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OSTEOARTHRITIS: OVERVIEW AND NOVEL TREATMENT APPROACHES

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ABSTRACT
Osteoarthritis is a degenerative joint disorder characterised by loss of articular cartilage leading to severe pain and restricted mobility in patients. It mostly affects the joints located in the hand, knees, spine, hips and shoulder region. Risk factors such as age, joint injury, excessive repetitive loading, joint dysplasia, gender, genetic predisposition, comorbidities these are some factors which are known to increase risk of osteoarthritis (OA). At molecular level, OA results from an imbalance between the peptides that promote the synthesis of the components of extracellular matrix of articular cartilage and those that induce remodelling of these components. The articular cartilage degradation in OA is due to complex interaction and upregulation of various catabolic molecules such as interleukin, TNF, MMP. Womens are more prone to osteoarthritis as compared to men. Many conventional treatments such as oral, topical, have been employed for OA but none of the them has given satisfactory results over long term therapy. Oral administration of drugs is associated with side effects such as gastrointestinal bleeding, abrupt cardiovascular events .The use of topical therapy avoids the adverse effect by reducing the systemic exposure which is associated with oral conventional NSAIDs medication. This review mainly focuses on current trends in development of drug delivery system of nano scaled based carriers, with increased localization of therapeutic agent to the target site and have prolonged action. The most significant advantage of novel systems such as microemulsion, vesicular systems, nanocarriers over the conventional drug delivery is to provide target specific drug delivery and sustained action.

KEYWORDS: Osteoarthritis, drug delivery, Microemulsion, Liposomes, Ethosomes, Nanoparticles.

INTRODUCTION
Osteoarthritis (OA) is a main cause of pain and disability in elderly population. Osteoarthritis means inflammation of joints and also referred as degenerative joint disorder, but it a misnomer as osteoarthritis is not only a process of wear and tear, but it is an unusual remodelling of joint carried out by inflammatory mediators in the affected joint area.[1]

It not only affects only articular cartilage but also affects synovium, joint capsule and bone. The joints in osteoarthritis involve knee, hip, spine, hand, foot. In the study conducted by Poole et al they have concluded that in patients with OA there is an imbalance between degeneration and reconstruction of cartilage leading to increased susceptibility and occurrence of the disease.[2]

Globally OA has been the eighth leading cause of joint disability.[3] Predominantly knee joints are worst and most frequently affected amongst the various joints.[4] In India prevalence of OA was reported to be in the range of 22 to 39%[5] and in rural India it was reported to be 5.78%.[6] OA accounts for half of all the chronic conditions in people over the age of 65 years with 25% of people over 60 year of age have significant pain and disability.

OA is divided into two types Primary OA and Secondary OA. Primary OA is the most common form of the disease with no predisposing factor apparent. Secondary OA cannot be distinguishable pathologically from primary OA but underlying causes like accidential joint injury, sports injury, obesity, congenital disorder etc. Onset and progression of OA depends on various risk factors such as age, joint injury, excessive repetitive joint loading, gender, obesity, genetic predisposition, co-morbidities.[7,10]

It is believed that cytokinins and growth factors (GFs) are involved in the pathophysiology of OA. They bring about functional alteration in cartilage, synovium and subchondral bone and are produced spontaneously on stimulation by joint tissue cells. GFs and cytokinin are first produced by synovial membrane, which are then diffused into the cartilage through synovial fluid. They activate the chondrocytes which in turn produce catabolic factors such as cytokines and protease.[11] OA occurs when there is increase local production of pro-

inflammatory mediators such as interleukin IL-1,IL-6,IL-8 etc. and tumour necrosis factor(TNF),which are overexpressed in chondrocytes and stromal cells in OA joints.[12] These cytokinins will degrade the cartilage through activation of nuclear factor, signal transduction and activator transcription pathway leading to upregulation of different metalloproteinases (MMPs) such as MMP-13, is the major type collagen II degrading MMP. Endogenous factors such as fibrinogen, breakdown products of hyaluronic acid released during inflammation and tissue injury in OA which will also activate cytokines and growth factors in the joints.[13,14]

