Injectable hyaluronic acid gels containing liposomes: formulation, characterization and evaluation for the treatment of inner ear diseases

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In this work, we designed injectable hyaluronic acid (HA) gels containing liposomes and we evaluated them as sustained drug delivery systems. The physicochemical properties (phase behavior, rheological behavior, microstructure, and mobility of the liposomes) of such mixtures were thoroughly assessed for HA at different concentrations and for liposomes characterized by different surface properties (positively or negatively charged, neutral, with a corona of polyethylene glycol (PEG)). Above the polymer entanglement concentration, the viscosity and the elasticity of the HA solutions increased with the addition of liposomes, the highest effect being observed with PEGylated liposomes. Despite their high viscosity at rest, all formulations remained easily injectable [1]. PEGylated liposomes displayed the best mobility into HA both microscopically (single particle tracking measurements) and macroscopically. This result might be explained by the bicontinuous structure of this gel, as observed by atomic force microscopy. Such systems appeared particularly attractive for transtympanic injections of drugs. Indeed, inner ear diseases are nowadays not adequately treated by systemic drug administration mainly because the inner ear remains one of the most challenging target organs due to the blood-perilymph barrier. Therefore, local drug delivery methods are currently developed to treat inner ear disorders more efficiently and transtympanic injection appears as a promising approach [2]. It involves the injection of the drug into the middle ear using a fine and long needle and relying on the diffusion of the drug through the round window membrane for access to the inner ear. However, this method requires a specifically developed pharmaceutical formulation in order to enhance its efficiency and reduce the number of injections. With our mixtures, HA may allow a long residence time into the middle ear thanks to its mucoadhesive properties whereas liposomes could act as a reservoir for a sustained release of the drug. The most promising formulation for transtympanic injection was obtained with PEGylated liposomes and was used for the encapsulation of a corticoid, dexamethasone phosphate (DexP), into the vesicles. The safety of the liposomal gel was then evaluated *in vivo* in Guinea pig and biodistribution studies were performed [3]. The administration of HA liposomal gel in the middle ear appeared to be a safe and efficient strategy to deliver corticoids to the inner ear in a sustained manner.

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