AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Novel Intra-articular Injections for Osteoarthritis.

Meghana S. Kamble[1]*, Rohini P. Chavan[1], Ashok V. Bhosle[2], Pravin D. Chaudhari[1],

1. PES's Modern College of Pharmacy, Pune, Maharashtra, India.

2. PDEA's S.G.R.S College of Pharmacy,Saswad,Pune, Maharashtra,India

ABSTRACT

Osteoarthritis (OA) is a group of chronic, painful, disabling condition affecting synovial joints. OA is the most common among elderly people. Approximately 80% of population above 65 years of age suffers from OA and this value reaches near to 100% with increasing age. Currently available treatments of OA provide symptomatic relief or slow the progression of disease. The oral or parenteral administration of these drugs causes serious systemic side effects leading to even withdrawal of certain drugs from market. To overcome these problems, localized IA drug delivery presents a new hope. A number of drugs have been investigated for their local effect after IA administration. A number of novel drug delivery systems are available for their own merits and demerits. This review discusses the pathophysiology of OA and formulation consideration of IA injections along with details of current and novel drug formulation for OA treatments.

Keywords: Osteoarthritis, Intraarticular, Microparticles, Liposomes, Nanoscaffolds

*Corresponding Author Email: formeghana@yahoo.com

Received 26 September 2012, Accepted 04 October 2012

Please cite this article in press as: Kamble M *et al.*, Novel Intra-articular Injections for Osteoarthritis. An important medicinal plant. American Journal of PharmTech Research 2012.

INTRODUCTION

Osteoarthritis (OA) is a major cause of disability. Patients with OA have pain that typically worsens with weight-bearing activity and improves with rest. Unlike the rheumatoid arthritis (RA) inflammation is usually mild and localised in the affected joint. Although the cause of OA remains unknown, biomechanical stresses and biochemical changes in the articular cartilage, sub-chondral bone and synovial membrane, and genetic factors, are all important in its pathogenesis. Multiple factors have been shown to affect the progression of OA, including the presence of polyarticular disease, increasing age, associated intra-articular (IA) crystal deposition, obesity, joint instability or malalignment, muscle weakness and peripheral neuropathy.[1]

In joints affected by OA, the synovial fluid's capacity to lubricate and absorb impact is typically reduced. These changes are partly due to a reduction in the size and concentration of hyaluronic acid molecules naturally present in synovial fluid (SF). There are no. of treatments available for OA which include use of NSAIDs, steroid drugs, disease modifying osteoarthritic drugs, dietary supplements and knee exercises. All the treatments have their own benefits and drawbacks. Oral NSAIDs, steroid drugs cause a no. of side effects because of their systemic absorption and then distribution in SF and then showing therapeutic effect. If the drug is administered and localised in affected joints, there will be significant reduction of systemic side effects of the drugs. The option for local administration of drugs is intraarticular injection. The local nature of OA makes IA drug injection an attractive treatment approach as the drug can be applied directly into the affected joint, minimizing systemic side effects. Furthermore, the joints which are frequently affected by OA, like the knee, hand and foot joints are well suited for IA injection. Direct delivery of the drug to the affected joint also offers the possibility to achieve appropriate drug concentrations at the site of action by applying low amounts of drug. In addition, IA injection also makes it possible to develop drugs which have good efficacy, but low oral bioavailability, which is an issue for many of the novel drug candidates in development.

Many drugs bear considerable risk of systemic adverse events as the cardiovascular events and gastrointestinal side effects observed for most NSAIDs and COX-2 inhibitors for the treatment of joint pain have demonstrated. The chronic nature of the disease requires the development of drugs suitable for chronic systemic treatment with minimal side effects, which is a challenging goal. Local drug application, i.e., the injection of drugs directly into the affected joint, is an option for the treatment of OA. Some are available clinically and some are in research phase.