Management of OA involves conventional pharmacological treatment consisting of non-steroidal anti- inflammatory drugs (NSAIDs), opioids and intraarticular injections while non-pharmacological treatment include physiotherapy. Surgical option should be reserved for the patient who are not responding to any of the therapy. Although these medication only relive the pain and symptoms, but they are not considered to be an ideal therapeutic agent. NSAIDs in particular have serious side effects like peptic ulcer, hepatotoxicity, renal failure etc. Neither of these classes of medications prevents or delays the progression of OA.[15,16] Nowadays, many types of nutrition and nutritional supplements enriched with antioxidants have shown promising results in relieving the symptoms associated with OA and also have shown reduction in the progression of the disease without any side effects.[17] Stem cells is also an alternative for the maintenance and regeneration of damaged cartilage.[18] Other delivery systems include magnetically retainable drug delivery system, carbon nanotubes which will retain the drug at the targeted site for prolong period of time and thus decreases frequency of dosing. Replacement therapy for knee is the last option when nothing works out and the condition becomes worse.

LOCATIONS OF OSTEOARTHRITIS

As OA can occur in various joints which include knees, hip, hand, spine. Different characteristics of the disease will depend on specific joint affected.

Hands-OA in hands can occur due to genetic reason. OA of the hands involve small, bony knobs which may appear at the end joint that are closest to the nails of the fingers. They are called as Heberdens nodes. Other knobs called as Bouchard's nodes can appear at the middle joint of the fingers. Fingers may become enlarged, stiff, numb and may pain during OA. Sometimes the base of the thumb is also affected by OA. Women are more likely to OA in hands then in men. Most of the women develop OA after menopause.

Knees-Among the joints knees are most commonly affected by OA due to presence of weight bearing joints. The cartilage pad present between the joint formed by the thigh bone and the shinbone plays an important role in protecting the joint. Its act as the shock absorber. Usually the joint is stable until the disease reaches the advanced stage when the knee becomes enlarged and swollen. Symptoms include pain, swelling, stiffness, reduced knee flexion, bony tenderness which causes difficulty in walking and climbing. Knee OA is the leading cause of disability.

Hips-About one in four people develop hip arthritis over the course of their life time. Obesity increases the risk. OA frequently strikes the weight bearing joints in one or both hips. As knee, the symptoms of hip OA are pain, stiffness of the joint itself. But sometimes pain is also felt in the groin, inner thigh, buttocks and may also radiate to knee. Hip OA may limit bending and moving, making daily activities challenging.

Spine-OA may affects the cartilage of the vertebral disk that form cushions between the bones of the spine, the moving joints of the spine itself or both. OA in this location may cause pain, muscle spasm and diminished mobility. Sometimes due to arthritis related changes in the spine such as bone overgrowth can cause pressure on the nerves of the spinal cord which is responsible for extreme pain which further radiate to arms and legs causing numbness, weakness and tingling in the advanced disease state. OA in the spine is considered to be most when it occurs in lower back or in neck, where it can cause difficulty in swallowing.

Shoulder-OA is less common in the shoulder joint area as compared to other joints. In such cases it may be associated with previous joint injury and patients develop pain and stiffness in the back of the shoulder.[19]

RISK FACTORS OF OSTEOARTHRITIS

Age-OA evidence increases as the age increases. The percent of people with age get affected, less than 5% people between 15-44 years, 25%-30% people between 45-65years and more than 60% people over 65 year. With age the cells synthesize less amount proteoglycan, function of chondrocyte decreases the ability of cells to restore and maintain articular cartilage.

Joint injury-Injury to the joint may occur due to joint impact loading, dislocation or intra-articular fractures increases the risk of progression of joint degeneration. Even the acute joint injury kills few chondrocytes and that lead to progression of OA.

Excessive repetitive joint loading- Repetitive loading involving people from different occupation include farmers, metal workers, pneumatic drill operators, construction workers; miners etc. are at the increase risk of joint degeneration. Particular activities such as repetitive loading exceed the ability of the joint beyond its tolerance which accelerates loss of chondrocyte function and thus degeneration of cartilage.

