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REVIEW ARTICLE

Emerging role of chondroitin sulfate based nanocarriers in improving the therapeutic outcome of NSAIDs in the treatment of osteoarthritis through the TDDDS

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A B S T R A C T

Osteoarthritis is characterized by joint destruction followed by severe inflammation caused by variety of proinflammatory mediators released due to upregulation of nuclear translocation of nuclear factor (NF-kB). Current treatment involves chronic administration of non-steroidal anti-inflammatory drugs (NSAIDs) that is associated with bewildering array of systemic adverse effects. Transdermal drug delivery system address challenges of systemic toxicities but toxic chemical penetration enhancers limit its utility. Novel drug delivery system explores the potential of bio-inspired materials for designing of safe and effective carriers that specifically deliver drug to site of action with enhanced transdermal penetration of the drug. Chondroitin sulfate, a biopolymer that mimic extracellular matrix, binds specifically with its overexpressed receptors (CD44, RHAMM and ICAM-I) at inflammatory site, biodegradable and possess intrinsic anti-inflammatory properties. These attributes render chondroitin sulfate an ideal carrier for the drug delivery in osteoarthritis. Chondroitin sulfate based nanocarriers serve as a potential drug delivery system that not only deliver anti-arthritis drug through the skin but also produce synergistic effect to improve therapeutic outcome. In this review, molecular mechanism of intrinsic anti-inflammatory effects of chondroitin sulfate in osteoarthritis is discussed in detail. Moreover, potential of chondroitin sulfate to perform dual role of therapeutic agent as well as serve as nanocarrier in transdermal drug delivery for the treatment of osteoarthritis is elaborated.

Keywords: *Osteoarthritis, Bio-inspired polymer, chondroitin sulfate, transdermal drug delivery system (TDDDS)*

Introduction

Osteoarthritis is known as one of the most disabling disease worldwide and current therapy for the management of this chronic disease is not free from adverse events. Patients not only suffer from the devastating effects of the disease but also have to bear bewildering array of adverse effects allied with non-specific systemic delivery of therapeutic agents.[1] Non-steroidal anti-inflammatory drugs (NSAIDs) are the first line drugs that are widely utilized for the pain management in osteoarthritis. Arthritis patient requires chronic administration of these drugs that leads to GI ulceration and bleeding after oral administration. Parenteral administration of NSAIDs is invasive and leads to cardiovascular and renal complications. Intra-articular injections reduce systemic toxicities but causes necrosis at chronic site of administration. Mostly NSAIDs have short plasma half-life, therefore required frequent administration that reduced patient compliance.[2] Targeted drug delivery system can be designed to address the challenges of systemic toxicities. Drug delivery carriers for targeted delivery in osteoarthritis can be fabricated by taking the advantage of anatomical physiology of inflamed

area (passive targeting) or utilizing homing devices or ligands to specifically bind with target site receptors (active targeting).[3,4] Novel route of drug administration with sustain and targeted delivery aid in reducing systemic toxicities. Transdermal drug delivery system (TDDS) aimed to deliver drug through the skin into systemic circulation. Potential advantages of TDDS includes controlled drug release, reduced systemic adverse effects, bypass first pass effect, prevent GI bleeding and ulceration. Therefore, for chronic pain management, delivery system for NSAIDs must provide targeted and control release of medicament for prolong period of time. Transdermal formulations provide targeted and sustain release of medicament while minimizing systemic adverse effects. Transdermal administration of NSAIDs is advantageous because this route alleviates associated GI complications. Drug delivery through the skin is non-invasive. Sustain release omits necessity of frequent administration. These benefits ultimately improve patient compliance. Thus, these favorable advantages depict the importance of transdermal route as a suitable alternative for chronic therapy.[5]

