment of arthritis, the large number of inexpensive natural products that can modulate inflammatory responses, but lack side effects, constitute 'goldmines' for the treatment of arthritis (Kamel *et al.,* 2004).

Injectable formulations

Two injectable compounds are available, (Myochrysine® and Solganal®). Gold compounds are rarely used now due to their numerous side effects and monitoring requirements, their limited efficacy, and very slow onset of action. Its usefulness is limited by low efficacy and poor tolerability (Joseph *et al.,* 2005). Gold is effective in the treatment of rheumatoid arthritis when it is given intramuscularly (Meyers *et al.,* 2003).

Delivery of Biological Disease Modifying Anti-Rheumatic Drugs (DMARDS)

The Tumor Necrosis Factor A (Tnf-A) Antagonists

TNF antagonists were the first of the biological disease modifying anti-rheumatic drugs to be approved for the treatment of RA and have also been referred to as biological response modifiers or "biologics" to differentiate them from other disease modifying anti-rheumatic drugs such as methotrexate, leflunomide, or Sulfasalazine (Barbara *et al.,* 2008). Tumor necrosis factor (TNF) plays a central role in rheumatoid arthritis by amplifying inflammation in multiple pathways that lead to joint destruction (Gohel *et al.,* 2009).

Infliximab

Infliximab is approved for use alone or combined with methotrexate for treating moderate to severe rheumatoid arthritis. FDA approved a new indication for Infliximab injection allowing its use to reduce the signs and symptoms of active psoriatic arthritis, defined as affecting at least five joints. Infliximab is administered intravenously (Yocum *et al.,* 2004).

Etanercept

Overall, etanercept is highly effective and well tolerated by patients with a safety profile. It cannot be administered orally, because the digestive system would destroy the drug (Erin *et al.,* 2008).

Tocilizumab

Tocilizumab is biologic disease modifying anti-rheumatic drug and a cost-effective strategy in the treatment of rheumatoid arthritis patients. The development of a targeted nanocarriers system for sustained drug delivery in rheumatoid arthritis is thus highly desirable. In addition, nanocarriers systems may increase the solubility of certain drugs and protect them against degradation in the circulation, further increasing their local bioavailability. Therefore, the use of nanocarriers promises to increase drug specificity and bioavailability while reducing unwanted off-target side effects (Alexander *et al.,* 2012).

Delivery of Corticosteroids

Oral formulations

Medium and high doses of glucocorticoid are useful for bridging the interval between initiation of disease modifying anti-rheumatic drugs and onset of their therapeutic effect. Corticosteroids work rapidly to control inflammation and pain (Ayhan *et al.,* 2008). Oral corticosteroids like prednisolone and prednisone are use in an alternative treatment in patients who have severe problems with NSAIDs. Oral corticosteroids are combined with disease modifying anti-rheumatic drugs significantly to enhance the benefits of disease modifying anti-rheumatic drugs (Singh *et al.,* 2005).

Injectable formulations

Corticosteroids are sometimes injected directly into joints for relief of flare-ups when only one or a few joints are affected. Steroid injections in the joints may be a safe and effective treatment for juvenile rheumatoid arthritis and reduce the need for oral medications. Intelligent use of glucocorticoids early in the disease has also improved rheumatoid arthritis care. Glucocorticoids remain an essential part of combination therapy in newly diagnosed patients with active disease, rapidly controlling both symptoms and radiographic disease progression. Combination disease modifying anti-rheumatic drug (DMARD) therapy that includes glucocorticoids should be the gold standard for early treatment (Lanza *et al.,* 2005).

PREDNISOLONE

Liposomes

Liposomal delivery improves the safety of glucocorticoid by allowing for lower effective dosing. In arthritis, the efficacy of prednisolone-loaded long-circulating liposomes is currently being evaluated in a phase II clinical trial. Liposomes offer increased therapeutic activity and improvement in the risk–benefit ratio (Rossum *et al.,* 2008).

Microspheres

Prednisolone-loaded microspheres were prepared. Dissolution results showed that all formulations gave prolonged release of prednisolone. In vitro release studies were performed. The spray-drying process of solutions of prednisolone with polymeric blends of cellulose derivatives leads to microparticles which, depending on their final formulation, can give a rapid or prolonged drug release.

The results indicate that sustain release prednisolone was at least as efficacious and at least as well tolerated as the standard formulation of the drug (Kirwan *et al.,* 2012).

Betamethasone Sodium Phosphate (Bsp)

Nanoparticles

Betamethasone encapsulated in PLGA nanoparticles. The observed strong therapeutic benefit obtained with PLGA-nanosteroid may be due to the targeting of the inflamed joint and its prolonged release in situ.

Targeted drug delivery using a sustained release PLGA-nanosteroid is a successful intervention in experimental arthritis. Treatment of experimental arthritis with nanoparticles encapsulating Betamethasone sodium phosphate was used in treatment of experimental arthritis (Whitmore *et al.,* 2006).

Novel Approaches and Developments in Colon Specific Drug Delivery Systems

Colon specific drug delivery has gained increased importance not for the treatment of local diseases associated with the colon but also as potential site for systemic delivery of therapeutic proteins and peptides. Different approaches are designed to develop colonic drug delivery system (Choudhury *et al.,* 2012).

Micro and Nano-Carrier Mediated Intra-Articular Drug Delivery Systems for the Treatment of Arthritis

The search for a clinically successful ideal carrier is ongoing, sustained-release systems, such as polymeric micro- and nanoparticles, liposomes, and hydrogels, are being extensively studied for intra-articular drug delivery purposes. The advantages associated with long-acting preparations include a longer effect of the drug in the action site and a reduced risk of infection due to numerous injections consequently (Zung *et al.,* 2012).

Immunosuppressive Exosomes: A New Approach for Treating Arthritis

Although certain biological therapies, including protein and antibodies targeting inflammatory factors such as the tumor necrosis factor, are effective in reducing symptoms of rheumatoid arthritis, these treatments do not reverse disease. However, it is important to note that while the clinical results are encouraging in terms of feasibility, safety, and efficacy, the blood plasma- or serum-derived exosomes have heterogeneous cellular origins and poorly defined composition. Taken together, there is considerable evidence supporting the ability of immunosuppressive exosomes to help control the over reactive immune system. Compared with gene and cell therapies, exosome-based therapy could provide a new and safe therapeutic approach for arthritis (Chenjie Yang *et al*., 2012).

CONCLUSION

Nonsteroidal anti-inflammatory drugs have side effects like gastric irritation. To avoid these problems novel vesicular system like pharmacosomes can be used. Pharmacosomes bearing unique advantages over liposomes and noisome have come up as potential alternative to conventional vesicles. They provide an efficient method for delivery of drug directly to the site of infection, leading to reduction of drug toxicity with no adverse effects. Unlike conventional drugs are designed to deliver therapeutic agents specifically to the site of inflammation, therefore avoiding potential systemic and off-target unwanted effects. Compared with gene and cell therapies, exosome-based therapy could provide a new and safe therapeutic approach for arthritis. Further experience in the use of these, and of agents not yet developed, alone and in combination with disease modifying anti-rheumatic drugs (DMARDS), is likely to lead to further changes in the manner in which rheumatologists treat this debilitating disease. Therefore, every new approach in the targeted therapy of rheumatoid arthritis could contribute to the effectiveness in treating the chronic disease.

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