Joint dysplasia-Sometimes due to disease the shape of the joint may get altered. This abnormal shape of joint

increases the risk of joint degeneration. Joint dysplasia occurs mostly in hip region.

Gender-The prevalence of men in developing OA is higher before 50year and after this age women are at the greater risk of developing OA due to menupause. With menopause estrogen defiency occurs which is associated with increased severity and incidence of OA in women. Estrogen therapy reduces the risk of OA compared to those who are not taking it.[20]

Obesity-Obesity is the risk factor for knee OA. There is increased stress on the weight bearing joints due to increased body weight and fat which is thought to influence obesity associated OA. Coggon et al found that overweight people with BMI>30 kg/m^2 were more likely to develop knee OA than normal weight people. Since excess of adipose tissue produces humoral factor which alter metabolism of articular cartilage which increases the risk of OA.[21]

Comorbidities-Two studies reported that CVS disease such as hypertension or ischemic heart disease are considered as the risk factor and one study also reported that respiratory illness can also contribute to OA.[22,23] Mork et al suggested that sedentary lifestyle exacerbated knee OA such association of the co-morbidities may accelerate the progression of each other. Depression was statistically linked with knee OA was concluded in two out of three studies.[24,25]

Genetic predisposition-OA is considered as the polygenic disease which has an important hereditary component.[26] Inheritance studies involving family groups and twin pairs have revealed a considerable genetic contribution to OA development, with heredity ranging from 39% to 78% at different joints.[27,29]

PATHOPHYSIOLOGY

At molecular level, OA results from an imbalance between the peptides that promote the synthesis of the components of extracellular matrix of articular cartilage and those that induce remodelling of these components. It has been proposed that the health of joint depends on expression of growth factors[30] eg. Transforming growth factor β (TGF-β), insulin like growth factor (IGFs)increases the synthesis of ECM. In contrast cytokines such as IL-1 and TNF α promote degranulation and chemotaxis of leukocytes and also increases expression of proinflammatory mediators such as prostaglandin E2 (PGE2), leukotriene B4, bradykinin and nitric acid.[31,32] IL-1 and TNF α increases the activity of various proteolytic enzymes such as matrix metalloproteinases (MMP). These substances perpetuate synovitis, initiate articular cartilage damage and also induce remodelling of subchondral bone.[33,34]

The articular cartilage degradation in OA is due to complex interaction and upregulation of various catabolic molecules such as interleukin, TNF, MMP. Interleukin IL-1β is an important catabolic cytokines involved in cartilage destruction. IL-1 is converted inside the cell by interleukin-1 converting enzyme(caspase1) to produce active form IL-1β.[35] The active form IL-1β promotes expression of transcription factor such as nuclear factor kβ.[36] This factor moves into the nucleus where it interacts with the promoter region of the various genes and participates in upregulation of genes including those that produce secondary proinflammatory peptides (eg:IL- 6,IL-8,IL-12),LTB4, chemokines, MMPs, PGE2 and nitric acid. IL-1β also inhibits the pathway in the chondrocytes that are used to repair ECM, release proteoglycans from ECM into synovial fluid and downregulates expression of natural inhibitors of MMPs called as tissue inhibitors of MMP(TIMPs).[37,38] Up regulation of MMPs such as MMP-2, MMP-3,MMP-9 in OA and these degrade the non collagen matrix components in the joint.[39] TNFα is secreted by chondrocytes, synoviocytes, macrophages and osteoclast which are activated by TNFα converting enzyme. The concentration of enzymes is increased during OA have been reported. TNFα drive inflammatory process it stimulates the release of IL-8 which further enhances the release of inflammatory cytokinins.[40]

EPIDEMIOLOGY

Worldwide estimates are 9.6% and 18% of men and women respectively, aged over 60 years have symptomatic OA. The epidemiology for OA in US ranges from 8% to 16.4%, UK estimated at 12.5% and approximately 8% to 13% in Australia, Europe. Around 10% of Canadians have OA and 4.1% and 11.3% accounts for India.[41]

CONVENTIONAL THERAPY

Conventional therapy can be categorized as oral, topical and injectable treatment.

