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Types of Delivery Routes and Polymeric Drug Delivery Systems For Effective Management of Arthritis

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ABSTRACT

Arthritis is a form of joint disorder that involves inflammation in one or more joints. Most common form of arthritis is osteoarthritis and rheumatoid arthritis in which joint pain is the major symptom. Management of arthritis can be done by reliefing pain using various classes of drugs. Steroidal and non-steroidal anti-inflammatory agents (NSAIDs) are commonly used for treatment. NSAIDs nowadays are combined with other drugs for the better therapeutic effects compared to NSAIDs alone. Management of arthritis can be made using various drug delivery systems like polymeric drug delivery system, controlled drug delivery system, sustained delivery using various routes like oral, nasal and topical route etc. This review suggests management of arthritis using polymeric drug delivery system. Polymeric drug delivery systems are based on the chain link of polymers, and liposomes, hydrogels, nano devices are some of the approaches. Polymeric systems used in the treatment of inflammatory diseases and infections along with some other vaccines. Non-steroidal anti-inflammatory agents such as aspirin, ibuprofen, ketoprofen and diclofenac are used in the management and/or treatment of arthritis. This review also suggests the various drug candidates used to treat the arthritis.

Keywords: Arthritis, Joints, Drug delivery, Polymeric system, NSAIDs.

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INTRODUCTION

Arthritis is characterized by pain, aching, swelling in and around one or more joints of the human body. Arthritis is a disorder which affects mainly the joints and it describes many rheumatic diseases and that affects the joints. It includes osteoarthritis (OA) and rheumatic arthritis (RA), which are the major disorders in the arthritis. In both the conditions inflammation of bone and cartilage damage occurs which leads to joint pain. Various drug delivery are used in the treatment of arthritis which includes polymeric drug delivery, controlled drug delivery, sustained drug delivery, intra-articular drug delivery etc.[1,2,3]

In which polymeric drug delivery is sufficient because in these delivery drug is encapsulated with the polymers which helps in the sustained release of the drug for the prolong action in the human body. Polymers are having unique properties that are not found with low-molecular-weight compounds. Polymers are used to improve the bio availability of the drug. After polymer degradation drugs get release to shows its systemic action. Polymers like PLGA, albumin, chitosan etc. are used in the drug delivery formulation as following advantages:

- Prolong drug action by entrapping the drug within matrices.
- Shift drug distribution in the direction of tumours.
- Shunt therapeutic genes or oligo nucleotides into cells.
- Enable drug absorption at optimum gastrointestinal tract absorptive sites.[4,5,6,7]

System which contain polymer as for the administration of drug various routes are selected based on the type of delivery, contents of the dosage form, type of drug used. They may be oral route, nasal route, topical route, parenteral route and target specific delivery are used for administration of the drugs.

ARTHRITIS

Arthritis is a joint disorder featuring inflammation. A joint is an area of human body where two or more different bones join together. It starts with small joints and feet then spreading to larger joints. Arthritis is more commonly seen in adults of age 65 years or older.

There are 15% of people is affected by arthritis in India. According to the CDC, 60% of people with arthritis are women than men in every age group. Its prevalence is higher than many well known diseases such as diabetes, AIDS and cancer. Rheumatic arthritis is a chronic disorder inflammatory disorder indicated by hyperplasia of synovial lining cells.[8] **Figure 1** shows various joints affected by arthritis.

