INTRA-ARTICULAR DRUG DELIVERY SYSTEMS FOR ARTHRITIC DISEASES: OVERCOMING THE INADEQUACIES OF THERAPY

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ABSTRACT
Arthritis is the painful disease caused in the joints of the bone. Rheumatic arthritis and osteoarthritis are the various disorders causes inflammation and pain. Various route of administration like oral, parenteral, topical and nasal routes are used but it may causes damage in gastro-intestinal tract, irritation hence it is administered through intra-articular route. It reduces the side effects and infections because it is given directly to the joints. Drugs are injected directly to the site which shows better action than oral delivery. When it is administered through other routes chances of degradation of drugs may takes place; which decreases the bioavailability of the drug or concentration of the drug. Drugs used for treatment of arthritis include steroids, non-steroidal anti-inflammatory drugs, anti-rheumatic drugs etc. Drugs like corticosteroids, glucocorticoids, ibuprofen, ketoprofen, selective cyclooxygenase 2 inhibitors are also used for treatment of arthritis which shows quick onset of action on the pain. They show the action as analgesic and antipyretics by reducing the pain in the bone joints and bones. NSAIDs are mainly used in acute and chronic conditions. Apart from the conventional formulations, diverse approaches like hydrogels, hyaluronic acid, microparticles, nanoparticles etc. have been proposed and used in order to improve the sustain release of the drug after administration; thereby improving the efficacy. Present article encloses a comprehensive review of various novel drug delivery systems implied for augmented arthritis therapy.


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INTRODUCTION

According to one of the estimation in U.S. 46 million peoples are suffering from arthritis among them 24.4% womens and 18.1% means are facing the arthritis. It is more in case of adults. Around 1% of adult population is affected by Rheumatic arthritis. Rheumatic arthritis is a chronic disorder inflammatory disorder indicated by hyperplasia of synovial lining cells. 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. More number of arthritis patients is due to stress and depression. Arthritis is a term covers a group of more than 200 diseases. Arthritis causes the painful inflammation and stiffness of joints. Arthritis are caused due few criteria like age, sex, genes, excess weight, injuries, infection etc. are the reasons for arthritis. Some forms of arthritis, such as rheumatoid arthritis and lupus, can affect multiple organs and cause widespread symptoms. Intra-articular drug delivery system is used for the treatment of arthritis as it is given directly into the bone joints. It avoids the side effects caused by other routes like oral, parenteral, topical etc. [1-3].

ARTHRITE

Arthritis is a disease condition which causes pain in the joints and it is a form of joint disorder that involves inflammation in one or more joints. Figure 1 represents pain or inflammation at several joints of the human body.

Figure 1: Diagrammatic representation which shows pain or inflammation at several joints of the human body.

Symptoms of arthritis include:

- Pain around joints
- Joints stiff
- Joints look red
- Difficulty in movement
- Muscle aches malaise and fatigue
- Loss of flexibility
- Decreased aerobic fitness [4].

Treatment of arthritis can be done incorporating painkillers, steroidal and non-steroidal anti-inflamatory drugs (NSAIDs), disease modifying anti-rheumatic drugs etc. Arthritis can be treated by using various drug delivery systems such as polymeric delivery, oral delivery, parenteral delivery, topical delivery, intra articular delivery. Drugs are given based on the type of disease suffering from through various drug delivery systems. Non steroidal anti inflammatory drugs have better action on arthritis in which gastric intestinal events are the major risk factors like peptic ulcer disease condition, continuous administration of NSAIDs leads co-morbid illness, bleeding from gastro intestinal tract and nephrotoxicity.

NSAIDs inhibits enzymes cyclooxygenase 1 (COX-1) and cyclooxygenase 2 (COX-2). Among them COX-2 inhibitors like celecoxib, rofecoxib and valdecoxib; these inhibitors helps in the reduction of gastro intestinal damage compared to other combinations of NSAIDs [5].