This review throws the light on currently available IA injections and potential of other agents for their IA injections.[2]

Patho physiology of Osteoarthritis

The primary changes with osteoarthritis occur in the articular cartilage, followed by associated changes in the subchondral bone. Recently, more focus has been placed on the subchondral bone as the primary cause of symptomatic disease which is true in case of young patients. Age is the major independent risk factor of osteoarthritis. Aging and osteoarthritis are inter-related but are not inter-dependent. Where cartilage deterioration is to some extent part of normal aging and the relationship between aging and the development of osteoarthritis is becoming apparent that aging changes in the musculoskeletal system contribute to the development of osteoarthritis by working in conjunction with other factors, both intrinsic (e.g., alignment, overloading) and extrinsic (e.g., genetics) to the joint . In the young patient, the pathogenesis of knee osteoarthritis is predominantly related to an unfavorable biomechanical environment at the joint, which results in mechanical demand that exceeds the ability of a joint to repair and maintain itself, predisposing the articular cartilage to premature degeneration. [3]

Articular Cartilage: Normal structure and function

Articular cartilage consists primarily of extracellular matrix with a sparse population of cells, lacking blood vessels, lymphatic vessels and nerves. It has a low level of metabolic activity, and there is little or no cell division or cell death in normal adult articular cartilage, although articular chondrocytes are in fact capable of cell division. The chondrocytes make up only about 1% of volume of adult human articular cartilage. These chondrocytes are responsible for both the synthesis and the breakdown of the cartilaginous matrix. The mechanisms that control the balance between synthesis and degradation are not fully understood, but cytokines with anabolic and catabolic effects appear to play important roles. For articular cartilage to exert its normal function within the joint, it needs to be elastic and have high tensile strength. The unique mechanical properties of articular cartilage depend on the extracellular matrix. This extracellular matrix consists of two components, tissue fluid and the framework of structural macromolecules consisting of type II collagen fibers, proteoglycans and non-collagenous proteins and glycoproteins, all produced in the appropriate amounts and assembled and organized into a highly ordered molecular framework by the chondrocytes. The collagen matrix gives cartilage its form and tensile strength. Proteoglycans and noncollagenous proteins bind to the collagenous network, help stabilize the matrix macromolecular framework and help chondrocytes bind to the macromolecules of the network.[3]

Osteoarthritis

Osteoarthritis results from failure of chondrocytes to maintain the homeostasis between synthesis and degradation of the extracellular matrix components. This disruption of homeostasis results in increased water content and decreased proteoglycan content of the extracellular matrix; and weakening of the collagen network due to decreased synthesis of type II collagen and increased breakdown of pre-existing collagen . Furthermore, there is increased apoptosis of chondrocytes. At first, compensatory mechanisms, such as increased synthesis of matrix molecules and proliferation of chondrocytes in the deeper layers of the cartilage, are able to maintain the integrity of the articular cartilage, but eventually loss of chondrocytes and changes in extracellular matrix predominate and osteoarthritic changes develop.[3]

Intraarticular Formulation Considerations

Intraarticular injections must comply with most the requirements of injections. IA injections must be sterile, isotonic and free from particulate matter. The pH of the formulation should be close to pH of SF (pH 7.4) to avoid possible side effects of non-physiological pH values such as activation of proteolytic enzymes. The polymers if used must be biocompatible and biodegradable. Various sterilization methods like moist heat sterilization or filtration can be followed for sterilization of IA injections depending on drug and formulation properties. For example thermolabile drug cannot be sterilized by moist heat sterilization, and if it is in suspension form cannot be sterilized by filtration. Such formulation can be made by aseptic processing. The excipients used in injections should be screened before use in IA injections. [4]