Oral

Oral medication for OA includes NSAIDS, Opioids, etc. Acetaminophen is considered as the first line approach for mild to moderate pain management but the disadvantage is that it causes hepatotoxicity at higher doses.[42] Patient taking acetaminophen 3-4g/day should have regular monitoring of kidney and liver function. Selective and Non selective COX inhibitors have analgesic, anti-inflammatory and antipyretic effects are widely used for relieving painful conditions. Other NSAIDs are slightly superior to acetaminophen for improving hip and knee OA with those having moderate to severe pain.[43] About 8 million patients in UK use NSAIDs regularly for OA and this contributes to the annual estimated 2000 deaths due to NSAIDs side effects in this country.[44] NSAIDs safety has been debated over the last few years and increased CVS risk finally led to withdrawal of Vioxx and also marketing restriction for other COX-2 inhibitors.(coxibs).[45] Non-specific NSAIDs have high risk of gastrointestinal side effects.[46] Estimated number of death due to NSAID-related GI bleeding vary and approximate figure about 3500 to

16500 per year are quoted for the US in the FDA report(2002).[47] So nowdays to overcome the GI bleeding doctors prescribe NSAIDs with proton pump inhibitors. Example combination of enteric coated naproxen and proton pump inhibitor esomeprazole (Vimovo) were shown to reduce gastric ulcers.[48,49] Both NSAIDs and COX-2 inhibitors are associated with cardiovascular risk, increase in blood pressure especially in hypertensive patient.[50,51] Of all NSAIDs naproxen has been found to have least cardiovascular risk as compared to other NSAIDs.[52]

Topical

- **Gels**

Gels are mostly preffered by the patient because they are easy to administer, non greasy, forms thin film which ensures rapid effect. Apart from gels being cost effective they are also preferred by manufacturer due to less formulation inputs. The use of topical therapy avoids the adverse effect by reducing the systemic exposure which is associated with oral conventional NSAIDs medication. Several factors such as drug, formulation and site of application are important factors that vary the efficacy.[53] The commercially available dermal preparations such as Diclofenac(Voltaren) is available as solution, gel or patch. The systemic effects are proportional to the surface area, method of delivery results in stable systemic diclofenac level compared to oral administration. Therefore diclofenac gel was found to be safe and effective used as the first line therapy for the symptoms of knee OA.[54] In a Cochrane review it was concluded that topical NSAIDs can provide better pain relief and reduce gastrointestinal adverse events are reduced as compared to oral NSAIDs.[55]

- **Ointment, Cream, Lotion**

Ointment are semisolid dosage form which contain high level of oils. Creams are semisolid emulsion containg two phases oil and water. Creams are more preferred then ointments as they are less greasy. The controlled trials of Capsaicin cream 0.025% (Zostrix) was carried out it was found to be more effective than placebo in relieving pain but was less effective than topical NSAIDs. Lotion are cream with less viscosity. Salicylic acid is available as lotion.[56]

Injectable

The intra-articular injection provides short term symptomatic relief in patients with knee osteoarthritis with low risk of adverse effects. Example of intra-articular injection of corticosteroid .In a systemic review of 28 clinical trials a significant short term reduction in pain and improvement in self-assessment with intra-articular corticosteroid injection as compared to placebo injection.[57] It was presumed that corticosteroid inhibit accumulation of inflammatory cell lines, reduce PG synthesis, inhibit leukocyte secretion from synovial cells and reduces interleukin secretion by the synovium.[58]

Hyaluronic acid (HA) intra-articular injection is FDA approved for knee OA. Hyaluronic acid injection is used as viscosupplementation to restore normal viscoelastic properties of the pathologically altered synovial fluid.[59] Hyaluronic acid(HA) intra-articular injection when compared to glucocorticoids intra-articular injection it was found that benefits from each injection was similar, at some point of time there were greater benefits of HA, although these benefits were not sustained for long periods.[60]

Table 1: List of Conventional drugs for Osteoarthritis[61]