CLASSIFICATION OF ARTHRITIS

Among the various types of arthritis joint pain is the primary factor. In general arthritis is classified into following which includes:

- Rheumatoid arthritis
- Osteoarthritis
- Gout
- Septic arthritis
- Juvenile idiopathic arthritis
- Still’s disease
- Fibromyalgia
Rheumatoid Arthritis

It is a disease condition in which body’s immune system attacks its own tissues. It mainly damages the joints and underlying bone. It mainly affects the fingers, thumbs, elbows, shoulders, knees and feet’s. It damages the cartilage, bone, and tendons by swelling of the synovial tissue. Cartilage bone becomes thinner and rougher. If it is not treated perfectly it leads to painful, stiff joints. Figure 2 gives diagrammatic representation of rheumatoid arthritis (RA).

![Diagram of Rheumatoid Arthritis](image)

**Figure 2: Diagrammatic representation of rheumatoid arthritis (RA).**

**Symptoms**

The symptoms of RA include:

- Fatigue.
- Fever.
- Weight loss.
- Eye inflammation.
- Lung inflammation.
- Difficulty in movement of legs.
- Weak bones.
- Low red blood cell counts.

It can be treated by using various forms of drugs like steroidal and non-steroidal anti-inflammatory drug and disease modifying anti-rheumatic drugs (DMARDs). DMARDs suppress the immune system. DMARDs pills like Leflunomide, Methotrexate, Sulfasazine etc. Intravenous administration of Abatacept, Infliximab, and Rituximab are used in the research studies of rheumatic arthritis. DMARDs reduce the swelling and helps in the prevention of joint damage [6].

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 [7, 8].

Osteoarthritis

Osteoarthritis (OS) also called as degenerative arthritis or degenerative joint disease; in which it breakdowns joint cartilage and led to joint stiffness. Symptoms of the disease include joint swelling, decreased range of motion, and when the back is affected weakness or numbness of the arms and legs. The most commonly involved joints are those near the ends of the fingers, at the base of the thumb, neck, lower back, knees, and hips (joints on one side of the body). OS is the most common cause of a joint effusion of the knee in smaller joints like fingers, hard bony enlargements, called Heberdey’s nodes [9, 10]. The diagrammatic representation of OS infected hands is shown in Figure 3.
Among over 60 years old about 10% of males and 18% of females are affected with osteoarthritis which affects knee and hip joint. Osteoarthritis cause gross cartilage loss and damage occurs in joint tissue. The collagen matrix becomes more disorganized and decreases in proteoglycan content within cartilage.

Non-steroidal anti-inflammatory drugs like acetaminophen are the first line for the treatment of osteoarthritis. Naproxen also used effective NSAIDs but it as side effects of gastrointestinal bleeding and COX-2 selective inhibitors causes’ myocardial infarction. Topical diclofenac have a risk of mild skin reaction but avoids gastrointestinal adverse effects [11].

Gout

Gout is a rheumatic disease that occurs due to the formation of uric acid crystal in tissues and fluids within the body. It occurs due to overproduction of uric acid from the body. It mainly affects the joints and changes the shape of the hand. Skin will turned into red colour due over inflammation and leads to the fever.

Symptoms of gout include swelling, inflammation, and extreme tenderness of the joint to even the light touch. It can be treated by using many drugs like ibuprofen, prednisone, colchocine etc. Hyperuricemia leads to gout at some point. Diuretics are also drug of choice for gout with combination of other drugs. Treatment for gout can be done by NSAIDs, colchicines, steroids, pegloticase are used. Pegloticase are approved in USA for treatment of gout [12]. Figure 4 depicts a leg affected by gout.

Gout affects 3 million people in the United States, with rates almost 5 times higher in those aged 70 to 79 years compared with those aged <50 years. Management of gout in elderly subjects can be complicated by co-morbidities and polypharmacy [13].