For TDDS, active ingredient diffuses through the multiple layers of the skin which act as a barrier for the entry of any antigen. Physicochemical properties of the therapeutic agent predict its ability to pass through the skin barrier. Low molecular weight drug with high lipophilicity can easily cross this barrier. To achieve minimum effective concentration in plasma, skin permeability of the active ingredient is an important parameter. Limited skin permeability of many drugs posed a great challenge in designing transdermal drug delivery system. Variety of techniques are employed to enhance skin permeability of drugs by reversibly disrupting the skin barrier by interaction with skin lipids. These techniques include use of chemical penetration enhancer, physical penetration enhancing techniques and nano-cargo.[6,7] Every technique is allied with some pros and cons. However, nanocarriers are widely explored to enhance skin permeability owing to their favorable size that allow skin penetration without disrupting its functional integrity. Different types of nanocarriers are extensively utilized in designing TDDS. A variety of materials can be utilized for fabricating nanocarriers including metals, semiconductors, ceramics, lipids and polymers. Polymers are mostly explored for this purpose because of their in-vivo safety. On the basis of origin, there are two types of polymers i.e., natural and synthetic. Both categories of polymers find extensive application in nanomedicine and helping researchers to achieve unreachable therapeutic objectives.[8, 9]

Natural polymers including polysaccharides due to their intrinsic biomimetic biocompatibility serves as an ideal platform for safer in-vivo drug delivery.[10,11] In recent years, hydrogel nanoparticles fabricated by polysaccharides grab substantial attention of formulation scientist as a novel tool for nontoxic delivery of drug molecules through the skin.[12,13] Properties of both hydrogel and Nano architecture are amalgamate in these hydrogel nanoparticles. Among polysaccharides, chitosan (CHS) is cationic polysaccharide serve as a potential carrier for drug delivery due to their favorable intrinsic hydrogel forming properties. CHS can formulate nanoparticles by crosslinking with negative ion cross linker or polymer. Chondroitin sulfate (CS) is an anionic disaccharide ionically crosslink with CHS to form hydrogel nanoparticles. These CHS-CS based nanoparticles are emerging nanocarriers for the delivery of variety of therapeutic agents particularly in tissue engineering and repairing. Their natural innate properties that mimic extracellular matrix (ECM) make them ideal nanocarrier.[14-17] In this review role of chondroitin sulfate in designing nanocarriers for the transdermal delivery of NSAIDs to treat osteoarthritis is discussed in detail. This review also elaborates molecular mechanism of action of chondroitin sulfate and NSAIDs for the treatment of osteoarthritis.

Osteoarthritis

Arthritis is a chronic inflammatory disease associated with serious repercussion of severe joint pain, edema and disability. Almost 150 different types of arthritis have been documented on the basis of complexity of underlying inflammatory mechanism. However, osteoarthritis (OA) is the most prevailing form of disabling arthritis. In developed countries, OA ranked among ten most disabling diseases.[18] Inflammation in OA is allied with trauma or distress because of tissue injury that stimulate release of damaged associated molecular patterns (DAMP). DAMP elicit immune response by upregulating NF-kB (nuclear transcription factor kappa B) directly or indirectly. This upregulation leads to activation of variety

of chronic inflammatory mediators. DAMP comprised plasma protein damaged associated pattern, intracellular alarmins, crystals of calcium and cellular mediators.[19,20] Activation of these patterns result in production of proinflammatory mediators i.e., IL-1β (Interleukin 1β), MMP (matrix metalloproteases), TNFα (Tumor necrotic factor α). DAMP pattern also stimulates destruction of cartilage by chondrolysis which in turn enhance the release of plasma protein damaging patterns. Inflammatory mediator's proliferation results in increased vascular permeability and stimulates angiogenesis. This further exaggerates inflammation by producing plasma proteins that act as DAMPs. As a result of this inflammatory cascade migration of neutrophils and monocytes occurs by chemotaxis at injury site. These immune cells further worsen the inflammation by stimulation of mediators' reactive oxygen species (ROS), interleukins (ILs) prostaglandins (PGs) that stimulate edema at injury site.[21,22] All these mediators sensitize pain receptors that result in production of inflammatory symptoms i.e., redness, swelling in joints, temperature, loss of function and pain as depicted in figure 1.