TREATMENT			ADVERSE EFFECT
Symptomatic	Oral	Acetaminophen	GI discomfort, bleeding, renal failure, hypertension, hepatotoxicity
		NSAIDS,coxibs	GI discomfort, bleeding, cardiovascular events, and renal events.
		Opioids	Constipation,vomiting,increase morbidity and mortality in elderly.
		Duloxetine	Constipation,nausea
	Topical	Topical NSAIDS	Skin reaction,GI events
		Capsaicin	Skin burning sensation
		Lidocaine patches	
	Injectable	Intra-articular corticosteroids	Local infection, systemic effects
		Intra-articular hyaluronic acid or viscosupplementation	Local reaction at the site of injection, swelling, flares of pain.
Slow acting symptomatic drugs	Oral	Glucosamine and chondroitin sulphate.	
		Diacerein	Lower GI effects

NEW APPROACHES FOR TREATMENT OF OSTEOARTHRITIS

As these conventional therapy will only relieve the pain and symptoms of osteoarthritic patients but not used to inhibit cartilage degeneration or induce cartilage regeneration which will reduce the progression of OA. The major advantage of local defects is that they are contained within the cartilage and bone and it is likely that delivery of the specific growth factors, Stem cell therapy, Nanoparticles to defect site will support cartilage healing. Early treatment of cartilaginous lesions can indeed be useful in slowing down the chronic development of OA.[62]

- **Microemulsion**

Microemulsion are thermodynamically stable translucent system with droplet size of 20-200nm. The microemulsion formulation include four main components oils, surfactant, cosurfactant, water. The advantages of microemulsion include increasing the solubility and bioavailaibility of drug, ease of preparation, low cost, enhancing drug permeability through skin, incorporate both lipophilic as well as hydrophilic drug. The major disadvantage include skin irritation due to higher level of surfactant.

Alper et al prepared microemulsion formulation containing flurbiprofen and optimized it in with invivo test. The optimized flurbiprofen microemulsion was compared with marketed gel and was found to be effective in inhibiting carrageenan induced rat paw edema and histopathological investigation of rat skin revealed the safety of microemulsion for topical delivery.[63]

In another study tenoxicam microemulsion was developed in which invivo antiarthritic and anti-inflammatory activity was evaluated on various mouse models such as air pouch model, xylene-induced ear edema, cotton pellet granuloma and carrageenan induced inflammation. It was concluded that tenoxicam microemulsion was effective in controlling inflammation compared to conventional topical formulation and therapeutic response showed similar efficacy to that of oral dosage form.[64]

- **Vesicular carriers**

Vesicular carriers such as liposomes, niosomes, ethosomes, transferosomes have been developed for optimization of topical penetration of drug and particularly for topical targeting. Vesiclular carrier have several advantages such as controlling the active ingredient release rate, localize the active ingredient in dermal layers. Although transdermal delivery of vesicular system also help to carry drug to systemic circulation.

Liposomes

Liposomes are lipid based microscopic particle. Liposomes are composed of Cholesterol, Phospholipid and fatty acids. Liposomes they are consider as ideal carrier because they have the ability to change the biodistribution profile of the entrapped drug. The advantage of this system is biodegradable, biocompatible, non-toxic, non-immunogenic, increased stability. Liposomes can be adsorbed or fuse through the skin. Fusion of liposomes through skin causes increased dermal penetration of drug.

Chih-Chang Yeh et al formulated Curcumin and bisdemethoxycurcumin(BDMC) loaded liposomes. The result showed 70% entrapment effiency of Curcumin and BDMC in liposomes. Both the liposomes downregulated the inflammatory markers on osteoblast and maintained the osteoblast function. In comparison of both liposomes, Curcumin loaded liposomes were found to be less cytotoxic and showed higher cellular uptake of Curcumin. Besides that Curcumin liposomes can prevent liposomes dependent inhibition of osteoblast differentiation but BDMC liposomes were not able to prevent. So it was concluded that Curcumin loaded liposomes slowed the progression of osteoarthritis.[65]