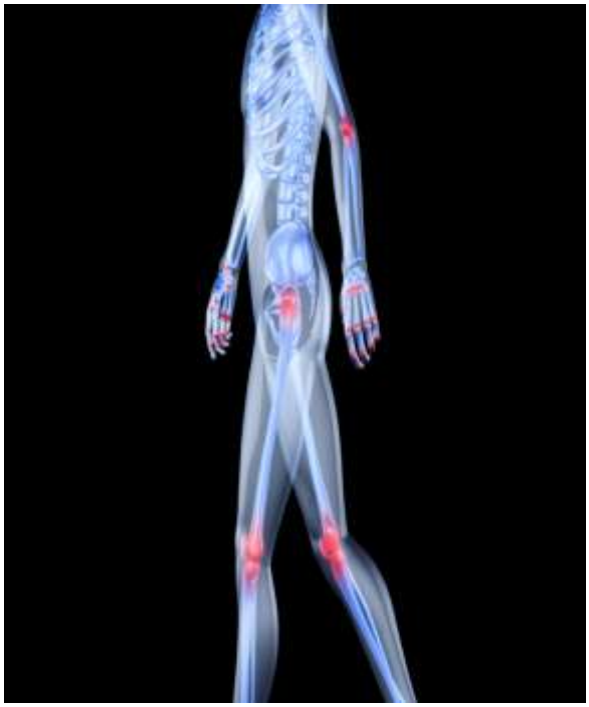

Figure 1: Various joints affected by arthritis.

TYPES OF ARTHRITIS

There are around 200 types of arthritis - or musculoskeletal conditions - which are split into seven main groups:

1. Inflammatory arthritis
2. Degenerative or mechanical arthritis
3. Soft tissue musculoskeletal pain
4. Back pain
5. Connective tissue disease
6. Infectious arthritis
7. Metabolic arthritis. [9]

Mainly there are four types of arthritis disorders namely:

1) Osteoarthritis

2) Rheumatoid arthritis

3) Fibromyalgia

4) Gout and lupus.

For rheumatic disease in Japan and USA, DMARDs are approved for treating RA using various drugs. Like oral gold, inject gold, sulfasalazine, D-penicillamine, methotrexate, actarit, abatacept are approved in japan and drugs like hydroxy-chloroquine, azathiopurine, minocycline and cyclosporine are approved by USA government.[10] Aceclofenac is well tolerated cox-2 inhibitor

and it is drug of choice for osteoarthritis, rheumatoid arthritis etc. It has shorter half life (2-4 hrs), hence the daily dose 100mg twice daily. Currently there are four general types treatments are established namely non steroidal anti inflammatory drugs(NSAIDs), selective-oxygenase-2(COX-2), disease modifying anti-rheumatic drugs (DMARDs) and biological agents.[11,12]

Figure 2 shows difference between healthy knee and osteoarthritic knee.

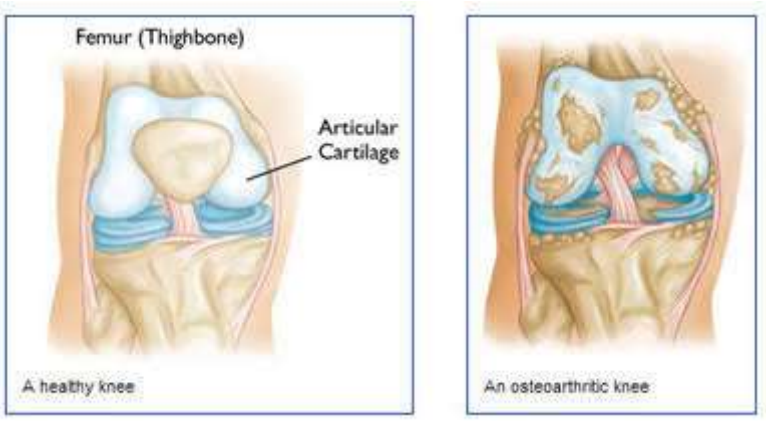

Figure 2: Difference between healthy knee and osteoarthritic knee.

TYPES OF DELIVERY ROUTES

Different routes are preferred for management or treatment of arthritis. It includes mainly:

A) Oral route
B) Parenteral route
C) Targeted delivery
   - Non specific targeting
   - Specific targeting
D) Topical route
E) Nasal route

A) Oral route:

In arthritis oral route is the common type of drug delivery for conventional and preferred route of drug administration.

Advantages of oral delivery:

- Patient non compliance increase drastically.
- Reduction of pain and inflammation.

Disadvantages of oral delivery:

It has side effects such as

- Gastric bleeding

- Impairment of renal blood flow.
- Nephrotic syndrome
- Hepatic injury
- Peptic ulcer
- Bone loss.