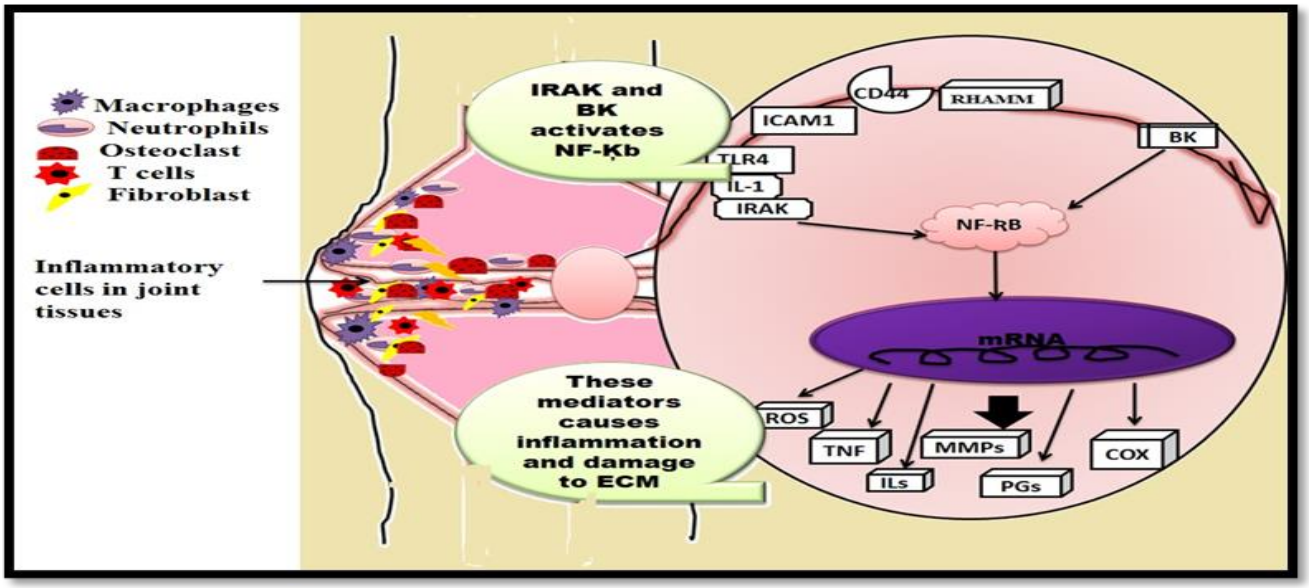

Figure 1: Inflammatory mediators in arthritis

[IRAK=Interleukin receptor associated kinase, BK=bradykinin, TLR4=Toll like receptor4, IL-1=interleukin-1, ICAM1=intracellular adhesion molecule1, CD44=Cell surface glycoprotein cluster differentiation44, RHAMM=Receptor for hylaronan mediated motility, NF-ķB= Nuclear transcription factor kappa B, ECM=extracellular matrix, ROS= reactive oxygen species, TNF= tumor necrosis factor, MMPs=matrix metalloproteases, PGs=prostaglandins, COX=cyclooxygenase].

Treatment of Osteoarthritis

Therapeutic objective of osteoarthritis treatment is to slow down the progression of inflammation and reduce pain. Current therapeutic regimen for the treatment of osteoarthritis comprised of NSAIDs,[23] Disease modifying anti-rheumatic drugs (DMARDs), glucocorticoids and biologics as key therapeutic agents.[24,25] Vivid progress in the development of innovative therapeutic agents that can effectively decrease the disease progression and slow down tissue damage thus improving quality of life of patient of this disabling disease. However, chronic nature of osteoarthritis requires long term application of drugs that leads to unwanted systemic adverse effects. NSAIDs are first line recommended therapy for symptomatic relief in acute and chronic stage. However, progressively damaging disease embroils use of DMARDs and biologics including immunosuppressant that are associated with severe life-threatening toxicities. As this chronic disabling disease prevails in old age patients who are less tolerant to these systemic toxicities. Localized delivery of drug by directly injecting drug into synovial fluid i.e. intra articular

injection may reduce side effects but frequent invasive injections also associated with patient compliance.

That's why today research goals prioritize development of targeted therapeutic strategies to alleviate systemic adverse consequences of non-targeted drug delivery [26] Conventional treatment of arthritis with associated adverse effects is described in table 1.

