



Modulating carbohydrate-based hydrogels as viscoelastic lubricant substitute for articular cartilages



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ABSTRACT

Viscosupplementation is a therapeutic approach for osteoarthritis treatment, where the synovial fluid, the natural lubricant of the joints, is replaced by viscoelastic solutions with rheological properties comparable or better than the starting material. This study presents the development of an innovative platform for viscosupplementation, based on the optimization of polysaccharide-based colloidal hydrogel, aiming to reduce on-site enzyme degradation and enhance the possibility of hyaluronic acid substitution with alternative biomaterials. Catanionic vesicles are proposed as physical crosslinker that can guarantee the formation of a 'soft', tunable network, offering a dual-therapeutic approach: on the mechanical relief perspective, as well as on the drug/gene delivery strategy. This research focuses on the fabrication and optimization of colloidal networks, driven by the synergistic interaction among catanionic vesicles and cationic modified cellulose polymers. This study tests the hypothesis that cellulose-like polymers can be arranged into functional matrix, mimicking the mechanical properties of healthy synovial fluids.

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1. Introduction

Joint performances are closely connected with the viscoelastic properties of synovial fluid, which determines the load transmission and distribution, providing for the lubrication and protection of joint cartilage and soft surfaces. In normal conditions, the synovial fluid is highly viscous and allows both lubrication and the attenuation of mechanical shock. The synovial fluid is a non-Newtonian viscoelastic fluid, thus its viscosity does not present a constant value but its magnitude depends on the load affecting the joint. In particular, synovial fluid shows a shear thinning behaviour [1].

The viscosupplementation is a therapeutic technique used in the osteoarthritis treatment, where the synovial fluid, the natural lubricant of the ligaments, is replaced by viscoelastic solutions derived from hyaluronic acid with rheological properties comparable or better than the starting material. The research of other polysaccharides for the application on viscosupplementation enhances the possibility of hyaluronic acid substitution with other more abundant and cheaper biomaterials.

Cellulose-based hydrogels have been proposed as cheap substitutes for cartilage regeneration [2] and gelating matrix for implant osteointegration [3]. Injectable hydrogels based on cellulosic materials exhibit a successful outcome as chondrocytes carriers for cartilage regeneration, both *in vitro* and *in vivo* [4]. For instance, several research groups investigated cellulose applications for biomaterial engineering replacement of both hard and soft tissues, as blood vessels [5–8], bones [9], cartilages [10,11] and dura mater [12].

Polymeric hydrogels based on non-covalent interactions, compared to chemical-crosslinked ones, are characterized by the absence of harmful, secondary products of the cross-linking reaction and by reversibility, thus these materials can be promptly responsive to external stimuli. [13,14] These features look interesting in the perspective of biomedical use. Highly diluted polymeric hydrogels can be achieved thanks to several non-covalent cross-linking methods: both electrostatic and hydrophobic interactions cooperate within these systems and their role is due to the specific chemical substances involved.

Cellulose is a natural polysaccharide produced by plants, algae, bacteria [15] and it consists of a linear chain of D-glucose units [16]. Since a long time, cellulose has been employed as a biomedical material in applications such as dialysis and wound care

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[17,18]. Thanks to an increasing importance of renewable and environment-friendly materials, cellulose research is the core of large and important worldwide industrial companies [19]. As the areas of tissue engineering and regenerative medicine continue to grow, however, increasing attention is being drawn to cellulose as a possible material for use in regenerative therapies. The properties and structure of cellulosic materials, as applicable to this area, depends on the source of the cellulose and the processing methods employed. The application of dressings to wounds and external tissue trauma is a standard practice [18]. However, clinical practice has recently moved from the use of simple protective gauze-type dressings to more sophisticated products, able to actively optimize the wound healing environment. There are complex and fine processes that occur during wound healing: for example, in patients with diabetes or compromised immune systems, these processes can become perturbed or unbalanced resulting in the formation of ulcers (chronic wounds) or inferior healing [20]. Cellulose-based materials have been developed to optimize wound healing conditions or to specifically address particular problems in abnormal wound healing. For instance, fibrous carboxymethylcellulose dressings exhibited a cooperative activity in wound healing regulation, by absorbing very large quantities of wound exudate, while maintaining a moist healing environment and preventing maceration [18].

Regenerated cellulose (i.e., purified cellulose in which short fibers coming from trees are chemically converted into the long fine fibers used in textiles and non-wovens) has been used for constructing three-dimensional tissue with capillaries [21] and, together with cellulose acetate, also for cardiac tissue engineering [22].