All these side effects can be overcome by using various approaches like oral pulsatile drug delivery system which involes the liberation of drugs after the time of administration. Drugs like corticosteroids, indomethacin and arthotec are given through oral delivery but long term administration is necessary.

Drugs like corticosteroids as rapid therapeutic action on the inflammation and joint pains. Alternatives of oral corticosteroids like prednisolone and prednisone useful in the problems with NSAIDs. Rheumatoid arthritis is caused due to the damage of overacting immune system it can be treated by using leflunomide tablets.[13,14]

Methotrexate is also a best oral drug in order to compare the relative bioavailability of orally administered methotrexate (MTX) with i.m. administration in patients with rheumatoid arthritis; we compared the pharmacokinetics of MTX at both the usual starting dose of 7.5 mg and at higher established maintenance dosages in 21 patients. Pharmacokinetic measures were repeated approximately 6 and 18 months after baseline while patients consumed their usual maintenance doses of MTX (17.0 +/- 3.8 mg). The relative bioavailability of the usual maintenance dose of MTX was reduced by 13.5% compared with the initial dose of 7.5 mg (P = 0.026). Clinicians using MTX should not assume constant and complete bioavailability across the dose range used to treat patients with rheumatoid arthritis.[15]

B) Parenteral route:

In parenteral delivery drugs are injected directly through the skin or mucous membrane into blood circulation.

Advantages:

- This delivery route has high patient noncompliance.
- Anti-arthritic drugs as a advantage of both targeted and sustained delivery.
- Rapid clearance of drug can be achieved.
- Maximum utilization drug enabling reduction in total amount of dose administered.

Disadvantages:

- Self medication is not possible.

- Sterility should be maintained.

Drugs which are administered through intra articular route produce the symptomatic relief in joint inflammation and pains.

For example:

- Nanoparticles like Beta-methasone sodium phosphate slow release after administration through intra articular delivery.
- Steroids injections are given directly into the joints which is effective in the treatment of juvenile rheumatoid.
- Mycochrysine and Solganal are rarely used because it as low efficacy and poor tolerability in the treatment of RA.[16,17]

C) Targeted delivery:

In these route of administration drug is targeted to specific organ or tissue. The main objective of targeted drug delivery system is to prolong, localize, target and protect drug interaction with diseased system.

It is based on the amount of drug targeted for specific organ for systemic effect.

It has two strategies

-Non specific targeting strategies

-Specific targeting strategies

Examples of drug used for non specific targeting delivery includes anti-TNF antibody and PEGlylated soluble tumour necrosis factor (TNF) receptor. Both have wider action on RA.[18] For effective enhancement of efficiency of drug delivery can be improved using specific targeting strategies. Liposomes are effective in arthritis.[19] Liposomes encapsulated with corticosteroids shows effective action on arthritis; when administered intra articularly.[20]

D) Topical delivery:

In these type of delivery system drug diffuses out onto the surface tissue of skin through stratum corneum. Penetration of drug through this route is rapid along with ease of application.

Topical application reduces the side effects like peptic ulcer, gastric bleeding and irritation. Most of non steroidal anti inflammatory drugs are administered through topical route of administration and as adverse effects through site specific delivery and controlled release delivery system by treating pain and inflammation.

Among NSAIDs diclofenac shows better action on acute and chronic painfull inflammatory conditions. Pharamacosomes of diclofenac have a getter action for improving dissolution and

reduces the gastrointestinal toxicity of drug. It was prepared by using dilclofenac and phosphatidylcholine. Even ibuprofen-phosphatidylcholine shows better gastrointestinal safety and analgesic for osteoarthritics. Salicylates work by decreasing pain and inflammation.

Capsaicin works by blocking the transmission of a pain-relaying substance called substance P to the brain. Patches likes ketoprofen patch sticks on skin releases the required amount of drug to inhibit the production of prostaglandin in the knee joint. This study indicates how transdermal better compare to that of oral route.[21,22,23]

E) Nasal route:

Nasal administration is a route of administration in which drugs are insufflated through the nose. Drugs whose shows minimum systemic effects are given as nasal sprays i.e. Decongestants.