CURRENTLY AVAILABLE TREATMENTS

Corticosteroids

The first joint injection was of hydrocortisone acetate by Hollander. It was found that his patients had a much better clinical response in a series of more than 100,000 injections in 4000 patients. Since 1950s corticosteroid injections have been used routinely to treat joint pain. Steroids possess anti-inflammatory properties. On the cellular level, steroids are highly lipophilic and are believed to bind to the cell's nucleus. It is believed that steroids act by altering transcription. Intra-articular steroids seem to reduce the number of lymphocytes, macrophages, and mast cells; this, in turn, reduces phagocytosis, lysosomal enzyme release, and the release of inflammatory mediators. Inflammation is reduced, particularly through reductions in the release of interleukin-1, leukotrienes and prostaglandins. With the reduction of these inflammatory mediators, pain symptoms often are improved. Because they are injected locally, intra-articular steroids avoid

most of the systemic effects of oral steroids, including muscle weakness, skin thinning resulting in easy bruising, peptic ulceration, and aggravation of diabetes. [5]

Hyaluronans

Hyaluronic acid (HA) is a high molecular weight polysaccharide of N-acetyl glucosamine and glucuronic acid building blocks. It is produced by synoviocytes, fibroblasts and chondrocytes and represents a main constituent of SF and hyaline cartilage. In articular cartilage, HA provides a backbone for the attachment of aggrecan side chains by link proteins. This HA–aggrecan complex interacts with water and type II collagen fibers to form the extracellular matrix of articular cartilage. Native HA has a molecular weight of 4–10 million Da and forms an extensive network at concentrations over 0.3mg/ml in aqueous solution. In joint fluid, the high concentration of HA (approximately 0.35g/100ml) is responsible for the viscoelastic properties of SF. The viscoelasticity of HA is crucial for the maintenance of joint homeostasis. Since HA behaves as a viscous liquid at low shear rates and as an elastic solid at high shear rates, SF acts as a viscous lubricant during low impact movements of the joint and as an elastic shock absorber during high impact movement. HA also has barrier and exclusion effects that limit the movement of cells and large molecules through normal SF. In joints affected by OA, the molecular weight and concentration of HA are diminished. This low HA concentration may be attributed both to reduced synthesis of HA and also increased volume of SF. This adversely affects the ability of SF to lubricate and protect articular tissues, and to absorb joint loads, which contributes to further progression of OA. The mechanism of action of hyaluronan was initially termed viscosupplementation to indicate restoration of normal viscoelastic properties of the pathologically altered synovial fluid. The purpose of viscosupplementation is to restore rheologic and metabolic homeostasis to the joint. It is thought that this temporary restoration and normalization produced by hyaluronan improves the protective, lubricating, and shock-absorbing effects of synovial fluid. Other possible mechanisms of action include control of synovial permeability, blockade of inflammation by scavenging oxygen free radicals, and inhibition of matrix metalloproteinases. Hyaluronan may also protect chondrocytes and promote cartilage matrix synthesis. Whether hyaluronan ameliorates or modifies disease progression has not been determined and remains the subject of much speculation. The duration of clinical benefit associated with the use of these agents far exceeds their synovial half-life of 2 to 8 days; accordingly, other mechanisms of action of equal or greater importance have been proposed on the basis of investigational studies. These mechanisms include inhibition of inflammatory mediators such as cytokines and prostaglandins, stimulation of cartilage matrix synthesis,

inhibition of cartilage degradation, protection against cellular damage by reactive oxygen species, and a direct effect on nociceptive nerve endings. [6]

NOVEL APPROACHES FOR TREATMENT OF OSTEOARTHRITIS

Local Anaesthetics

Local anesthetics, such as lidocaine are used by some clinicians for IA injection either alone or in combination with glucocorticoids. Lidocaine can itself have some mild anti-inflammatory effect during its relatively short half-life. When mixing lidocaine with glucocorticoids, the prompt effect of the local anesthetic providing temporary relief of symptoms can help confirm proper placement of the injection and support that the site injected was the source of the pain. Relief is temporary and this is not recommended for sole therapy. [6]