Several characteristics of tissue engineering scaffolds may affect their performance. It has been suggested that scaffolds must be three-dimensional, porous (with interconnected pores), biodegradable and biocompatible. They must also possess mechanical properties that match those of native tissue and degradation properties that match the rate of synthesis of new extracellular matrix [23].

Modifications on cellulose are under extensive scientific research: many type of cells have been used to test these novel celluloses in terms of biocompatibility and bioactivity [24]. On the other hand, the use of catanionic vesicles as physical crosslinker can guarantee the formation of a 'soft', tunable network, offering also the chance to use them as nanoreservoirs for a dual-therapeutic approach: on the mechanical relief perspective, as well as on the drug/gene delivery strategy. Indeed, catanionic vesicles can be considered part of the nano/micro-reservoir systems class, which encounters also nanomicelles, functionalized copolymer nanovesicles, liposomes, hollow spheres and so on [25–27].

Thus, the aim of this study focused on the fabrication and optimization of colloidal networks, driven by the synergistic interaction among catanionic vesicles and cationic modified cellulose polymers. This study tests the hypothesis that cellulose-like polymers can be arranged into functional matrix, mimicking the mechanical properties of healthy synovial fluids, by optimizing their interaction with catanionic vesicles.

2. Experimental

2.1. Materials

High-purity surfactants sodium dodecylsulfate (SDS) and cetyltrimethylammonium bromide (CTAB) were purchased from Aldrich and used as received. The polymers were supplied by Amerchol Corporation, subsidiary of Dow Chemical Company, Greensburg, LA.

Their trade name is SoftCAT™, and they pertain to the INCI (International Nomenclature of Cosmetic Ingredient) series Polyquaternium-67 (PQ-67) [28]. They are chloride salts of *N,N,N*-trimethylammonium derivatives of hydroxyethylcellulose with molecular weights in the range 200,000–800,000 g mol⁻¹, bearing some dodecyltrimethylammonium residues as hydrophobic substituents [29]. The information provided by the manufacturer, concerning viscosity, charge density and hydrophobic substitution (HS) [30] are reported in Table S1 (supplementary information).

2.2. Sample preparation

Both SDS and CTAB 6 mM solutions were prepared, with distilled water. The catanionic vesicles, at 6 mM total surfactant concentration (assuming negligible partial volume changes), were obtained simply by mixing volumes of the SDS and CTAB solution in the ratio due to the desired SDS/CTAB molar ratio (R). Although different R were considered, most of the characterisations were performed on R=2.2 systems as this value, thanks to previous experiments, ensures an appropriate hydrodynamic radius for drug delivery [31].

The system turned milky, when mixed, showing out the formation of multilamellar catanionic vesicles. Indeed, the catanionic vesicles herein proposed are characterized by a thermally induced transition from multilamellar, polydisperse, spontaneously formed vesicles to unilamellar ones [32,33]. Moreover, mixing a polyelectrolyte (i.e. an ionic charged polymer) with oppositely charged vesicles leads to a wide variety of associations, which depends on vesicle composition, size, concentration and charge, together with polymer flexibility, charge density and effect of the chain substitution [34].

The hydrogels were prepared by adding the polymer to the vesicles solution to get a polymer concentration of 1% wt. The mixtures were homogenized by stirring and then left to equilibrate for at least 1 week. In order to remove the presence of air bubbles, the systems were subsequently centrifuged at 4000 rpm for 5 min. The different samples will be referred to the SL grade of the polymer (see Table S1) and the surfactants ratio, R, in the vesicles, e.g., SL-5 R=2.2, with both polymer and total surfactant at fixed concentration.

2.3. Rheology

Rheological measurements were performed by using a Haake Rheo Stress 150 rheometer equipped with water bath for the temperature control. Cone-plate geometry was employed for the determination of flow curves (viscosity vs strain/stress and zero shear viscosity) at different temperatures. In particular, zero shear viscosity (η_0) was measured as a function of temperature in the range 30–70 °C in order to evaluate the activation energies, E_a , according to the Arrhenius model [35]:

$$\eta_0 = A \cdot e^{\frac{E_a}{RT}} \quad (1)$$

Plate-plate geometry (gap = 1 mm) was employed for the rheological tests performed under oscillatory conditions at 30 °C. In particular, the linear viscoelastic region was assessed, at 1 Hz, through stress sweep experiments (stress range (τ) 1–1000 Pa) while frequency sweep tests were carried out in the frequency (f) range 0.01–10 Hz at constant stress $\tau = 2$ Pa (consistently within the linear viscoelastic range for all studied systems). In order to minimise possible evaporation, a solvent trap system was used in all the performed tests.

2.4. Dynamic light scattering (DLS)

The mean particle diameter of the aggregates and poly dispersity index were determined by dynamic light scattering using a

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