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Review Article

Liposomes as Delivery System of Chondroitin Sulfate to the Arthritic Joint by Intra-articular Administration

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Abstract

Osteoarthritis is the most prevalent rheumatic disorder affecting the musculoskeletal system; osteoarthritis is a degenerative form of arthritis that results in gradually breakdown of joint cartilage; osteoarthritis can be also viewed as an inflammatory disease. Currently applied therapies consist of physical therapy, oral medication, intra-articular injections and surgical interventions, their main goal being to reduce pain and improve function and quality of life. Intra-articular administration of drugs has potential benefits in osteoarthritis treatment because it minimizes systemic bioavailability and side effects associated with oral administration of drugs and enhances their therapeutic effect in the joint. However, the residence time of the drug is short and several drug delivery systems were explored to obtain a sustained release. This review is focused on the use of chondroitin sulfate as bioactive molecule in the treatment of osteoarthritis and the liposome ability as suitable drug delivery system for chondroitin sulfate.

Keywords: Liposomes; Chondroitin sulfate; Intra-articular; Osteoarthritis

Background

Osteoarthritis (OA) is a degenerative disease, but not a systemic one, characterized by progressive loss of articular cartilage, subchondral bone sclerosis and osteophyte formation, changes in the synovial membrane and increased volume of synovial fluid with altered coefficient of friction [1-3]. In some aspects, it can be also viewed as an inflammatory disease, leading to chronic pain and decrease of life quality [4]. Presently, there is no prevention or efficient treatment that can stop the pathological processes involved in OA progression [5], since available treatments are directed to symptoms, pain relieve and function regain [6]. The administration of nonsteroidal Anti-Inflammatory Drugs (NSAIDs), analgesics compounds [5] and corticosteroids [7,8] is achieved through oral, parenteral or intra-articular (i.a.) route, targeting to reduce or revise joint damage and inflammation.

The oral drug administration has major disadvantages, such as limited bioavailability and risk of side effects. As OA has a localized nature, i.a. administration of drugs provides the opportunity to improve the treatment by local depot formation and prolonged drug action [9]. To treat local diseases, like joint disorders, i.a. route is very useful. However, the efficacy of i.a. administration of different anti-inflammatory bioactive molecules (e.g., glycoproteins, proteoglycans) is limited due to their poor stability and delivery in the harmful biological milieu [10,11]. Several delivery systems, including liposomes, microparticles, nanoparticles and hydrogels have been investigated for the sustained drug delivery and for prolonged drug release in the joints [12]. *In vitro* studies have demonstrated that the phospholipidic layer acting as a boundary lubricant was missing from the articular surface of osteoarthritic degenerated cartilage and changes in the structure of Chondroitin Sulfate (CS) occurred in case of OA [13-15].

This review highlighted the advantages offered by liposomes as i.a. delivery system in treatment of OA. Data regarding the physico-chemical properties, biocompatibility, anti-inflammatory and regenerative potential of the liposomal formulations of CS are summarized. It is also discussed the trend in i.a. therapy of arthritis using this promising technology.

Intra-Articular Therapy -Advantages and Limits

Intra-articular (i.a.) therapy improves drug delivery to joint cartilage and thus, it can increase the therapeutic efficacy in OA treatment by minimizing systemic bioavailability and side effects associated with oral administration. A very well structured review of Evans et al. presented the progress, clinical performances and advantages of i.a. therapy of arthropaties [16]. Being discrete cavities, most diarthrodial joints are well suited for the local drug delivery via i.a. injection. The advantages offered by i.a. delivery of therapeutics in diarthrodial joints are also presented by Chen & Yang. They have noticed the importance of delivering drugs not just on the surface of the articular cartilage, but also into its matrix, in order to obtain a deeper zone treatment. Moreover, it should be fully considered that the drug biodistribution following delivery is quite different in i.a. administration from systemic administration or local injection into other tissues or organs. Many corticosteroid formulations are available for i.a. injection in OA and several studies have compared their effectiveness in OA. The conclusion was that they offer a short-term solution for a chronic problem, reducing pain in the knee for at least 1 week [17]. An alternative treatment for joints affected by OA that have not responded to NSAIDs or analgesics is the i.a. administration of natural bioactive substances that can influence the pathophysiology of OA joints, such as lubricin, also known as proteoglycan 4 [18] and hyaluronate, a component of the cartilage extracellular matrix [19].

