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# Cerasomal doxorubicin with long-term storage stability and controllable sustained release

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## ABSTRACT

Liposomal nanohybrid cerasomes display a remarkable ability to maintain their size and retain encapsulated doxorubicin (DOX) over a period of 90 days under storage conditions in solution compared with liposomes and liposils. Cerasomes retained  $92.1 \pm 2.9\%$  of the drug payload after 90 days storage, much more than liposomes ( $35.2 \pm 2.5\%$ ) and liposils ( $53.2 \pm 5.5\%$ ). Under physiologically relevant conditions cerasomes exhibit a low initial burst in the first 5 h and subsequent sustained release of DOX over the next 150 h. Moreover, the magnitude of the initial burst and the rate of sustained release of DOX from cerasomes can be modulated by incorporating dipalmitoylphosphatidylglycerol (DPPG) in the cerasome structure and altering the ratios of the cerasome-forming lipid and phospholipids. Consequently, a wide range of release profiles can be achieved by altering the vesicle composition. Finally, human ovarian cancer cells are effectively killed by DOX released from cerasomes. Together these results suggest that cerasomes may be a promising drug delivery system for the long-term storage and controllable sustained release of the anticancer drug DOX.

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## 1. Introduction

Doxorubicin (DOX) is the first line treatment used for a wide range of cancers. Despite the relative efficacy, unformulated DOX is not specifically toxic to tumor cells and is toxic to all tissues with which it comes into contact, so creating undesirable side-effects as a result of its interaction with normal tissues [1–9]. It has been proved that long-term exposure of ailing tissues to moderate drug concentrations using controlled or sustained release formulations is more beneficial than a pulsed supply of the drug at higher concentrations [10,11]. Nevertheless, administration of unformulated DOX by intravenous injection/infusion leads to an initial burst release and a subsequent fall in the drug concentration, below the therapeutic level in blood. Attacking this problem head on, researchers are seeking new and innovative strategies to entrap this drug in different carriers.

Among numerous carriers, liposomes have received increasing attention because of their biocompatibility, degradability, and ability to encapsulate a wide range of drugs [12–14]. However, liposome-based drug formulations have not entered the market

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in great numbers so far due to a lack of stability [15] and to aggregation [16]. To improve their biochemical and physical stabilities and circulation times in the blood polyethylene glycol (PEG) has been used to modify the surface of liposomes [17]. However, PEGylated liposomes have led to skin toxicity, known as "hand-foot syndrome". As an alternative strategy liposils were created by introducing a 4 nm silica shell on the surface of liposomes [18-20]. However, silica nanoparticles also have serious drawbacks, including inherent non-biodegradability, high rigidity and low biocompatibility compared with liposomes. Thus cerasomes were fabricated from trialkoxysilane [16,21-23]. Recently cerasomes have received much attention as a novel drug delivery system because the polyorganosiloxane surface layer imparts higher stability than that of liposomes and its liposomal structure greatly reduces the overall rigidity and density compared with silica nanoparticles [16]. In addition, the interface between the organic and inorganic components in cerasomes seems to be structurally distinct and controlable at the molecular level compared with liposils [21,24-26].

Besides vesicle stability, the ability to retain encapsulated drug during storage is also critical to the development of drug carriers. Since natural lipids such as dipalmitoylphosphatidylcholine (DPPC) display a phase transition at temperatures slightly above 37 °C the composition of liposomes can be modulated so that their permeability increases dramatically with temperature and the release

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