William et al investigated methotrexate liposomal IA injection on joint inflammation in antigen induce arthritis in rat using multilamellar vesicle(MLV) and small unilamellar vesicles(SUV). The study concluded that MLV were more efficient in suppressing the joint inflammation as compared to SUV.[66] In other study it was also found that methotrexate liposome would locally accumulate in the synovial membrane and allow sustained release at the local site of action.[67]

Niosomes

Niosomes are microscopic vesicular system prepared with non ionic surfactant, cholesterol and aqueous media for hydration. Niosomes can entrap hydrophilic and phobic drugs and they have better stability than liposomes. Niosomes are widely studied for dermal and transdermal delivery because niosomes prevent transepidermal water loss. Niosomes act on lipid structure with high amount of surfactant and thereby overcome the stratum corneum barrier, enhance penetration potential of vesicle and also cause dermal retention of dug. Proniosomes are surfactant coated carrier dry formulation, and whenever required rehydration by brief agitation in hot water. Proniosomes are considered superior drug delivery due to better stability, low cost, biocompatible, non toxic, non immunogenic as it is non ionic in nature.[68]

Niosomal gel of Etodolac was prepared it possessed better skin permeation than conventional gel. Invivo studies also showed good inhibition of inflammation than plain gel. Topical niosomal gel of Etodolac provided sustained and prolonged delivery of drug.[69] Ex vivo study showed that niosomal gel possessed better skin permeation study than the plain topical gel. Further in vivo study revealed good inhibition of inflammation in case of topical niosomal gel than plain gel and niosomal

formulation. The present study suggested that topical niosomal gel formulations provide sustained and prolonged delivery of drug.

Lornoxicam loaded proniosomal gel was formulated and was further assessed for invitro permeation studies. It was found that cumulative permeation of lornoxicam from proniosomes resulted in significant increase in permeation as compared to 1% lornoxicam loaded conventional gel. The gel showed sustained release of drug for more than 24hour.[70]

Transferosomes

Transferosomes are highly deformable unilamellar vesicles nearly about 100nm which squeeze through pores. These first generation elastic vesicles are composed of phospholipid and edge activator. Edge activators are single chain surfactant which provide flexibility to the liposomes structure .Classical liposomes have 100nm to 200nm diameter which are to large to permeate through stratum corneum. Transferomes reach deeper dermal tissue and even systemic circulation due to their flexibility in nature. Transferosomes have been successfully used as carriers for topical and transdermal delivery of drugs.[71]

Lornoxicam loaded Transferosomal gel was prepared. The percent entrapment efficiency of lornoxicam in the vesicles was in the range of 82.84 - 89.85%. Transferosomes showed prolonged drug delivery and had good stability characteristics. It was concluded that lornoxicam loaded transferosomal gel had the potential for transdermal drug delivery system.[72]

Ethosomes

Ethosomes are classical liposomes which contain phospholipids, high concentration of alcohol and water. It has been found that components of ethosomes reach deeper layers of the skin or even enter systemic circulation.[73] The size of ethosomes varies from 30nm to few microns. Mechanism of these carriers helps in improving the permeation of the drug due to their alcohol content as penetration enhancers and also phospholipids act by disrupting the intercellular lipid structure of SC.[74,75]

Ethosomal formulation of diclofenac potassium was prepared which showed high cumulative percentage of drug permeation (60.37±5%) and enhanced skin retention (619.60±18µg/cm2) after 12 hrs than other formulations. Invivo studies showed enhanced antiinflammatory activity of ethosomal gel compared to marketed gel formulation.[76]

Aceclofenac ethosomal formulation was prepared which showed higher entrapment efficiency(95.7%) and good stability. The optimized ethosomal formuation showed greater transdermal flux (226.1 µg/cm²/hr) which advocates the potential to treat rheumatic disease, where penetration of drug into muscle and synovial fluid is desirable.[77]

- **Nanocarriers**

Solid Lipid Nanoparticles(SLN) and Nanostructured lipid carrier(NLCs)

SLN are spherical in shape with average diameter of 10 to1000nm. SLN are w/o emulsion containing solid lipid or blend of lipids as oil phase. The core of the lipid is stabilized by surfactant.[78] NLCs are new generation lipid particles which have been develop to overcome the limitations of SLNs. Nanostructured lipid particles (NLCs) contain mixture of solid lipid and liquid oils. Smaller the size of lipid particles ensures closer contact with stratum corneum and increase the dermal penetration of drug.[79]