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However, i.a. administration of drugs presents some limitations. Depending on the chemical structures of drugs, some active compounds are rapidly cleared from the joint. In order to increase the residence time of the administered substance, several injections are required, which could result in infection or joint disability. The direct injection is the simplest method for i.a. delivery of drugs, but not the most effective one [5].

Drug Delivery Systems for Intra-Articulartherapy-Advantages and Limits

Alternative approaches for local drug delivery were proposed by researchers in the Nanomedicine area that have developed efficient systems, for specific therapeutic agents, able to increase the specificity and selectivity of the drug [20] and also to promote regenerative processes [21,22]. Several Drug Delivery Systems (DDS), including liposomes [11,23-26], micro- and nanoparticles [27-29], polymers [30] and hydrogels [31-33] have been investigated for the sustained drug delivery to the joints. An important observation related to i.a. administration of microspheres was their up taken by synovial macrophages [28]. This property offers a strategy to sustain drug delivery within the joint and to deliver NSAIDs directly to pivotal inflammatory cells in order to improve the drug therapeutic potential.

The necessity for a suitable carrier able to protect the drug, to form a depot at the site of administration and to release it in a controlled manner helped increased the interest in designing DDS, specifically for the i.a. environment. Among all DDS, liposomes and microspheres have been evaluated *in vivo* in relation to i.a. drug delivery, being used to develop preclinical tests and new efficient products on the market. The encapsulation of the drugs was also proposed to improve their performances and sustained with good argumentation by Butoescu et al. and Janssen et al. [30,34].

Future innovations in this field should be directed toward the development of functionalized DDS targeting specific regions and thermo responsiveness for prolonged drug release in the joints. Further advances are in progress to bring forth new biocompatible and biodegradable materials, as drug carriers or new combination regimens [33]. Besides pain relieve, these complex DDS will aim to solve tissue regeneration for OA patients.

The benefits of i.a. therapy of OA are not achieved using currently available medications and delivery vehicles, due to their rapid clearance from the synovial space [28]. The limits of DDS used for i.a. drug delivery are presented by Chen & Yang. Although many natural or synthetic polymers have been used for DDS development, they showed significant limitations in retention time and drug efficiency. The drug release is controlled after polymer encapsulation, but the delivery system doesn't make easier the penetration of therapeutic substances into the cartilage matrix. Besides, many proposed DDS have a complicated fabrication technology and few studies addressed their toxicity limit for clinical applications. All these observations denote the need for a more effective and safer i.a. DDS.

Liposomes as DDS for Intra-Articular Therapy of Arthritic Diseases

Liposome science and technology is one of the fastest growing scientific fields [35]. The technological process for fabrication of liposomes with optimized properties, as controlled DDS, was reviewed by Allen & Cullis [36]. Liposome drug products were the first type of therapeutic nanoparticles being introduced in the market [37,38]. Stability of the liposomal formulations in physiological conditions is a key issue in drug delivery [36]. In order to increase liposomes stability in the presence of synovial fluid, data from available literature show that polar lipids should be included in the bilayer [11]. On the other hand, cholesterol incorporation in the bilayer increases the membrane stability and the encapsulation efficiency of both hydrophilic and lipophilic bioactive molecules in the liposomes. Increased cholesterol concentration in the phospholipids bilayer can cause a gradual disappearance of the phase transition without affecting the transition temperature [29].