Table 1: Therapeutic regimen for osteoarthritis

Therapeutic class of drugs	Mechanism of action	Route	Systemic adverse effects	References
NSAIDs	COX inhibitors	Oral and parenteral	GI bleeding, ulcers, cardiovascular toxicity, renal toxicity	(22, 26)
Glucocorticoids	Phospholipase A2 inhibitors, Immunosuppressant	Oral and parenteral	Reduce calcium absorption. Osteoporosis, insulin resistance, obesity, CVS risk	(23, 27)
DMARDs	Cytotoxic and immunosuppressive	Oral and parenteral	Bone marrow suppression, hepatotoxic, nephrotoxic, cardio toxic	(23, 28)
Biologics	Monoclonal antibodies blocking receptors for inflammatory mediators	Parenteral	Reactions at injection site, neutropenia, fibrosis and increased chance of acquiring infections	(24, 29)

NSAIDs: Non-steroidal anti-inflammatory drugs
DMARDs: Disease modifying anti-rheumatic drugs.
COX: Cyclooxygenase

Role of NSAIDs in osteoarthritis

Non-steroidal anti-inflammatory drugs (NSAIDs) are first line cornerstone drugs prescribed for pain management in arthritis and osteoarthritis (OA). NSAIDs exert their therapeutic action by reversibly inhibiting cyclooxygenase (COX) that block the production of prostaglandins (PGs) from arachidonic acid (AA). Elevated level of PGs sensitizes peripheral nociceptors and exacerbate painful stimulus. In arthritis and OA, activation of signal transduction pathway promotes synthesis of proinflammatory mediators including COX and phospholipase A2 which ultimately produce more PGs in cartilage tissues and synovium that cause pain. This cascade of inflammatory process progress with disease that is responsible for chronic pain [22,31] NSAIDs chronic administration aid in reducing pain but prolong use allied with side effects of GI bleeding and ulceration.[32] Localized delivery of NSAIDs directly into joints by intra-articular injection reduces systemic effects but frequent injections for chronic use are not patient friendly and causes necrosis and pain at injection site. These side effects are eradicated by utilization of alternative route of drug administration i.e., transdermal route.

Transdermal drug delivery system

Transdermal drug delivery system emerges as an appealing substitute to minimize limitations allied with enteral and parenteral routes of drug administration. Drug delivery system that exploits the skin as an executable route for the purpose of producing systemic effects of drug is called transdermal drug delivery system. It includes application of drug to skin that is delivered to viable layer of epidermis and dermis which comprises capillary network from where it is absorbed and reaches systemic blood circulation. Transdermal differs from classical topical drug delivery system as later involves drug application for localized effect to skin for the treatment of skin diseases. This route is endorsed for the treatment of long-term chronic diseases such as pain management, arthritis, diabetes, cancer and hypertension due to sustain and control release of medicament over extended period of time. Feasible dose adjustment and monitoring, avoidance of first pass metabolism, reduction in side effects, zero order drug release and non-invasive

drug administration clearly depicts advantages of transdermal drug delivery system over other drug administration routes.[33]

Conventionally transdermal drug delivery system was designed in the form of adhesive patch. In 1979, US FDA approved first transdermal control release patch of scopolamine that results in opening of new gateway to transdermal drug designing for pharmaceutical design researchers. Today a number of transdermal patches have been approved for market use. Transdermal patches grab more than US $3 billion of annual US market. Despite the achievement of patch technology only a few numbers of drug candidates can be administered successfully through transdermal route due to constraining characteristics of human skin.[34]

The objective of drug delivery is to administer drug in a concentration that is safe to produce therapeutic effect to specific site of action for a particular time period. Transdermal route encompasses drug administration by way of the skin which is not only largest organ of human body but also perform protective function and control traffic of foreign materials and microbial population. This protective layer not merely impedes influx of foreign particles/toxins likewise serve as a barrier to drug delivery through skin that leads to reduced bioavailability of therapeutic agent. Only potent drugs with high lipophilicity and low molecular weight less than 500 Daltons could be administered through transdermal route. Therefore, a number of novel formulation designs and techniques have been employed to auspiciously subvert skin barriers. Advances in transdermal drug delivery system can be categorized into three successive generations as depicted in figure 2.

First generation comprises drugs having favorable characteristics for transdermal delivery. Second generation includes formulations to disorganize stratum corneum barrier by incorporating chemical penetration enhancers and physical permeability enhancing low voltage devices named as iontophoresis. Third generation of transdermal drug delivery encompasses physical and chemical techniques that reversibly disrupt or remove stratum corneum layer and bypass this permeability barrier to enhance delivery of macromolecules, proteins and vaccines.[35]