Aceclofenac loaded chondrointin sulfate conjugated SLNs(CS-SLN) for treatment of osteoarthritis was prepared. The entrapment efficieny was found to be (65.38 ± 1.7). SLNs showed invitro sustained drug release for more than 24hrs.Invivo studies showed highest uptake of SLNs(18.54 ± 0.43%) by knee joint compared to unconjugated plain SLNs. The percent inhibition of edema was higher from CS-SLN compared to unconjugated plain SLN.[80]

Ibuprofen loaded NLCs was developed to enhance the skin permeation and thereby improve the condition for osteoarthritis. The drug loading was found to be 9.85% and the entrapment efficiency was 98.51%. In vitro drug release, In vitro permeation, In vivo studies of ibuprofen NLC gel resulted in better permeation compared to reference after 6hours. Ibuprofen loaded NLCs gel had the great potential to enhance the dermal permeation and thereby had the efficiency for the treatment of chronic joint inflammation.[81]

Magnetically Retainable Nanoparticles

Several studies have been carried out on novel carries that vary from micro to nano to improve conventional intra-articular drug delivery system. Efforts are been made to make the formulation that have targeted drug delivery, low systemic side effects, longer duration of action due to sustain release, amount of drug required is less, reduces the frequency of dosing, improve bioavailability and therapeutic efficacy of drug.[82]

This approach of drug delivery system makes use of magnet which will attract matrix microparticles loaded with drug, encapsulated with superparamagnetic nanoparticles toward the target area. The main objective of using this delivery system is to retain drug at the target site for longer period of time.

Advantages

- High drug concentrations are achieved at the site of action.
- Limit the systemic toxicity.
- Smaller amounts of drug are required.

- Frequency of dosing is reduced.

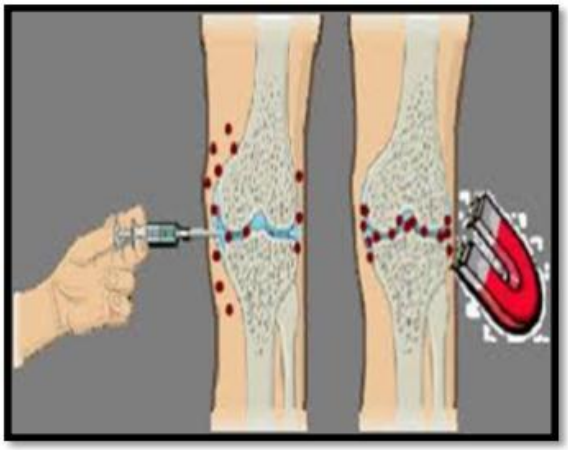

Figure 1: Intraarticular administration of superparamagnetic nanoparticles into OA joint.[83]

In magnetic targeting, a drug is bound to the magnetic carrier which is administered to the patient and then this magnetic carrier is stopped with the help of powerful magnetic field in the target area. The drug is slowly released from the magnetic carriers over the period of time. Magnetic carriers used are iron, nickel, cobalt, magnetite etc. Dexamethasone-containing biodegradable super paramagnetic micro particles have been administered by intra-articular injection.

Conventional corticosteroid suspensions for the intra-articular treatment of osteoarthritis have disadvantage of crystal formation leading to pain and rapid clearance from the joint. So to overcome this drawback, corticosteroid were formulated as magnetically retainable drug delivery system which will not only prevent crystal induced pain but also prevent rapid clearance from the joint. Use biodegradable microparticles containing dexamethasone 21-acetate, from which the drug substance could be slowly released over the period, avoiding the problem related to the appearance of crystals in the joint. The rapid clearance from the joint could be overcome by coencapsulating with dexamethasone, superparamagnetic iron oxide nanoparticles (SPIONs). This would confer magnetic properties to the microparticles, thus allowing their retention with an external magnetic field and increasing their retention in the joint.