Septic Arthritis

Septic arthritis is caused due to infection of synovium and synovial fluid. It affects hip joint in the children and knee joint in adults. Symptoms of septic arthritis include fever, fatigue, anorexia, nausea etc. A hand affected by the septic arthritis is depicted in Figure 5.
fibromyalgia
Symptoms of fibromyalgia include the following:
- Widespread pain (specific tender points are common)
- Sleep disturbance
- Fatigue
- Psychological stress
- Morning stiffness
- Tingling or numbness in hands and
- Headaches, including migraines

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.

Intra-articular drug delivery is drug and dose dependent. In which maintenance of drug in the same place is more important for systemic effect. Absorption of drug takes place quickly as that it is given directly into the systemic circulation. Few polymers are also used in the preparation of drugs to increase the weight. Polypeptides like elastin acts as thermo sensitive i.e, changes the temperature with change in the climatic conditions. Such drugs are given to increase the prolong action. Advantages of this system are high concentration drugs can be given easily because of its sustained drug release. It is difficult to administer to the joints because of various species. Nano devices are the Drug dosage cannot be calculated.

Intra-articular delivery are associated with the polymeric nano-microparticles, hydrogels, liposomes etc. for sustain release of drug to the human body.

Osteoarthritis and rheumatoid arthritis are the major disorders associated with arthritis which causes pain in the joints. It can be treated with steroidal and non steroidal anti inflammatory drugs through intra-articular drug delivery system because oral and parenteral may cause some side effects in the body and through these delivery drugs shows faster action on the joints. Major disorder of arthritis includes osteoarthritis and rheumatoid arthritis. It can be treated using intra articular delivery system [14-16].

management of osteoarthritis
Symptoms of OS include stiffness of joints, pain during movement of legs. Factors for the development of osteoarthritis includes joint injuries, age, sex, due to less mineral constituent in the bone crystals in the joint fluid etc. Day by day patient affecting from arthritis is getting increased in every country. Methods used for management of osteoarthritis mainly concentrate on the reduction of the pain and inflammation with few measures like pharmacological and non-pharmacological measures and prevention measures. Prevention measures include development of peri-articular muscles to give a support to the joints. Few guidelines suggests the use of NSAIDs, analgesic and anti-articular agents. NSAIDs show the side effect of gastrointestinal, renal effects which causes damages to the intestine and kidney. Paracetamol is also recommended for release of pain in osteoarthritis. The Osteoarthritis research international suggests that topical agents and capsaicin are the better alternatives to oral analgesic and anti inflammatory agents.
Intra-articular administration of corticosteroid injection shows systemic effect on the cartilage of the bone and reduces the inflammation. Effect of corticosteroids is obtained by multiple mechanisms. Corticosteroids are generally administered by combination with lidocaine or bupivacaine. Side effects of this drug include pain, crystal synovitis joint sepsis and steroid cartilage and systemic effects such as aggravation of hypertension. Replacement of hyaluronic acid in the knee joint is also another method i.e., viscosupplementation method and restores the elasticity and viscosity of synovial fluid to normal extend. When compare to corticosteroid suspension hyaluronic acid shows delayed onset of action and exhibits prolong action. It should not be repeated within 3 to 6 months.

If there is no improvement in the above methods then radioactive synovectomy is used which removes the synovial lining and reduces the pain in the joints. It is a drawback of radioactive leakage from the place of administration. Triamcinolone acetonide suspension is used in the treatment of short time pain relief [17, 18].

Management of Rheumatoid Arthritis

Rheumatoid arthritis treatment is mainly includes reduction of joint inflammation and pain the joint, it maximise the growth of muscles and function of the joints and prevent the destruction of the bone in the hand, shoulders and legs. Treatment of this type of arthritis decides mainly by age, strength of the joints, sex, health of the person and various combinations of medications. For treatment of arthritis analgesics, non steroidal anti inflammatory drugs, corticosteroids, drug modified anti rheumatic drugs are used. Analgesic and non steroidal anti inflammatory drugs are rapidly ineffective in this type of arthritis. Steroid drugs are administered through intra articular administration which reduces the pain and inflammation. In another way drug modified anti rheumatic drugs like penicillamine and hydroxychloroquine are used for treatment.

