Characterization, stability and cell viability tests on ionic-gradient liposomes designed for the delivery of etidocaine

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Abstract

Liposomes are lipid carriers widely used in drug-delivery, and a number of liposome-based products have been approved for clinical application, so far (1,2). Local anaesthetics interact with liposomes, distributing themselves in the lipid bilayer and in the inner aqueous core, prolonging the anaesthesia time (3,4). In ionic gradient liposomes (IGL) the ionisable drug is loaded in preformed vesicles that exhibit a trans-membrane ionic gradient (Fig.1), leading to high drug upload and, subsequently, prolonged drug release (5,6). Objectives: to develop IGL for the sustained release of etidocaine (EDC). Methods: Large unilamellar vesicles (LUV, 20 mM) composed of soy phosphatidylcholine:cholesterol (6:4 mol%) plus 250 mM sulfate gradient, were prepared for the upload of 0.5% EDC. Dynamic light scattering (DLS), nanotracking analysis (NTA) and transmission electron microscopy (TEM) were used to characterize the liposomes' size, polydispersity (PDI), zeta potential (PZ) and number of particles. The *in vitro* release of EDC was measured in Franz diffusion cells, at 37 °C. Cell-viability assays were done in primary cell cultures (Schwann or sciatic nerve cells from *Wistar* rats). Results: IGL were successfully prepared with size, PDI, PZ and concentration in the range 500 nm, 0.2 and -20 mV, and 4-5.10^{12}, respectively, and they kept stable over 60 days at 37±37°C. TEM data revealed the spherical morphology of the liposomes that was able to encapsulate 41% of EDC. At 37°C, the time for 100% release of the anaesthetic increased from 3 h (EDC in solution) to 24h in IGL_{EDC}. Cytotoxicity tests revealed that encapsulation into liposomes decreased the intrinsic toxicity of the anaesthetic. Conclusion: IGL are very interesting carriers for the delivery of local anaesthetics. In this study sulphate-gradient LUV were found promising increase the upload, and release of etidocaine. *In vivo* tests are under course to evaluate the antinociceptive effects of the formulation.

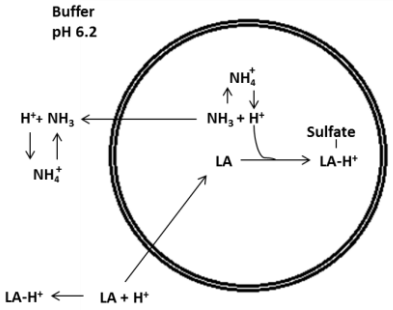


Figure 1: Schematic representation of a liposome with sulphate transmembrane-ionic gradient, showing the incorporation of local anesthetics (LA).

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