Intranasal administration helps in accurate and effective dosing. Device used are prefilled with drug. It shows both systemic and local effects.

Advantages:

a) Drug molecules transferred quickly across the single epithelial cell layer directly to the systemic blood circulation without first-pass hepatic and intestinal metabolism.
b) Drugs which show poor absorbtivity can be given in this route.

Limitations:

a) Drugs for continuous and frequent administration may be less suitable because of the risk of harmful long term effects on the nasal epithelium.
b) Variables in the amount of drug absorbed after nasal administration should be comparable to that oral administration.

Intranasal vaccination with drugs like cholera toxin B subunit (CTB) reduces the collagen induced arthritis.[24,25]

Capsaicin can be used topically which shows better results. In this double-blind randomized study, 70 patients with osteoarthritis (OA) and 31 with rheumatoid arthritis (RA) received capsaicin (asubstance P depletor) or placebo for four weeks. The patients were instructed to apply 0.025% capsaicin cream or its vehicle (placebo) to painful knees four times daily. Pain relief was assessed using visual analog scales for pain and relief, a categorical pain scale, and physicians' global evaluations. Most of the patients continued to receive concomitant arthritis medications. Significantly it was more relief of pain was reported by the capsaicin-treated patients than the placebo patients throughout the study; after four weeks of capsaicin treatment, RA and OA patients demonstrated mean reductions in pain of 57% and 33%, respectively. These reductions in pain were statistically significant compared with those reported with placebo (P =

0.003 and P = 0.033, respectively). According to the global evaluations, 80% of the capsaicin-treated patients experienced a reduction in pain after two weeks of treatment.[26]

DRUG DELIVERY SYSTEMS

In the 1960 Folkman recognized that a silicone rubber tube acted as a constant rate delivery device in rabbit anaesthesia. Then Ratcliffe *et al*. concluded that microspheres can delay clearance of a drug from the joints. In 1980-90s it is improved towards microparticle and a sustained release of drug. On 1990s onwards development in the system takes place with the introduction of nanoparticles. Techniques like spray, compression, and dip coating are adopt the drug in drug delivery system.[27] Diverse drug delivery systems implied in effective arthritis therapy are depicted in **Figure 3**.

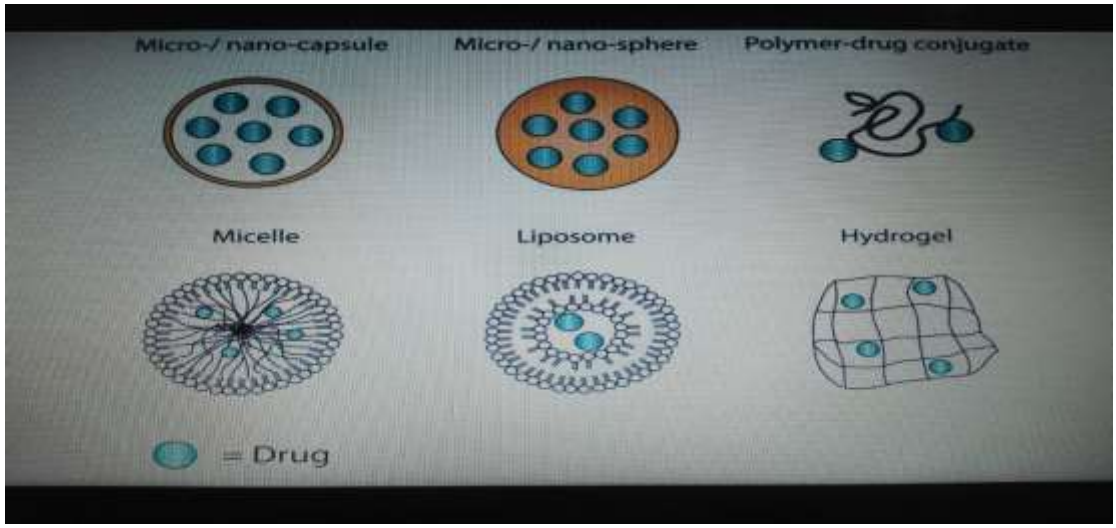

Figure 3: Diverse drug delivery systems for arthritis therapy.