Immunosuppressive drugs like azathioprine, cyclo-phosphamide and cyclosporine shows aggressive action the arthritis. For development of effective treatment in arthritis like RA are based on the inflammatory mediators such as TNF-α and IL-1 representing the novel approach.

Corticosteroids are also used in the therapy of rheumatic arthritis. It is associated with the side effects like hypertension, increased appetite, glaucoma, CNS effects etc. It also increase the anti inflammatory cytokines effects in the arthritis treatment. Inhibitors of non steroidal anti inflammatory drugs like COX-2 enzymes exhibits action of analgesic. Side effect may be gastric complications [19-21].

Intra-articular Injection Technique

Intra-articular drug delivery can be made using injections which are directly given into the joints which causes pain. Selection of this injection will reduce the side effects compare to systemic administration. It is a common technique for knee or other joints pain relief. Difficulty in injection is placement of the needle for the particular place which is affected. Post injection flare, crystal synovitis and steroidal arthropathy also causes the side effect. Presence of crystals in the joint causes the transient synovitis in few patients. In this method post injection rest is required to increase the residence time of drug which is administered. It has few technical draw backs like patient compliance, rapid movement of drug, cost and procedure followed for the treatment of arthritis. But this route of administration as minimised side effects compare to other routes of administration [22, 23].

Management of arthritis can be made using various routes also but intra articular delivery is more advantageous compare to oral, parenteral, topical, site specific, nasal route of administration.

In oral administration of corticosteroids like prednisolone and prednisone are 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. It as many disadvantages like peptic ulcer, hepatic ulcer, nephritic syndrome etc. It can be overcome by using various approaches like oral pulsatile drug delivery system which involves the liberation of drugs after the time of administration [24, 25]. Through parenteral route drugs like steroids injections are given directly into the joints which are effective in the treatment of juvenile rheumatoids. Mycochrysine and Solganal are rarely used because it as low efficacy and poor tolerability in the treatment of RA. Drugs which are administered through intra articular route produce the symptomatic relief in joint inflammation and pains [26].

While in case of target delivery Liposomes which are encapsulated with corticosteroids shows effective action on arthritis when administered intra articularly. It as an advantage of prolong localize, target interaction with diseased system rather than other route [27]. Among NSAIDs diclofenac shows better action on acute and chronic painful inflammatory conditions. Pharmacosomes of diclofenac have a getter action for improving dissolution and reduces the gastrointestinal toxicity of drug. It was prepared by using diclofenac and phosphatidylcholine. Even ibuprofen-phosphatidylcholine shows better gastrointestinal safety and analgesic for osteoarthritis [28]. Intra-nasal drugs also have better advantage over drugs showing poor absorption [29].

APPROACHES TO IMPROVE INTRA-ARTICULAR DRUG DELIVERY

Joint diseases are cause of pain and disability in the adult population. Various attempts have been made over the years to cure the pain accompanying these diseases and to decrease the incidence of joint degeneration. Several delivery systems such as hyaluronic acid systems, microparticles, nanoparticles, hydrogels, and thermoreversible systems have been developed in order to allow sustained drug delivery to the joint and to achieve high drug concentrations at the site of action [30].
Hyaluronic Acid based Systems for Intra-articular Delivery

Hyaluronic acid (HA) is a non sulphated glycosaminoglycan which is one of the chief components of the extracellular matrix. It is a major component of articular cartilage and synovial fluid. Hyaluronic acid is used in treatment of joint disorders such as OA and RA. In these diseases, the molecular weight and concentration of HA in synovial fluid are diminished and the synovial fluid becomes thinner and loses its elasticity and viscosity, the knee joint causing the cartilage to wear down with time, this deterioration can contribute to pain and stiffness of the knee. Such treatments, called visco supplementation treatments are administered in the form of injections in the knee joint and are believed to supplement the viscosity of the joint fluid, thereby lubricating and cushioning the joint, and producing an analgesic effect by buffering load transmission across articular surfaces.