Butoescu et al incorporated superparamagnetic iron oxide nanoparticles in PLGA microparticles loaded with dexamethasone in mice and achieved residence time in the joint for atleast 3 months.[84]

Nanotubes

Several studies were conducted to investigate the use of intaarticular injection of liposomes and polymeric particles to improve the therapeutic index of anti-arthritic drug but the efficacy into chondrocytes of OA mice has not been assessed yet.[85] Intraarticular(IA) administration provides high concentration of therapeutic agent at the target site but these injected small molecules or biomacromolecules are quickly cleared through lymphatic system which restrict their residence within synovial cavity to few hours.[86,89] So to increase IA persistence of therapeutic agent it should be combined with nanotechnology derived drug delivery system.

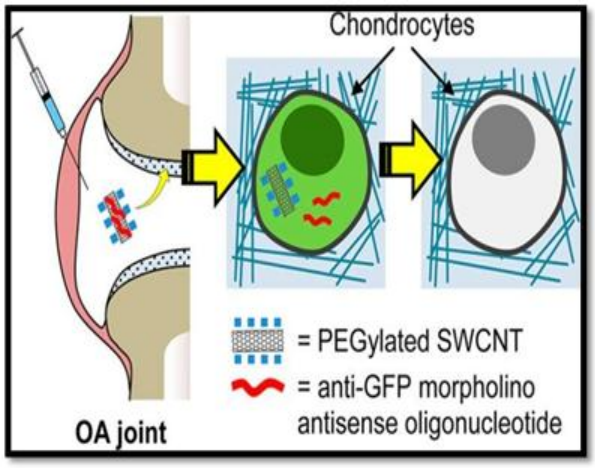

Figure 2: Intraarticular administration of Polyethylene-Glycol-Modified Single-Walled Carbon Nanotubes (PEG-SWCNTs) into OA joint.[90]

The methods such as electro spinning and self-assembly are used to create the scaffold known as nano-scaffold. In this technique proteins are then added to the scaffold surface which will promote cell differentiation and growth. Adding the charged covering on the surface of the scaffold it can help to increase the concentration of growth factors which would aid in proliferation of the cells. One such nano scaffold is the carbon nanotube are used enhance the mechanical and electrical conductive properties of the tissue. Carbon nanotube are the special form of carbon where carbon chemical bond forms tubes from carbon atom. Carbon nanotubes can be single (one tube) or multi walled(more than one tube) cylindrical sheet and diameter range in various nanometre. They also improve adhesive property, control the release of growth factors and it physically shape the tissue to create the required structure.[91] Example of intaarticular(IA) delivery nanosystem based on single walled carbon nanotube(SWCNTs) which is modified with PEG. It showed that PEG-SWCNTs was able to persist in the joint cavity for a prolonged period of time, enter the cartilage matrix, and deliver gene inhibitors into chondrocytes in both healthy and OA mice.[92] This IA-PEG-SWCNTs have the ability to enter the cartilage extracellular matrix and accumulated into chondrocytes in vivo in both healthy and OA mice as 3 days after IA injection.[93] It was seen that more than 25% of the starting dose of IA-PEG-SWCNTs was retained in healthy joint 14 days after administration.[94] Due to conflicting toxicity report, its use have been limited for drug delivery.[95]

CONCLUSION

Conventional therapy only reduces the pain and symptoms of Osteoarthritic patient but does not really treat the actual cause of the disease which is actually imbalance of regeneration of the damaged articular cartilage. These conventional therapies are also associated with several systemic side effects. The various nanotechnological approaches such as Microemulsion, vesicular systems, nanocarriers ensure drug permeation to much deeper layer of skin and thus reach the synovial fluid. Intraarticular(IA) administration of nanoparticles, liposomes provides high concentration of therapeutic agent at the target site thereby provide the symptomatic relief and improves the condition of osteoarthritic patient. These newer systems provide more target specific drug delivery in the affected area, reduction in dose, increases efficacy and frequency of dosing and therefore reduced systemic toxicity and prolonged duration of action due to sustained drug release. So it can be anticipated from these finding that the novel carrier systems providing localization of drugs to the target site could come into the market.

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