A) INTRA-ARTICULAR DRUG DELIVERY SYSTEMS

Intra-articular drug delivery system is the administration of drug directly into the joints of the bone. Through this system drugs of high concentration can be given directly into the particular site. It follows sustained release of drug advantages of these system is the highly dosed drug releases for a long time. It is more effective than oral and topical delivery system for the administration of higher dose. It improves the rapid movement of drug from the site of administration and avoids the degradation of the drugs.[28]

Various polymers like natural, synthetic or combined origin polymers are used. Synthetic polymers like chitosan are given through intra articular drug delivery system. Other drugs like liposomes, hydrogels are widely used in the polymeric drug delivery system.

B) POLYMERIC DRUG DELIVERY SYSTEM

Polymeric drug delivery for effective management of arthritis

Nowadays for better pharmaceutical product manufacturing polymers are widely used. Polymers are very large macromolecules consisting of repeating units of monomers. Polymers are used as materials in many fields such as drug delivery system, implantation of medical devices, bone repair etc. The combination of polymers and pharmaceutical science are incorporated in the development of novel drug delivery system .Polymers should have some properties like defined structure, biocompatible and non toxic. Polymers are combined with novel drug delivery to increase effect of drug and for reduction unwanted side effects. In which drugs are coated with polymers such that it increases the bioavailability of the drug.

Polymeric drug delivery systems are classified based on the controlled release of drug from the polymer. This are target specific drug delivery system concentrate mainly on specific targets like bones, inflammations etc. after the administration of drug it get released because of erosion in the polymer. Degradation of polymers leads to breakdown of polmers which is controlled by Kreb's cycle to carbon dioxide and water. Drugs such as ibuprofen, ketoprofen, and aspirin are used to reduce the inflammation. Drug passes between the polymeric chains through controlled release.

Using polymeric drug delivery system treating efficiency will be improved. It has a better action to that of other routes such as oral, nasal, parenteral drug delivery. Therapeutic effectiveness can be achieved using this system with varieties of polymers. Most non steroidal anti inflammatory drugs are used in the management of arthritis which acts directly on the inflammation and reduce the pain in the joints. Through intra articular drug delivery, most of the polymers have proven to be biocompatible. PLA has been shown to be biocompatible in rabbit knees, polyethylene glycol (PEG), often combined with other polymers is biocompatible and able to control release characteristics of the incorporated drug, however, by far, the most used synthetic polymer is PLGA. This synthetic polymer has a good biocompatibility and is able to incorporate many different types of drugs. Several studies have been published on the incorporation of proteins in different DDSs, a common problem in the classical models.[29,30]

Liposomes

Liposomes are the polymer based microspheres which are composed of one or more concentric phospholipid bilayers and used in the delivery of microscopic drug into the cells. It is a carrier for intra articular drug delivery. Reduction of inflammation in monosodium iodo-acetate induced osteoarthritis rat knee after a liposomal dexamethasone and diclofenac combination. It shows a systemic action on the joints by reducing the pain and inflammation.[31,32] Liposomes are effective and biocompatible intra articular residence time is relatively short compared to other drug

delivery system. There are two main mechanisms of uptake for liposomes. They are engulfed with phagocytosis then it fused with endosomes or lysosomes. Mechanism of drug release is based on micro environment. Liposomes are very effective carriers for delivery of actives across the BBB.[33]

Hydrogels

Physical properties of hydrogels are insoluble, water swollen, cross linked, three dimensional structures of polymers.[34] Its activity is based on its lubricity, viscosity and restoring some joints physiology.[35] PEG-hydrogel microsphere in order to reduce the amount of the forgein materials injected. In other studies drugs like ibuprofen are combined with hydrophilic PEG hydrogel which release the ibuprofen for the long time for prolong action of drug over the pain and inflammation. Other drugs like chitosan microsphere dispersed in the chitosan hydrogel for management of osteoarthritis.[36] Type of hydrogel used was based on oligo (ethyelene glycol) which is a water soluble polymer which can form a biodegradable and biocompatible hydrogel for improvement of delivery route or factor.[37]

