

MICROFLUIDIC-BASED DEVELOPMENT OF pH-SENSITIVE OLAPARIB-LOADED LIPOSOMES FOR OVARIAN CANCER: ASSESSMENT IN 2D AND 3D TUMOR MODELS

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Epithelial ovarian cancer is one of the most lethal gynecological malignancies, with high-grade serous carcinoma (HGSC) as its most prevalent histological subtype. In this setting, poly(ADP-ribose) polymerase (PARP) inhibitors such as Olaparib target homologous recombination deficiencies, observed in approximately 50% of HGSC cases. Currently, the oral bioavailability of PARPi is quite low; thus, it is a major challenge to effectively and safely deliver PARPi during clinical cancer therapy. To further enhance efficacy and safety, liposomes provide a biocompatible and versatile delivery platform with controlled release. This study investigates the impact of microfluidic parameters on liposome (composed of DMPC, DOPE and Cholesterol, with and without Oleic Acid, OA) physicochemical properties through of a multi-technique approach. Additionally, empty and Olaparib-loaded liposomes were optimized and evaluated in 2D and 3D ovarian cancer models. All systems were characterized in terms of stability, in vitro pH-responsiveness with fluorescent probes, and Olaparib release profiles. Biological evaluation was performed on SKOV-3 cells in 2D monolayers and 3D spheroids. Cytotoxicity, cellular uptake, kinetics, and spheroid penetration were assessed for empty and Olaparib-loaded liposomes using confocal microscopy. Since in the tumor microenvironment the extracellular matrix (ECM) and fluid shear stress are key regulators of ovarian cancer cell invasion, ovarian cancer-on-chip (OC-chip) and ECM-based models have been employed.

Liposomes containing OA showed pronounced pH-responsive behavior, enabling selective activity in the acidic tumor microenvironment.

Overall, while 2D models confirmed liposomal efficient uptake, 3D models provided a more physiologically relevant and discriminative assessment. Integrating microfluidic parameter control with advanced *in vitro* models represents a rational strategy for developing pH-responsive liposomal platforms for ovarian cancer therapy.