Liposomes are the most investigated carriers for targeted drug delivery [39] and for their potential in the treatment of arthritic diseases [29,40-43]. Their successful application in therapy depends on their composition and physical properties, including size, dispersity, morphology and surface charge [44,45]. Also, due to their capability to incorporate hydrophilic and hydrophobic molecules, good biocompatibility, low toxicity, activation and targeted delivery of bioactive compounds to the site of action, liposomes offer many advantages, such as protection and efficiency of encapsulated material, solubilization of lipophilic molecules, prolong the duration of action and present targeting option [46-49]. Many reviews highlighted the important role of liposomes in joint boundary lubrication and protection of articular cartilage from degenerative changes, as demonstrated by *in vitro* studies [50-52]. A major advantage of using liposomes is the larger quantity of drug that passes through the cell membrane into the cell cytoplasm. Besides, lipophilic drugs could be solubilized by entrapment into the lipid bilayer of the liposomes [53]. The i.a. route of administration could offer several beneficial advantages for drug uptake due to the presence of phospholipids in both cell membranes and the double layer of lipid vesicles (liposomes).

Liposome ability to modify the pharmacokinetics and biodistribution of the encapsulated drug after i.a. administration was underligned in several studies [25,26]. Furthermore, liposomes encapsulating anti-inflammatory drugs, i.a. administered in an animal model, exhibited a prolonged residence time in the joint [11,25], enhanced reduction of inflammation [26] and reduced adverse systemic effects [41,54,55]. A series of studies related to i.a. administration of liposomal formulations of NSAIDs reported a significantly higher anti-inflammatory activity than that of the free drug in rat induced arthritis model. Studies on drug retention and slow release found a close correlation with the method of liposome preparation, lipid composition, and liposome size and charge and lipids-drug ratio [56]. Also, the i.a. administration of liposomal glucocorticoids resulted in superior therapeutic efficiency, compared to that of free drug [57], at both early disease stage and peak of the disease [58]. Three different glucocorticoids (dexamethasone, budesonide and prednisolone) were encapsulated in long circulating liposomes and their therapeutic activity and adverse effects were investigated in rats with adjuvant arthritis and collagen induced arthritis. Encapsulation of drugs in liposomes not only increased their therapeutic efficacy, but also decreased their clearance from the body [59]. Previous *in vivo* studies in DBA1 mice with collagen induced arthritis (CIA) demonstrated the liposome ability to protect Lactoferrin (Lf), an antinflammatory

bioactive molecule, from harsh biological environments, to change its pharmacokinetics and biodistribution and to release it in a controlled manner [11]. Comparative studies showed that Lf entrapped in positive multivesicular liposomes was retained longer (2 weeks) in the injected joint, compared to free protein and other liposome formulations after i.a. administration, demonstrating a prolonged anti-inflammatory effect [11].

In a recent review, it was indicated that cytokines play a critical role in the pathological process of OA development [60]. *In vivo* studies on lymph node T cells in DBA1 CIA mice showed decreased proinflammatory cytokines (TNF-α and IFN-γ) level, accompanied by increased anti-inflammatory cytokines (IL-5 and, especially, IL-10) after i.a. treatment with liposomes encapsulating Lf, compared with free Lf treatment. The results suggested that the ability of positively charged liposomes to enhance Lf therapeutic effect is mediated by a change in Th1/Th2 cytokinebalance [25].

All these data indicate liposome ability to enhance the anti-inflammatory properties of bioactive molecules after i.a. administration *in vivo* and encouraged further studies on liposome formulation technology for i.a. administration of another bioactive compound, Chondroitin Sulfate (CS).

CS as Bioactive Molecule in OA Treatment

CS, a major component of the extracellular matrix of cartilaginous connective tissue, is a natural polysaccharide and an important component of the Glycosaminoglycans (GAGs) class, which plays an important structural role in articular cartilage [2,15,61-63]. GAGs are attached as side chains to a core protein to form proteoglycans that are needed to stabilize cell membranes and to increase the intracellular ground substance. The use of CS to improve the clinical symptoms of OA is based on the assumption that administration of a cartilage matrix component would help chondrocytes to replace lost or damaged tissue [64]. CS has been proposed as safe and tolerable chondroprotective agent in the oral treatment of OA and named symptomatic slow-acting drug for OA (SYSADOA) [29,61,65-67].

CS has been shown to reduce proinflammatory factors, modify the cellular death process and improve the anabolism/catabolism balance of the cartilage extracellular matrix [63]. The anti-inflammatory and anti-apoptotic effects of CS are increasingly used to treat OA [68]. Recently, Bishnoi et al. (2016) highlighted CS key role in the regulation of cell development, adhesion, proliferation and differentiation [69]. The applications of CS were also focused on repair of damaged structures in different biological tissues, alone or in combination with other biopolymers [69].

