

# pH/thermo-responsive Nucleolipid-containing Liposomes for Triggering Delivery of Doxorubicin <sup>†</sup>

Mónica C. García <sup>1,2,3,\*</sup>, José Manuel Calderón-Montaño <sup>4</sup>, Manuela Rueda <sup>5</sup>, Marcela Longhi <sup>1,2</sup>, Antonio M. Rabasco <sup>3</sup>, Miguel López-Lázaro <sup>4</sup>, Francisco Prieto-Dapena <sup>5</sup>, María Luisa González-Rodríguez <sup>3,\*</sup>

<sup>1</sup> Departamento de Ciencias Farmacéuticas, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Ciudad Universitaria, Haya de la Torre and Medina Allende, Science Building 2, Córdoba X5000HUA, Argentina; mgarcia@unc.edu.ar (M.C.G.); mrlonghi@unc.edu.ar (M.L.)

<sup>2</sup> Unidad de Investigación y Desarrollo en Tecnología Farmacéutica, CONICET, Consejo Nacional de Investigaciones Científicas y Técnicas, UNITEFA, Córdoba X5000HUA, Argentina

<sup>3</sup> Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, Universidad de Sevilla, C/Prof. García González 2, 41012 Seville, Spain; amra@us.es (A.M.R.); malugoro@us.es (M.L.G.-R.)

<sup>4</sup> Department of Pharmacology, Faculty of Pharmacy, Universidad de Sevilla, C/Prof. García González 2, 41012 Seville, Spain; jcalderon@us.es (J.M.C.-M.); mlopezlazaro@us.es (M.L.-L.)

<sup>5</sup> Department of Physical Chemistry, Faculty of Chemistry, Universidad de Sevilla, C/Prof. García González s/n, 41012 Seville, Spain; marueda@us.es (M.R.); dapena@us.es (F.P.-D.)

\* Correspondence: mgarcia@unc.edu.ar (M.C.G.); malugoro@us.es (M.L.G.-R.);

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**Abstract:** The pH gradient between normal and tumoral tissues and their rapid metabolism that induces hyperthermia to encourage the development of pH- and thermo-sensitive liposomes (Lip) as nanocarriers for anticancer drugs. Nucleolipids have been studied as scaffolding material of Lip, mainly for cancer therapy. Hence, we report the use of 1,2-dipalmitoyl-*sn*-glycero-3-(cytidine diphosphate) (DG-CDP) for developing pH/thermo-sensitive nucleolipid-containing Lip based on 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) and cholesterol for triggering delivery of doxorubicin (Dox). Thin-film hydration and transmembrane pH-gradient methods were used to prepare the Lip and Dox loading, respectively. Morphological and interfacial properties and encapsulation efficiency (EE%) were analyzed. Drug release studies toward different media (pH 7.4 and 5.1 at 37 °C and 42 °C) and cytotoxic activity against breast and ovarian cancer cells were analyzed. Unloaded and Dox-loaded Lip exhibited nano-scale sizes (415-535 nm), acceptable polydispersity indexes (<0.3), almost spherical shapes, and negative Z-potential (-23- -14.7 mV) because of the phosphate groups of DG-CDP. High EE% was achieved (82 %), and although an efficient control in the Dox release towards both receptor media was observed, the release of Dox was triggered at acidic pH and hyperthermia temperature, demonstrating responsiveness to both stimuli. Dox-encapsulated Lip preserved its antiproliferative activity against cancer cells. Overall, Lip-Dox showed promising properties for cancer nanomedicine.

**Keywords:** pH-sensitive nanocarriers; temperature-sensitive nanocarriers; lipid vesicles; drug delivery; anticancer drugs.

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## **Conflicts of Interest**

The authors declare no conflict of interest.