Morphine and other NSAIDs

Interestingly IA morphine provided significantly more prolonged pain relief compared to intravenous morphine plus IA saline placebo in a small study with knee OA patients and a parallel study comparing IA dexamethasone, IA morphine and saline placebo both the morphine and dexamethasone groups demonstrated similar reduction in pain over a period of 7 days. Similarly, the 5-HT blocker tropisteron has demonstrated benefit in OA in a small pilot study. It remains to be seen whether IA injection of opiates or 5-HT blockers will become a more widespread therapy for OA pain. [7]

Local anaesthetic is frequently injected intraarticularly and around the sites of the portals at the end of arthroscopic procedures to provide analgesia. Studies of intra-articular analgesia following arthroscopy of the knee have demonstrated that bupivacaine is both safe and effective.For the NSAIDs, phenylbutazone and tenoxicam, some benefit was observed upon IA injection in studies with small groups of knee OA patients. However, IA indoprofen failed to demonstrate any additional benefit in hip joint distensions.[7]

Microparticles

The drug delivery from oral and parenteral routs provides low therapeutic concentration in the joint cavity. The intra-articularly injected drug solutions are rapidly cleared from the joint spaces and needed frequent injections to maintain the drug concentration within the joints. Therefore, polymer-based microparticulate drug delivery systems (microspheres/microparticles), for the purpose of controlled drug delivery for desired period of time, have been extensively studied. In order to achieve controlled drug release, chitosan polymer, a deacetylated derivative of chitin, has been commonly used in the formulation of microparticulate drug delivery. Biocompatibility

and biodegradability of chitosan is appropriate for biomedical application.[8]

Table 1:- Review of Research on Intraarticular Drug Delivery:-

Sr. no	Author & Year	Dosage Form	Drug	Ref. No.
1	Kawadkar J. et al 2012	Microspheres	Flurbiprofen	8
2	Saravanan M.et al 2011	Microspheres	Diclofenac Sodium	10
3	Butoescu N. et al 2009	Microspheres	Dexamethasone	11
4	Williams A.S. et al 1996	Liposomes	Methotrexate	12
5	Hou S M et al 1997	Liposomes	Lidocaine	13
6	Thakkar H et al 2007	SLN	Celecoxib	14
7	Dominique A et al 2008	Nanoparticles	Biofunctional Polymers	15
8	Zhang J X et al 2006	Nanocarriers	Indomethacin	16

Liposomes

Liposomes are spherical vesicles or cavities made up of phospholipids that usually, but not by definition, contain a core of aqueous solution and have been proposed as efficient carriers for controlled drug delivery. They are able to entrap hydrophilic drugs in the large aqueous interior and lipophilic drugs inserted in the lipid bilayer. Moreover, hydrophobic drugs such as dexamethasone are incorporated in the bilayer structure of liposomes, whereas hydrophilic drugs such as diclofenac are encapsulated in the internal aqueous chamber. Derived from naturally occurring, biodegradable and nontoxic lipids, liposomes are good candidates for local targeting of therapeutic agents to the site of interest, while reducing systemic toxicity. The residence of encapsulated drugs within the knee joint was greatly prolonged as compared to drug's conventional formulation. Liposomes are good candidates although a liposomal corticosteroid formulation containing dexamethasone-21-palmitate (Lipotalon) available in Germany is the only intra-articular liposomal product used in human patients. [9]

Nanoscaffolds

Nanotechnology provides the tissue regeneration field with nanostructures that might accurately simulate the natural 3-dimensional microenvironment of cells. This approach provides a complex network of nanoscale fibers and extracellular ligands, such as many types of collagens, laminin and fibronectin, that are poorly reproduced in the conventional 2-dimensional systems. Growth of cells in 2-dimensional cultures has been shown to reduce the production of particular extracellular matrix proteins, with consequent morphological changes and increase in spreading. The advancement in the technology of nanostructures enhances the scope of fabricating 3-dimensional nanoscaffolds that could potentially mimic the architecture of natural human tissue. These nanostructured scaffolds could control and direct cellular behaviour and interactions with the extracellular matrix. Scaffolds have been designed in the form of nanofibers, nanotubes,