Nanoparticles

Nanoparticles show high toxic activity. Nanoparticles those encapsulated with collagen II-binding peptide are seen by fluorescence measurement a fold preferential accumulation of 38-nm mean diameter nanoparticles within the cartilage relative to 96-nm diameter ones. Such results show the importance of limiting particle size to enhance drug permeation into cartilage. Nano-devices can present multiple functions other than as a drug carrier.

Examples of nano particles includes super paramagnetic iron oxide nanoparticles (SPIONs) fabricated with dexamethasone loaded PLGA can be directed by a magnetic field and they achieved a joint residence time of at least 3 months of course, the complex functions and structures of nano-devices also increase the difficulty and cost to synthesize them. They show the effective action on the inflammation and swelling of synovial fluid. It acts directly on the joint for the treatment of rheumatic and osteoarthritis.[38,39,40,41,42]

CANDIDATES FOR TREATING ARTHRITIS

Many different drugs have been used for treatment of arthritis. The limitations includes to which drugs can be incorporated in a DDS. The incorporated drug has to be able to withstand the manufacturing process of the carrier vehicle (i.e., compression, heat, stirring, etc.). As the final goal of manufacturing these vehicles (particles) is injecting them intra-articularly, the DDSs have to be sterilized.[43]

A. NSAIDs, Coxibs, Glucocorticoids, and Hyaluronan

The rationale for the use of these drugs is that their mechanism of action has been abundantly investigated in the perspective of OA treatment, their ability to give symptomatic relief and their potential to slow down disease progression. Drugs currently used in DDSs in the OA joint are mostly derived from the drugs normally used in arthritis treatment (NSAIDs, Coxibs, Glucocorticoids, and HA).[44,45], these drugs are developed and studied for use in oral OA treatment or an intra-articular injection without a DDS. A great progress has been made in DDSs, and as such more other potential drugs may be used for treatment of OA. Due to systemic side effects, short half time, etc.

B. DMOADs

Based on their method of action, roughly three groups of DMOADs can be identified:

(i) Inhibitors of degrading enzymes and inflammation,

(ii) Growth factors, and

(iii) Drugs which target sub chondral bone changes.

Enzymatic or proteolytic degradation causes short half-lives when administered without a DDS. In addition, a DDS can protect the protein or peptide against degrading environmental factors when prepared or stored.[46] The structure and function of often fragile protein based drugs during DDS processing, formulation, sterilization and subsequent degradation. Release is far from trivial and as a result very few protein based DDS products are on the market today. Peptides are already successfully incorporated in DDSs in other fields of research. These positive results are promising for the application of peptidal DMOADs in a DDS.[47,48]

C. Cytostatic Drugs

Cytostatic drugs are able to inhibit inflammation and can even be chondroprotective, though they are not used in OA treatment because of their high toxicity and often severe side effects when administered systemically. When categorizing candidate drugs/DMOADs for use in a DDS, attention should be paid to their chemical nature and the possibilities to incorporate them in a drug delivery system.[49,50]

CONCLUSIONS

Encapsulation of drug with the polymer exhibits slow release for prolonged action of drug, but it does not help the bioactive molecule into the cartilage matrix. Hence nanoparticles or nano devices are modern approach for the development of polymeric drug delivery system as it has potential of avoiding the shortfalls and multifunctions at the same time. For the management of arthritis i.e. rheumatic arthritis and osteoarthritis using the pharmaceutical development is more

effective and safe through the intra-articular drug delivery. Polymers helps in the prolong action of the drug over the pain which is not shown by other drug delivery as it is injected directly without any polymers. The developments in the field of DDS and the increasing number of drugs day by day, it is expected that more clinical trials should start to fulfil the need for effective treatment of arthritis. Various drug candidates in conjugation with polymeric drug delivery system would be promising alternative to conventional therapy in near future.

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