BIORESPONSIVE MICROEMULSION FOR PREVENTION OF BREAST CANCER DEVELOPMENT

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Introduction. Although breast cancer is the most common type of neoplasm in woman worldwide, few pharmacological strategies for its chemoprevention are available and well-accepted by high-risk patients, especially due to the serious adverse effects that current strategies present, highlighting the need for new and safe forms of prevention therapies. Fenretinide is a retinoid, considered a promising candidate for chemoprevention due to its ability to regulate cell growth and differentiation and accumulate preferentially in the breast tissue. However, the serious systemic adverse effects and low bioavailability limits its systemic use. To overcome these limitations, we developed a bioresponsive, phosphatidylcholine-based microemulsion, capable of transitioning into a liquid-crystalline system upon intramammary administration for sustained release of fenretinide locally in the breast.

Methods. Selected microemulsions and liquid crystalline phases formed upon water uptake were characterized using dynamic light scattering, polarized light microscopy and small angle X-ray scattering (SAXS). Subsequently, we evaluated the ability of the system to (i) sustain the in vitro fenretinide release, (ii) decrease cellular viability and migration in 2D and 3D models using T47D cells, and (iii) reduce breast cancer incidence in vivo in a chemically induced breast cancer model.

Results. The precursor microemulsion displayed size of 175.3 nm (PDI=0.106), and was capable to form lamellar liquid crystalline gels when water was added at 5% and up. The system released 30% of its fenretinide content at 9 days, highlighting its ability of sustained release. Migration of T47D cells was inhibited by the formulation at IC₁₅ (concentration necessary to reduce cell viability by 15%) compared to the unloaded formulation and control solution in approximately 4-fold. Treatment for 4 days at a dose equivalent to IC₃₀ reduced the viability of T47D spheroids compared to untreated or unloaded ME-treated cells (1.4-fold), while fenretinide in solution precipitated in the culture medium. Using an in vivo model of n-methyl-n-nitrosourea-induced carcinogenesis, intramammary administration of the fenretinide-loaded ME every 3 weeks for 3 months reduced the incidence of breast tumors by 4.5-fold compared to untreated animals.

Conclusion. These results demonstrate the strong potential of the formulation to provide an effective and much needed platform to inhibit breast cancer development.