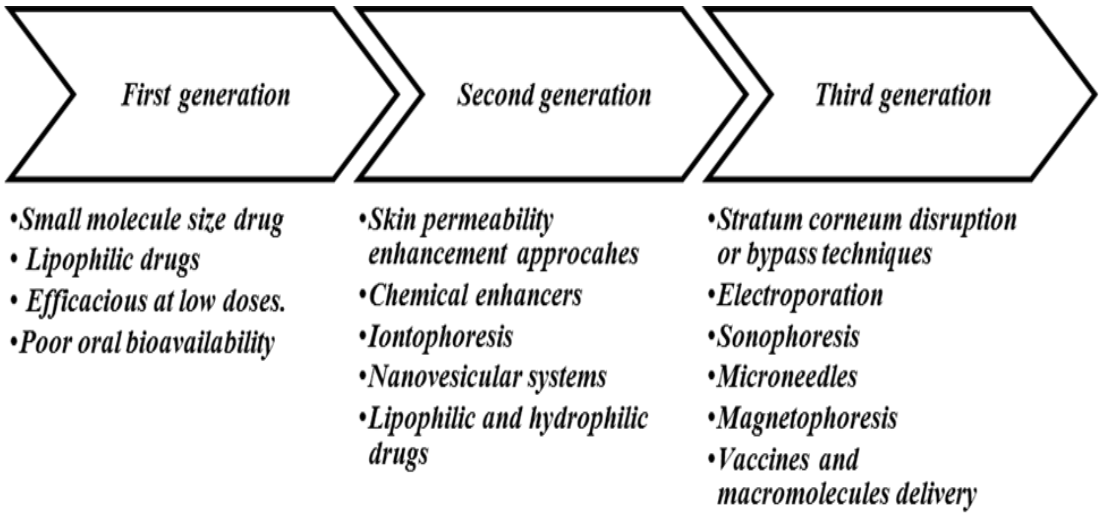

Figure 2: Advancement in development of TDDS Penetration pathways through the skin

There are two documented pathways for diffusion of substances through skin i.e., trans appendageal and trans epidermal conduit. Trans appendageal or trans follicular pathway composed of natural openings i.e., hair follicles; sebaceous glands, sweat glands so called shunt passage. This archway is area of interest for transdermal drug delivery designing researchers because of colossal network of capillaries adjoining pilosebaceous division. Meanwhile, mature SC is absent at the distal end resulting in entrance of drug candidate directly to contiguous tissues capillaries that successively deliver it to the systemic circulation. This passage is considered

suitable for delivery of hydrophilic drugs and macromolecules but foremost constrain in applicability of this passage is it comprises only 0.1% of total surface area of skin.

Other route is trans epidermal which is further assorted into two micro-conduits; transcellular (intracellular) and paracellular (intercellular) route. Intracellular route involves diffusion across SC composed of keratin protein so molecules diffuse through this protein layer and lamellar envelop however this route is not so important for transport of hydrophilic molecules because trans appendageal route is mostly utilized for this purpose. However, the important penetration enhancers enhanced transdermal penetration by reversibly altering secondary coiling of keratin proteins. Intercellular pathway is more preferred as this is continuous meander pathway between lipids domains. Lipophilic and amphiphilic molecules usually diffuse by this pathway. This pathway is composed of SC lipids in a specific hexagonal packing. Lipophilic molecules directly interact with these lipids and change their hexagonal packing. This alteration in lipids packing enhanced fluidity that allows drug penetration through the paracellular passage.[36, 37] Figure 3 portrayed skin anatomy and penetration pathways