CS for Intra-Articular Administration

The therapeutic benefits of CS have been studied for more than 20 years by high-quality meta-analysis and its efficacy was explained through three main mechanisms: stimulation of extracellular matrix production by chondrocytes, suppression of inflammatory mediators and inhibition of cartilage degeneration [70]. These *in vitro* findings motivate the consideration of CS for i.a. injections used in the treatment of painful joints and as a potential prophylactic compound against the progression of cartilage degeneration [29]. To improve the efficacy of CS as a therapeutic agent in osteoarthritic knee treatment, David-Raoudi et al. suggested the necessity to deliver it directly into the synovial cavity [71]. In this way, CS injected into the synovial fluid would be in direct contact with both synoviocytes and superficial chondrocytes and, therefore, would exert similar effects to those found *in vitro* [70]. In support of such approach, i.a. delivery of CS has been shown to be effective in a rabbit model for the repair of joint defects [31].

CS stimulates the proteoglycan synthesis of bovine and human chondrocytes [72,73], whereas it decreases interleukin-1β (IL-1β)-induced expression of matrix metalloproteinase-1, -3, and -13 (MMP) and aggrecanase-1 and -2 [63,70,73]. Furthermore, some anti-inflammatory properties have been attributed to CS based on its ability to inhibit human leukocyte chemotaxis and phagocytosis, to protect the plasma membrane from oxygen reactive species [74] and to reduce cyclooxygenase-2 (COX-2) expression and prostaglandin E2 production by chondrocytes [70,73]. Moreover, CS can up-regulate the local hyaluronan synthesis by joint cells and, thus, can probably provide the supply of hyaluronan for a longer period of time than single injection of exogenous hyaluronan, which is known to have a short-life period [71].

Hui et al. have evaluated the efficacy of i.a. injection of CS carried by hydrogel in the treatment of chondral defects in adult rabbit models, compared to free CS [31]. The optimal formulation regarding the biocompatibility and the release kinetics of CS was CS-α-CD-EG 4400 hydrogel that improved the biomechanical and histological properties of the cartilage and induced the tissue repairing process [31]. Rivera et al. have demonstrated the therapeutic effectiveness of sodium hyaluronate plus CS in reducing pain, improving mobility and reducing the consumption of analgesics after i.a. administration of hyaluronate and CS in human patients with OA using a multicenter prospective study [75]; their results should be confirmed in a randomized controlled study.

Liposomes-CS for i.a. Administration

In vitro, *in vivo* and in human studies have demonstrated the biocompatibility, the anti-inflammatory and regenerative effect of CS alone, associated with hyaluronan or included in hydrogel for local therapy of OA. Because of the greatly prolonged drug residence time at the administration site, liposomes have been proposed as suitable carriers of bioactive molecules in i.a. therapy of inflammatory diseases [34,40,41,54]. The therapeutic profiles of many biological and pharmacological agents can be improved by incorporation into lipid-based carrier systems. Liposomes have proven to be very effective to form a depot and to protect the drug from the harsh biological environment by virtue of their size and chemical composition [11,25,29]. Taking into account all these findings, the i.a. administration of CS entrapped in liposomes could prolong its retention time in joint and could have therapeutic potential in OA and other local inflammatory conditions.

To improve CS entrapment efficiency and to obtain a suitable liposome system, able to form a depot and to release CS in a controlled manner in the synovium, Trif et al. have selected the method for liposome-CS (L-CS) preparation [76]. The ultra structure of L-CS population was observed and its *in vitro* biocompatibility was proved in a human dermal fibroblast culture system. The cell viability tests

have indicated no cytotoxic effects induced by empty liposomes, CS and L-CS systems, while cells maintained their normal morphology, similar to control fibroblasts. The liposomal system consisting of Multilamellar Vesicles (MLV) and CS presented a good electrostatic interaction between the two components and transmission electron micrographs showed the entrapment of CS particles within the liposomes [76]. Another optimal L-CS formulation as small unilamellar vesicles (SUV) was selected after characterization in terms of size, polydispersity index and zeta-potential and its therapeutic efficiency was investigated *in vitro* using a model of fibroblasts inflammation [77]. The results demonstrated a more efficient cell protection against oxidative damage using L-CS treatment than CS alone. Also, L-CS exhibited a higher anti-inflammatory activity than CS in stimulated cells by reducing the level of IL-8 and TNF-α proinflammatory cytokines [77].