nanowires, nanorods, nanocrystals and nanofilms. These nanostructured scaffolds with their biomimetic features and excellent physicochemical properties, stimulate cellular adhesion, growth, morphology, proliferation, alter gene expression and promote cellular differentiation. The structural features of these nanoscaffolds were engineered according to the nature of cell response which is desired. The scaffolds are designed in a manner that provide a surface to promote cell attachment, spreading and growth while encouraging the formation of a porous network that offer a suitable path for nutrient transmission and tissue ingrowth . These novel nanoscaffolds have excellent mechanical properties that offer structural support until the new tissue would be formed, as they degrade at a rate matching the new tissue formation and provide substrate for cell migration and survival. They are biocompatible and the products of their degradation are also biocompatible. These nanostructured scaffolds provide the functional role of the native extracellular matrix with growth factors that regulate the cell fate and bioactive peptide sequences that can bind receptors and activate intracellular signalling pathways. Several techniques have been designed for the fabrication of nanofibrous scaffolds to be employed in tissue regeneration.[17]

Electrospinning techniques have been the most commonly used. An electric field is applied to draw a polymer solution from an orifice to a collector, producing polymer fibers with diameters ranging in size from 50 nm to several microns. These resulted lengths mimicked that of native collagen fibrils. Several types of synthetic and natural biomaterials have been used to form nanofibrous scaffolds such as poly (caprolactone) (PCL), poly (lactic-co-glycolic acid) (PLGA) poly (L-lactic acid) (PLLA), collagen, gelatine and fibrinogen; molecules that have been applied extensively in tissue regeneration.[18]

Another technique for nanofibrous fabrication is self-assembly. Molecular self-assembly has been applied to produce supramolecular architectures. This technique produces nanofiber diameters much smaller than those produced using electrospinning. Molecular self-assembly has been less effective in producing macropores for mass transport and cell accommodation. Phase separation techniques have also been also employed to fabricate nanofibers with diameters ranging from 50 – 500 nm and much higher surface –to-volume ratios than produced by other techniques.[19]

Bone and Cartilage Regeneration

An important criterion for designing orthopaedic implant materials is the formation of sufficient osteointegration between synthetic materials and bone tissue. Studies have demonstrated that nanostructured materials with cell-favourable surface properties could promote greater amounts

of specific protein interactions to more efficiently stimulate new bone growth compared to conventional materials. This is one of the underlying reasons that nanomaterials are superior to conventional materials for bone growth. Therefore, by controlling surface properties, various nanophase ceramic, polymer, metal and composite scaffolds have been designed for bone/cartilage tissue engineering applications.[20]

Nanofibrous and nanotubular scaffolds were fabricated to mimic collagen fibers in bone and cartilage. Natural collagen is a triple helix self assembled into nanofibers of 300 nm in length and 1.5 nm in diameter. A new nanofiber composite is designed with the same self-assembly pattern as collagen and hydroxyapatite crystals in bone by directly nucleating and aligning the hydroxyapatite on the long axis of a nanofiber. Mesenchymal stem cell behaviour on self-assembled peptide amphiphile nanofiber scaffolds has been investigated. Significantly enhanced osteogenic differentiation of mesenchymal stem cells has been recorded in the 3-dimensional scaffolds compared to 2-dimensional static conventional tissue cultures.[20]

