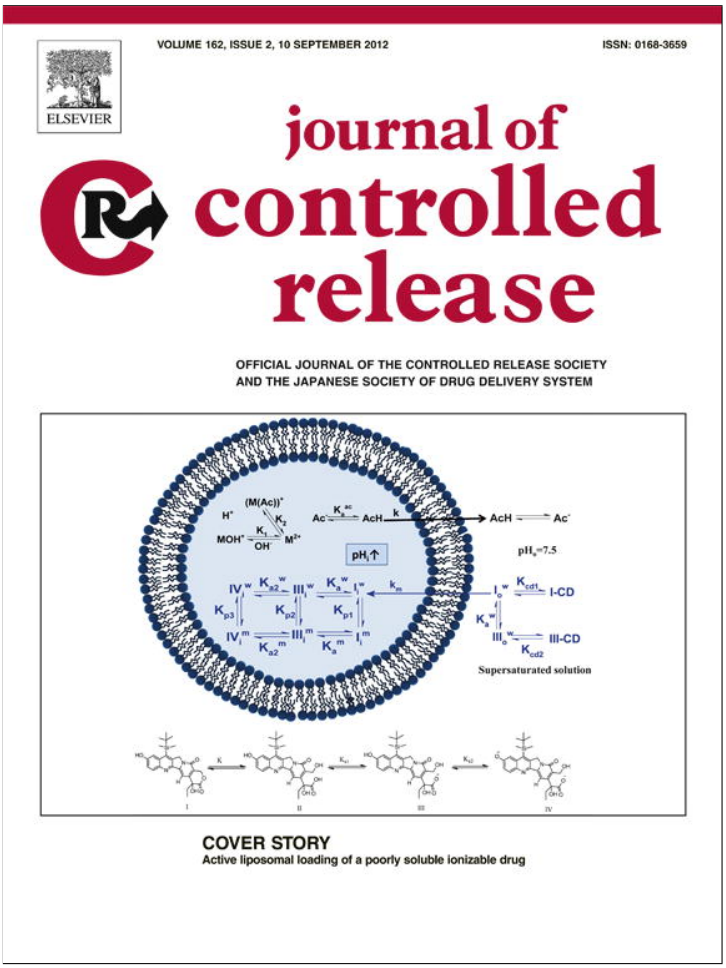

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Cover story

Active liposomal loading of a poorly soluble ionizable drug

Since their discovery in 1964 by Bangham et al. [1], liposomes have become one of the most widely adopted nanoparticle drug delivery systems, particularly for the improvement of therapeutic efficacy in cancer chemotherapy. Unilamellar liposomes in the 100–200 nm range are attractive as drug carriers for delivery to solid tumors because of their enhanced permeability across the leaky tumor microvasculature due to their small size and their prolonged retention as a result of the poorly developed lymphatic system in rapidly growing tumors. For liposomes to realize their full clinical potential in terms of minimum toxicity and maximum efficacy, however, the liposomal drug loading has to be maximized. Reliable and scalable formulation strategies are necessary to reproducibly maximize encapsulation of the drug payload and optimize the kinetics of in vivo drug release after localization of the carrier to its site of action.

Both hydrophilic and hydrophobic drugs can be encapsulated into liposomes during their preparation, a process referred to as passive loading. However, owing to the limitations of the passive loading technique in terms of the percentage of drug encapsulated and the drug to lipid ratios achievable, active loading strategies have been widely explored to enhance liposomal drug encapsulation. In active loading, drug uptake occurs into preformed liposomes driven by a transbilayer chemical potential gradient of the permeable drug species across the bilayer. Active loading has been generally limited to ionizable compounds that can be readily solubilized by pH adjustment. Many of the drug candidates entering pharmaceutical development today are highly lipophilic and poorly water soluble, and thus, present significant challenges in terms of their delivery. In the case of liposomal delivery systems, such compounds may present problems of inadequate drug loading and poor retention or sub-optimal release kinetics. Their low solubility in water reduces the external driving force for liposomal uptake resulting in a reduced ratio of encapsulated drug to lipid. An excellent example of the class of drugs posing such challenges is AR-67, a blood-stable camptothecin analog currently in phase II clinical trials.

In this issue, Professor Bradley Anderson and his colleagues propose a novel method for active loading of poorly soluble drugs in liposomes by creating supersaturated solutions using AR-67 as a model drug candidate [2]. They contribute to a mechanistic understanding of the process by developing a quantitative mathematical model. The model takes into account various intra- and extra-liposomal ionic and binding equilibria and transport kinetics of the permeable species to predict the rate and extent of active drug loading. Their model represents advancement over those previously developed in that it incorporates all of the known intra- and extra-vesicular equilibria and kinetic processes and parameters that govern the activity gradient for liposome loading of this drug.

The authors used 2% sulfobutyl ether-β-cyclodextrin to maintain drug supersaturation by inhibiting nucleation and crystal growth [3]. While there are several ways to enhance solubility, the authors emphasize that the key is to enhance the concentration of the permeable drug species that drives the transport across the liposomal bilayer. They demonstrate that supersaturation achieves this outcome by increasing the concentration of the membrane permeable lactone, while other methods, such as pH adjustment and complexation, may increase solubility but not drug loading. Their quantitative mathematical model illustrates how an elevated intraliposomal pH, ring-opening of the drug and ionization due to the high intravesicular pH, and membrane binding of the various drug species reduce the intraliposomal concentration of the permeable drug species, which, when combined with extravesicular supersaturation drives the loading process. This drug loading strategy and the mechanistic understanding derived from mathematical modeling accompanying these studies should be increasingly useful for the current antitumor drugs. It is common that only a few percent of the intravenously administered liposomes, and all other nanovehicles for that matter, find their way to the target tumors. Thus, maximizing the drug loading into liposomes is critical for improved efficiency of the liposome formulations. Of course, the approach presented by Professor Anderson and his team will also be highly useful for formulation of more poorly soluble and hydrophobic agents entering the drug discovery pipeline.

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