The physico-chemical characteristics of L-CS systems vary with the preparation technology, liposomal lipids composition, lipids-drug ratio, liposomes size and charge. Depending on their application, a suitable method involving different mechanisms of liposomal population formation should be used [78,79].

Liposomes Entrapping CS in Different Models of Inflammation

It is known that OA produces inflammation of the synovial membrane that attracts macrophages and alters synovial fibroblasts and chondrocytes activity. The down-regulation of proinflammatory cytokines, such as TNF- α, IL-6 and IL-8, as important mediators of inflammation and the chondroprotective effect of L-CS formulations were analyzed using *in vitro* experimental models: human monocytic cells (THP-1) differentiated to macrophages and inflamed with lipopolysaccharide (LPS) [80] and rabbit chondrocytes inflamed with IL-1β [81]. L-CS inhibited the release of IL-6 and TNF-α in the culture medium in the highest proportion, compared to CS. The IL-8 secretion was also inhibited by L-CS, but to a lesser extent. Similar results were obtained for cytokines production in IL-1β-stimulated rabbit chondrocytes and LPS-stimulated macrophage cells treated with L-CS [82]. These studies demonstrated that entrapment of CS into liposomes significantly enhanced the anti-inflammatory capacity of the free compound.

Hofkens et al. (2011) showed that liposomes entrapping an anti-inflammatory agent induced a dose-dependent suppression of IL-1β production and a significant reduction in MMP-3, -9, -13 and -14 expression, indicating that liposomal targeting of the anti-inflammatory drug to macrophages offers an effective strategy to inhibit the factors that contribute to destruction of cartilage matrix during arthritis [83]. In this way, MMP-liposomes interaction studies were performed inIL-1β inflamed rabbit chondrocytes treated with CS and L-CS in the culture medium, for 48h [82]. Gelatin-zymography results showed that the liposomal treatment of the inflamed chondrocytes influenced the MMP activity in the culture medium. These results confirmed the observation of Banerjee et al. regarding modulation of high levels of MMP-9 upon liposomal content release [84]. Due to its ability to modulate the secretion of destructive MMP in inflamed chondrocytes, liposomal formulation of CS could be further investigated as chondroprotective therapeutic agent in arthritis.

Several studies have described the benefits of CS in applications for cartilage tissue engineering. Liposomes have been widely used as carriers to encapsulate and to protect bioactive agents from the surrounding environments. Monteiro et al. highlighted the potential role of liposomes as a platform for the sustained and local delivery of bioactive agents for tissue engineering and regenerative medicine approaches [85]. A suitable drug carrier can up-regulate tissue regeneration by controlled delivery of a biomolecule in a localized space [86]. As a result, local therapy using liposome-scaffolds in tissue engineering and regenerative medicine could be very efficient [85]. In this direction, a 3D porous matrix of collagen embedding the liposomal formulation of anti-inflammatory bioactive molecule (L-CS) was prepared and physico-chemically and biologically characterized [87]. This matrix system could be used in local delivery of therapeutic agents. Its morphological appearance was similar to that of collagenic scaffold, but more investigations are required to confirm its *in vitro* and *in vivo* anti-inflammatory and regenerative capacity. However, the potential of this strategy has to be investigated in order to optimize liposome formulations and select the best material for specific applications.

Conclusion

I.a. therapy can increase the efficacy in OA treatment, although it presents limitations. DDS represent an alternative approach for local drug delivery in a controlled manner. Liposomes as DDS offer beneficial advantages in drug uptake into the cytoplasm after i.a. administration. CS is an efficient therapeutic agent in knee OA treatment. Delivery of CS in liposomal formulation could improve its potential in i.a. treatment of OA.

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