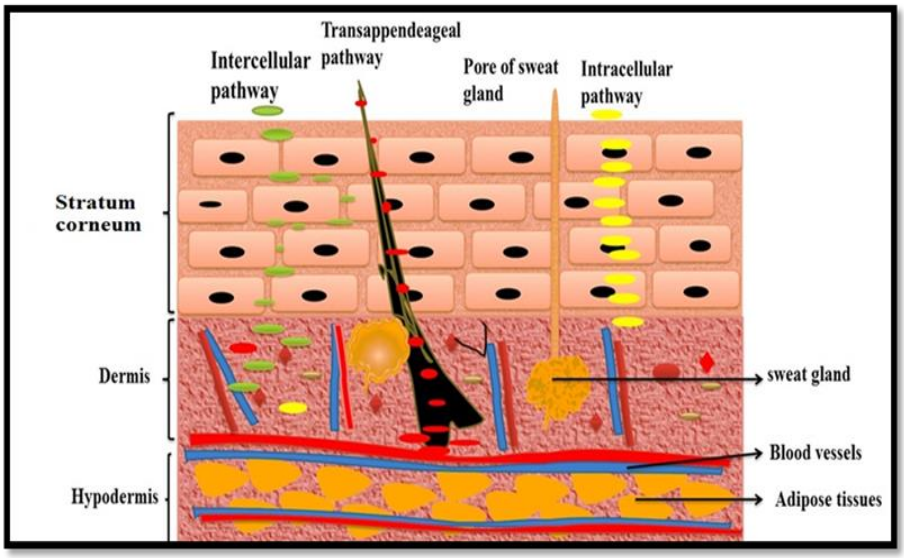

Figure 3: Drug penetration pathways through the skin nanocarriers for transdermal delivery of NSAIDs

Nanocarriers are extensively explored for their potential to overcome skin barrier and enhance penetration due to their size and surface properties. Therapeutic regimen of osteoarthritis requires long term drug administration with minimum adverse effects. To design drug delivery system for osteoarthritis, following important parameters must be considered. Primarily, drug delivery carrier provides sustain or control release of drug for longer period to avoid frequent administration. Then, carrier must be non-toxic and inert. Lastly, ideal carrier must deliver drug to specific inflammaed site to minimize systemic toxicities.[38] Therefore, NSAIDs therapeutic effectiveness can be enhanced by designing novel targeted drug delivery carriers that can alleviates associated systemic adverse effects.

Targeted drug delivery systems based on two basic strategies i.e., active targeting and passive targeting. Passive targeting entails advantage of pathophysiological condition of inflamed and tumorous tissue that is enhanced permeability and retention (EPR) effect due to leaky vasculature and angiogenesis. Carriers are specifically designed for passive targeting by controlling particle size, shape and nature. Active targeting implies utility of targeting ligands or homing devices that can specifically bind with intrinsic receptors at particular site of action. Targeting moieties includes peptides, polysaccharides, antibodies and nucleic acids. Nano-sized carriers made possible the utility of these targeting strategies.[39]

Polymeric nanoparticles are extensively employed for targeting in osteoarthritis as their surface can easily be modified with homing carriers for active targeting. Polymeric nanoparticles penetrate by way of skin appendages as well as transcellular and paracellular pathways depends on physicochemical properties, lipophilicity, molecular weight, surface charge and composition of polymer. Natural polymers possess intrinsic properties to mimic biological system and specifically interact with receptors so can be utilized for targeting therapy.[40] Hyaluronic acid (HA) specifically targets CD44 receptors overexpressed in synovial fluid utilized for delivery of salmon calcitonin. HA enhanced retention of calcitonin at inflamed joint and enhanced osteoprotective function as compared to free drug in animal models. [41] Chitosan also utilized for gene delivery in OA and results revealed chitosan as a successful gene vector for the delivery of IL-1Ra gene. Chitosan and chondroitin sulfate (CS) based hydrogel nanoparticles prepared by polyelectrolyte complex formation emerges as a suitable tool for pH based targeted drug delivery, transdermal drug delivery, protein drug delivery, tissue and cartilage regeneration. Chitosan-CS form polyelectrolyte complex (PEC) nanoparticles by electrostatic interaction between oppositely charged groups. Polysaccharides emulate the natural composition of ECM rendering them suitable drug delivery carriers in tissue and cartilage regeneration. Chitosan and CS based PEC membrane was designed for cartilage engineering and results depicted that this biomimetic membrane promotes chondrogenesis and tissue repair. Biomimetic microbeads composed of chitosan and CS based PEC film was utilized for delivery of mesenchymal stem cells (MSC).[42, 43]

This strategy promotes application of bioinspired polymers for fabrication of cell encapsulation system that cost effectively mimic natural cell environment of ECM for chondrogenesis and aid in healing process of damaged cartilage. These nanoparticles negate the need of surgical implantation into tissues owing to their enhanced penetration through membranes and cells thus improving patient compliance and safety. Meanwhile, hydrogel properties of nanoparticles provide sustain release of drug over long a period of time at desired physiological pH.

