Supramolecular structural characterization of cholesterol-rich vesicles to be used in drug delivery: influence of the preparation method

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In the past 30 years, the explosive growth of nanotechnology has promoted challenging innovations in pharmacology, which is currently revolutionizing the delivery of biologically active compounds[1]. Indeed, some existing drugs and new therapeutic compounds emerging from drug discovery processes present special delivery challenges, pushing nanotechnology towards the development of new drug nanocarriers that enhance the bioavailability of drugs[2]. Such nanocarriers or drug delivery systems (DDS) are intended not only to protect drugs from degradation but also to achieve their temporal and spatial site-specific delivery.Vesicles constitute one of the most studied DDS since their discovery in the mid 60s[3]. However, in order to achieve optimal performance of these self-assembled structures as functional materials, a high grade of structural homogeneity is required. For example, the behaviour of vesicles as drug delivery systems (DDS) is highly affected by their homogeneity, not only in size or morphology, but also in their membrane composition and supramolecular organization. Concretely, the vesicular membrane plays an important role in terms of vesicles stability, rigidity, permeability, functionalization or response to external stimuli[4]. In the latter case, the homogeneity in the membrane composition and supramolecular organization between the different vesicles forming a certain system would be a crucial issue in order to have sharp responses that allow homogenous triggering of the drug at the site of action (Figure 1). Attending to this, methods for the preparation of homogeneous vesicular systems, not only in terms of size and morphology, but also regarding the supramolecular organization of the membrane constituents are required for fully exploiting the potential of these self-assembled structures as functional materials.

In the early 90's, compressed fluid (CF)-based processes emerged as an alternative to conventional methods using liquid solvents, attracting enormous interest for the production of micro- and nanoparticulate materials[5]. Our research group has experience in using these novel technologies for the controlled nanostructuration of materials to be used in drug delivery[6,7]. Recently, a CF-based method, DELOS-susp, has been developed for the production of vesicular systems. This one-step process allows the achievement of stable, nanoscopic and unilamellar cholesterol-rich vesicles[8,9], which present higher structural homogeneity regarding size and morphology than those produced by a conventional multi-step hydration method (Figure 2). In this work, by analyzing the membrane composition and supramolecular organization of vesicles prepared by both methodologies, we demonstrate that apart from size and morphology, the superior homogeneity observed for vesicular systems produced by CFs is also present in the molecular assembly of the membrane constituents, which is crucial for an optimum performance of these supramolecular structures as pharmaceutical carriers.

References

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Figures

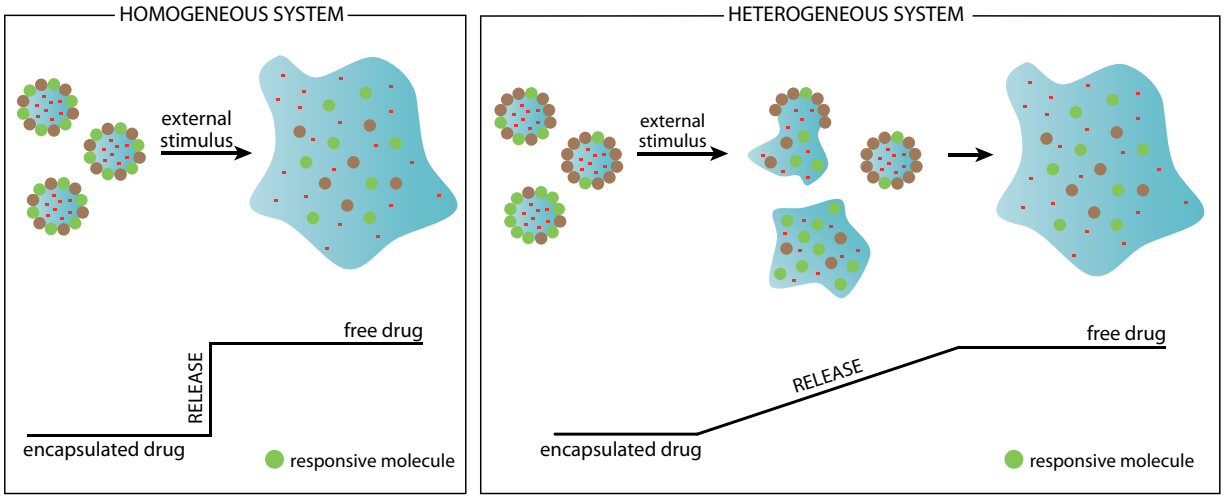

Figure 1. Schematic illustration of the response to an external stimulus presented by a vesicular DDS with homogeneous (left) and heterogeneous (right) vesicle to vesicle composition and supramolecular arrangement.

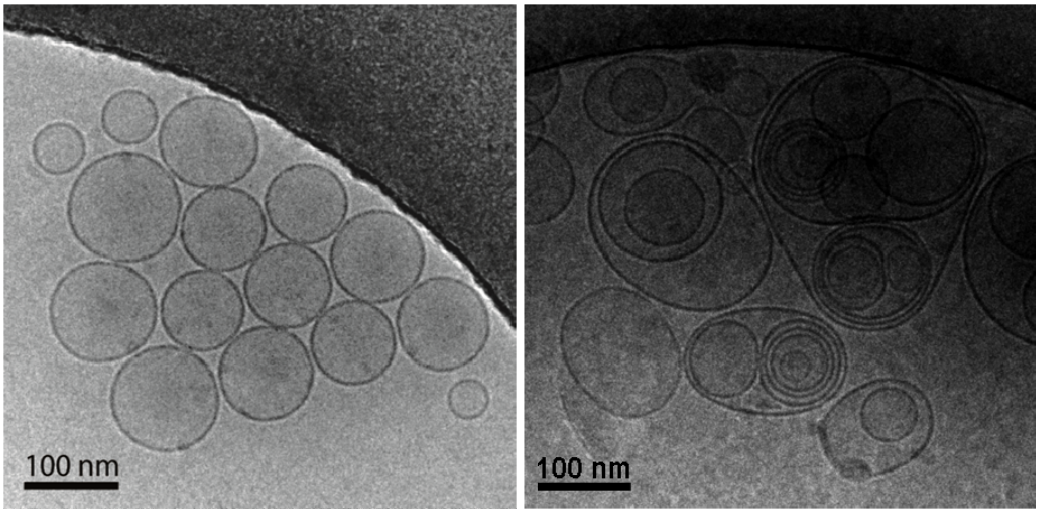

Figure 2. CryoTEM images corresponding to cholesterol-rich vesicles prepared by DELOS-susp (left) and the hydration method (right).