Other types of nanofibers used in bone regeneration include the natural polymers. Natural polymeric nanofibers, such as poly(caprolactone) (PCL), poly(lactic-co-glycolic acid) (PLGA) poly(L-lactic acid) (PLLA), collagen, gelatine and fibrinogen, are excellent candidates for bone and cartilage tissue engineering applications. These biomaterials possess properties that are useful for bone regeneration, such as biodegradability, flexibility, shape availability and ease of fabrication. Poly(caprolactone) (PCL) was first suggested to be a degradable nanofiber matrix for bone regeneration, and it demonstrated good support of the rat bone marrow stromal cells and *in vitro* matrix formation at 4 weeks, including collagen I and calcium phosphate. A cell-nanofiber construct was implanted in rat omenta for 4 weeks. It revealed the formation of collagen I and mineralization similar to bone like extracellular matrix, highlighting its usefulness in bone tissue regeneration. A combination of degradable polymeric nanofibers with bioactive inorganic metals was proved to enhance osteogenic differentiation and calcification of bone matrix. The inorganic phase improved the biological properties of polymers in the bone forming process. Gelatin-hydroxyapatite nanofibers were fabricated. Hydroxyapatite nanocrystals were distributed in the gelatin matrix and produced an organized hybrid matrix. This composite enhanced osteoblastic differentiation and could be applied usefully in dentistry. In a similar way, collagen-hydroxyapatite and chitosan- hydroxyapatite nanofibers were generated mimicking the extracellular matrices.[21]

An additional excellent choice of nanomaterials for the reconstruction of bone tissue is the bone-bioactive inorganics such as bioactive glass, ceramics and calcium phosphates. Silica based sol-

gel glass mixed with a polymer binder is generated into a nanofibrous mesh by an electrospining technique. Fibers ranging from 84 nm to 640 nm in size are produced. The large surface area of the nanofibers, and the consequent ionic reaction with the surrounding medium, induce the formation of a bone mineral-like apatite phase on their surfaces. Osteogenic proliferation and differentiation of rat mesenchymal stem cells are found to be enhanced on the bioactive glass nanofiber substrates more than on conventional bioactive glass. Nanophase metals have been investigated for orthopaedic tissue regeneration. They are characterized by the presence of more particle boundaries at their surfaces than the conventional micron metals. Linear patterns of nano-features of titanium are created via electron beam evaporation. These patterns induce greater osteoblast adhesion than the micron-rough regions and guided osteoblast morphology and alignment. Highly porous titanium dioxide nanotube layers are fabricated on titanium by anodization. Titanium is anodized electrochemically in dilute hydrofluoric acid electrolyte solutions to produce nanotubes with diameters of 100 nm and lengths of 500 nm into the titanium dioxide layers of titanium. Nanotubular anodized titanium greatly improves osteoblastic function and increases chondrocytic adhesion, promoting bone and cartilage cellular growth.[21]

CONCLUSION

Osteoarthritis is a disease that results from cartilage degeneration. The most common symptom of OA is pain and inflammation in the affected joints. Treatment for OA usually involves a combination of medication, exercise, lifestyle modification and in severe case a surgical procedure. There is no drug yet found to cure arthritis, the current treatment available aims to reduce joint pain and inflammation while improving joint functions. Various categories of drugs such as analgesics, steroids, disease modifying osteoarthritic drugs, biologic response modifiers administered orally, topically or parenterally, provide symptomatic relief but at a high price of serious side effects. These systemic side effects of these drugs can be drastically reduced if the drugs are administered intraarticularly i.e. directly into affected joints. This localisation of drugs is expected to significantly reduce the dose required for treatment. A variety of novel drug delivery systems such as microspheres, liposomes, nanoparticles can be used intraarticularly. Though IA injection is an attractive delivery method yet the challenge of rapid clearance of drug from synovial fluid still remains unmet. Further research is necessary to determine toxicity, cost and efficiency of novel IA drug delivery systems. With help of novel drug delivery technologies, the drawbacks of current therapy will be overcome and in near future promising IA therapy for OA treatment will be available clinically.