Role of Chondroitin sulfate in osteoarthritis

CS is a natural glucosaminoglycans (GAGs) with sulfate groups consist of N-acetylgalactosamine and glucuronic acid subunits. CS is present in connective tissues that is ECM of cartilage, skin, ligaments, blood vessels and tendons. CS is anionic disaccharide, attached with proteins in ECM forming key component of proteoglycans which is embedded in meshwork of collagen and elastin thus forming gel like consistency around cells. CS plays an important role in regulating cartilage function by stimulating synthesis of proteoglycan and type II collagen. Deficiency of CS results in osteochondral angiogenesis that leads to the progression of osteoarthritis. Thus, CS is approved nutraceutical agent for the treatment of osteoarthritis. NSAIDs when administered along with CS result in dose reduction of NSAIDs so is its associated side effects. CS plays its role to slow down the progression of osteoarthritis due to its intrinsic anti-inflammatory properties along with enhance synthesis of matrix protein of cartilage.[44]

CS display protective role in osteoarthritis and its detail mechanism of action is investigated to completely understand its potential. It has positive effect on articular chondrocytes, synovial membrane, and sub-chondral bone. CS play anti-inflammatory role by interaction with its receptors i.e., CD44, ICAM1, RHAMM and TLR-4. These receptors when activated results in reduction of signal transduction pathways for inflammatory mediators. Binding of CS with CD44 and ICAM1 stimulates production of IL-1 receptor associated kinases-M (IRAK-M) which inhibit IRAK that further slowdown the NF-kB nuclear translocation that ultimately reduced inflammation. IL-1 stimulates matrix metalloproteases expression i.e., MMP-3, MMP-9, MMP-13, COX-2, phospholipase A2. Inhibition of IL-1 indirectly result in reduction of all these inflammatory mediators that ultimately reduced inflammation in articular chondrocytes. CS also interacts with integrins which are responsible for enhanced expression of TGF-β1 that stimulates the production of collagen II and hyaluronic acid. Meanwhile, CS also reduced proteolytic breakdown of kininogen to bradykinin (BK) that also block signal transduction pathways as depicted in figure 4. Thus, by reducing inflammatory mediators and stimulating protective proteoglycans CS plays its chondroprotective function in

osteoarthritis.[45] CS due to its specific binding with receptors overexpressed in ECM during inflammation can also utilized as a homing device for designing active targeted drug delivery system in osteoarthritis. CS binds with CD44 receptors, annexin 6 and lectin receptors and transported inside the cell by receptor mediated endocytosis as shown in figure 4. Thus, CS can be utilized as a ligand for intracellular targeting. This innate property of CS makes this polymer as a promising biomaterial for designing of nanocarriers.