Another attainment was made by Callegaro and Renier to modify HA in which sulphated HA for intraarticular injection was developed Sulphated HA showed pharmacological superiority compared to the non sulphated form in the treatment of chronic forms of degenerative OA by slowing degradation and stimulating the regeneration of the basic structure of the extracellular matrix to a greater extent than the non sulphated counterparts. Sulphated form of HA can be combined with the non sulphated counterpart to further increase the viscosity of the preparation. These modified formulations have succeeded not only in the symptomatic relief of the joints [31, 32].

Micro and Nano carriers for Intra-articular Drug Delivery

The use of micro- and nano-carriers for intra-articular delivery in order to avoid inflammation caused by intra-articular injection of these particulates, all formulation attempts were made using biodegradable and biocompatible materials such as polylactic acid (PLA), polyglycolic acid (PGA), polylactic/coglycolic acid (PLGA), polyvalerolactone (PV), albumin, gelatin and chitosan. The formulation of diclofenac PLA, PLGA, PV microspheres for intra-articular administration; Thakker et al. Lin et al. described and characterized the formulation of celecoxib chitosan and albumin microspheres resulting in ten fold increase in the concentration of the drug in the joint; Lu et al. described the preparation of biodegradable flubiprofen gelatin microspheres for treatment of RA; Tuncay et al. and Bozdag et al. described the formulation of diclofenac sodium and naproxen sodium respectively in biodegradable albumin microspheres. Bozdag et al. found that PLGA was better than albumin in the treatment of arthritis. Nanocapsules were prepared using a biocompatible polymer such as lactic acid or glycolic acid to provide sustained activity and in the same time overcome the problem of crystals-induced pain which is encountered when the drug is in an undissolved suspension form. Similarly, PLGA nanospheres and nanoparticles of betamethasone sodium phosphate were prepared [33-40].

Hydrogel based Intra-articular Delivery

The HA preparations which are currently available can be classified as hydrogels. The use of polyacrylamide hydrogel as a prosthetic device is well established for supplementing, augmenting or replacing cartilage in the intra-articular cavity of a joint for the treatment of arthritis. A novel class of hydrogel was also described by Holland et al. Which is based on oligo(poly (ethyelene glycol) fumarate which is a water soluble polymer that can be cross linked to form a biodegradable and biocompatible hydrogel for the delivery of growth factors. In order to achieve sustained release of these growth factors they could be first encapsulated in gelatin microparticles [41-43].

CONCLUSIONS

Intra-articular drug delivery system plays a vital role in the treatment of osteoarthritis and rheumatic arthritis as it is given directly into the joints. It reduces the leakage of tissue or organs, the active medicament gradually released into the target site. The synovial lining can be removed by using non-steroidal and steroidal drugs. Usage of intra-articular injection technique is to reduce the side effects compare to the systemic administration of drug, to relief pain. Among the various drug delivery systems, liposomes are supposed to be the advanced carrier for intra-articular drug delivery administration. In order to improve efficacy of intra-articular drug delivery systems, encapsulation technique should be used with specific targeting strategies for joints; which helps more in the treatment of rheumatic disease treatment. Using other approaches like hydrogel, microparticles, nanoparticles, hyaluronic acid etc. are other ways to improve the sustain release of drug to the systemic circulation through intra-articular route. Thus, extensive research on intra-articular delivery, development of novel intra-articular delivery systems and timely review of research in this area are need of the hour.
REFERENCES