REFERENCES

1. Hassanall S, Oyoo G. Osteoarthritis: A Look at Pathophysiology and approach to new treatments: A Review. East African Orthopaedic J 2011; 15:51-57.
2. Goldring SR, Goldring MB. Clinical Aspects, pathology and pathophysiology of Osteoarthritis. J Musculoskelet Neuronal Interact 2006;6(4):376-378.
3. Heijinik A, Gomoll A, Madry H, Biomechanical considerations in pathogenesis of osteoarthritis of the knee,knee surg sports Trumatol Arthrosc2012;20:423-435
4. Brazeau GA, Persky A, Napaporn J, Dosage Forms Parenterals. In, Swarbrick J (Ed) Encyclopedia of Pharmaceutical Technology. 3rd edition, Vol. I, Inc. Newyork: Informa Healthcare USA; 2007: 1001.
5. Lavelle W, Demers E, Lavelle L, Intra-articular Injections, Anethesiology Clin 2007;25:853-862.
6. Gerwin N, Hops C, Lucke A, Intaarticular drug delivery in osteoarthritis, Advanced Drug Delivery Reviews 2006;58:226-242.
7. Middleton F, Coakes J, Umarji S, The Efficacy of IA Bupivacaine for relief of pain following arthroscopy of ankle, The Journal of Bone and Joint Surgery(Br) 2006;88-B,No.12:1603-1605.
8. Kawadkar J, Kanwar Chauhan M, Intra-articular delivery of genipin cross-linked chitosan microspheres of Flurbiprofen: Preparation, characterization, In vitro and In vivo Studies. Eur J Pharma Biopharma 2012; 81:563-572.
9. Zhang Z, Huang G, Micro and Nanocarrier mediated IA Drug Delivery Systems for Treatment of Osteoarthritis. J Nanotechnology2012;1-11.
10. Sarvanan M, Development of gelatin microspheres loaded with Diclofenac Sodium for Intraarticular administration. J Drug Targeting2011;19:96-103
11. Butoescu N. Jordan O, Burdet P, Dexamethasone containing biodegradable superparamagnetic Microparticles for Intraarticular administration: Physicochemical and magnetic properties, In vitro and In vivo Drug Release. Eur J Pharma Biopharma 2009;72:529-538
12. Williams AS, Camilleri JP, Goodfellow RM. A Single Intraarticular Injection of liposomally conjugated Methotrexate suppresses joint inflammation in rat antigen induced arthritis. Br J Rheumatology,1996;35(8):719-724.

13. Hou S. M, Yu HY, Comparison of Systemic absorption of aqueous and liposomal Lidocaine following Intraarticular Injection in rabbits. J Farmos Med Assoc,1997;96(2):141-143.
14. Thakkar H, Sharma R, Murthy RSR, Enhanced Retention of Celecoxib loaded Solid Lipid Nanoparticles for Intraarticular administration. Drugs Res Dev 2007; 8(5):275-285.
15. Dominique A, Rothenflu, Bermudez H, Biofunctional Polymer Nanoparticles for Intraarticular targeting and retention in cartilage. Nature Materials2008;7:248-254.
16. Zhang J, Li X, Aiu Li, Indomethacin –loaded Polymeric Nanocarriers based on amphiphilic polyphosphazenes with poly(N-isopropylacrylamide) and ethyl tryptophan as side groups: Preparation, In vitro and In vivo evaluation, Journal of Controlled Release2006;116(3):322-329.
17. Chen VJ, Ma PX. Nano-Fibrous Poly (L-Lactic Acid) Scaffolds with Interconnected Spherical Macropores. Biomaterials, 2004; 25:2065-2073.
18. Baker BM, Handorf AM, Ionescu LC. New Directions in Nanofibrous Scaffolds for Soft Tissue Engineering and Regeneration. Expert Rev Med Device 2009; 6:515-532.
19. Chen VJ, Smith LA, Ma PX. Bone Regeneration on Computer-Designed Nano- Fibrous Scaffolds. Biomaterial, 2006; 27: 3973-3979.
20. Zhang L, Webster TJ. Nanotechnology and Nanomaterials: Promises for Improved Tissue Regeneration. Nanotoday 2009; 4: 66-80.
21. Vasita R, Katti DS. Nanofibers and Their Applications in Tissue Engineering. Int J Nanomedicine 2006; 1: 15-30