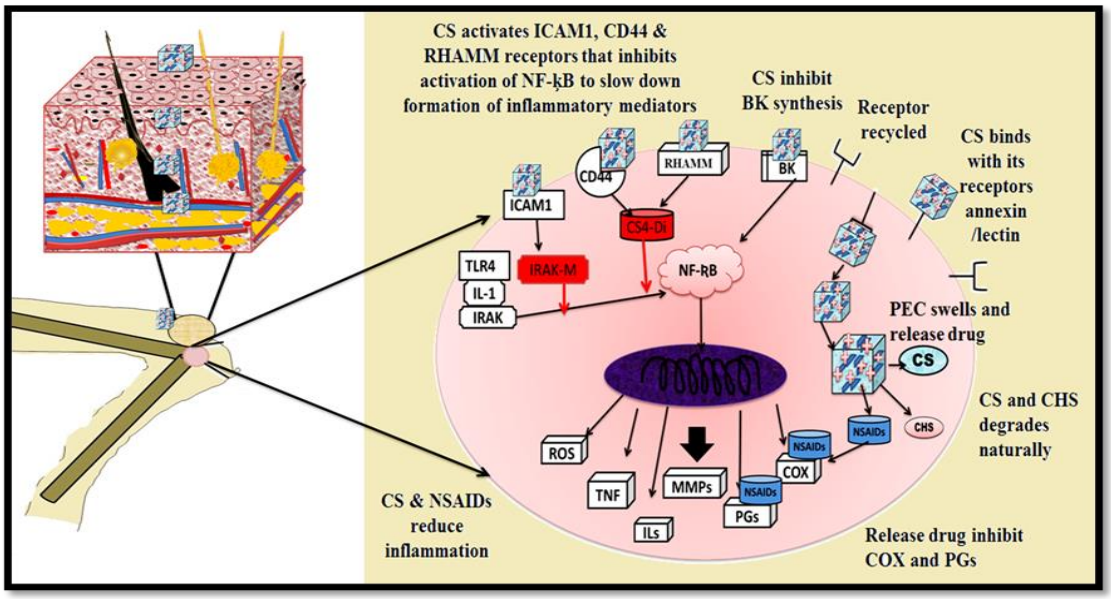

Figure 4: Mechanism of action of NSAIDs and CS

[ = Chitosan chondroitin sulphate PEC nps interacts with CS receptors and enter inside cell by receptor mediated endocytosis, IRAK=Interleukin receptor associated kinase,IRAK-M=inhihitor of IRAK,CS4-Di= monosulfated diasaccharide of chondroitin, BK=bradykinin, TLR4=Toll like receptor4, IL-1=interleukin1, ICAM1=intracellular adhesion molecule1, CD44=Cell surface glycoprotein cluster differentiation44, RHAMM=Receptorr for hylaronan mediated motility, NF-ķB= Nuclear transcription factor kappa B, ECM=extracellular matrix, ROS= reactive oxygen species, TNF= tumor necrosis factor, MMP=matrix metalloproteases, PGs=prostaglandins, COX=cyclooxygenase, NSAIDs=Nonsteroidal anti-inflammatory drugs, CS=chondroitin sulfate, CHS=chitosan].

CS can be attached on surface of variety of nanocarriers as a ligand. Surface functionalization of diacerein loaded solid lipid nanoparticles with CS deliver drug specifically to the inflammatory site in OA. Formulations with surface coating of CS showed higher accumulation in rat-inflamed joints as compared to formulation without CS. In another study, CS serves as homing device for delivery of aceclofenac loaded SLN and in vivo results revealed that CS functionalized SLN specifically accumulates in knee joints of rat.[42, 46] CS also finds utility for constructing polymer drug conjugates for targeted therapy. CS-glycyl-prednisolone drug conjugate showed better anti-inflammatory effect owing to enhanced retention at targeted site.[47]

CHS a linear cationic polysaccharide can form nanocarrier with CS by ionic crosslinking method. CHS also possess favorable intrinsic, biomimetic properties that enlighten its wide spread utility in drug delivery. [48] Chitosan can easily be formulated into hydrogels, membrane films, 3D scaffolds and nanoparticles for cartilage healing. Chitosan along with other GAGs serve as an ideal drug delivery carrier for tissue and cartilage repair owing to their innate properties of mimicking ECM structure and provide sustain release of drug at specific site. Biodegradability of these polymers further adds to their benefits as their degradable products are non-toxic and eliminate from body by natural catabolic processes. Chitosan being cationic polysaccharide ionically interact

with anionic polysaccharides that is CS to form polyelectrolyte nanocarrier. CHS-CS hydrogel mimic ECM and stimulate chondrogenesis. This hydrogel cultured on chondrocytes in laboratory showed chondrocytes retain their normal structure and function and promotes synthesis of collagen.[49] CHS-CS nanoparticles are also effectively utilized to deliver anti-arthritis drug through the transdermal drug delivery system.[42, 50] These intrinsic properties of biopolymers made possible to design the formulation with multiple functions i.e., targeting, therapeutic effect and enhanced skin permeability.

Conclusion

Engineering of novel biocompatible, biodegradable nanocarriers by utilizing natural sources is a promising strategy to achieve safer drug delivery systems. Biopolymers are ideal candidate for transdermal drug delivery system as these polymers improves skin permeability without producing any harmful effects on the skin. Chondroitin sulfate and chitosan not only enhance the skin permeability of the drug but also imparts synergistic effects in treatment of osteoarthritis by multi-dimensional targeting of the complex disease etiology. Chondroitin sulfate reduced the inflammation in osteoarthritis by down regulating number of inflammatory mediators by slow down the signal transduction of Nf-ǩB by binding with its specific receptors over expressed in inflammatory cells. These promising innate properties of natural polymers open a new gateway for researchers to design novel targeted synergistic drug delivery system with improved therapeutic outcome. However, a very few biodegradable and safer nanocarriers was explored for targeting in osteoarthritis. Thus, there is need of more research studies to investigate potential of biodegradable nanocarriers for targeted delivery of anti-arthritic drugs. To establish importance of natural carriers in drug designing, detailed understanding of carrier is very important. Furthermore, to achieve clinical outcome of experimental accomplishments more detailed in-vivo studies need to be addressed.

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