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Cover Story

Probing the mechanism of drug release from liposomes

The research of utilizing liposomes as a carrier to deliver drugs dates back to 1965 when Bangham and his colleagues discovered the spontaneous formation of bilayer vesicles from phospholipids [1]. Despite the extensive research in this area, however, successful translation of liposome technology into clinical applications has been limited. Only 11 liposomal drug products have been approved to date by the U.S. Food and Drug Administration (FDA) [2]. While the likely cause of the limitation may be multifaceted, one of the reasons could be due to an incomplete understanding of the mechanism of drug release from liposome structures.

In vitro release testing (IVRT) has gained increasing value as a surrogate test to evaluate a drug product's quality and sameness, as it can provide critical information about the formulation behavior. When designed methodically, an IVRT coupled with appropriate physicochemical characterization techniques reveals fundamental information pertaining to the behavior of the complex dosage forms. This innate information reveals changes in the morphology and release mechanisms, as well as release kinetics, and thus enabling a rational and scientific approach to development of new and generic liposome products. Therefore, along with conventional *in vivo* bioequivalence studies, *in vitro* tests including IVRT have been recommended by the FDA as a part of the bioequivalence evaluation of liposome products [3,4]. Yet, despite the recognition of its importance, no compendial or regulatory standards on IVRT are available for liposome drug products.

The paper by the researchers at the FDA in this issue presents a modified USP 2 apparatus-based IVRT method (e.g., a reverse dialysis setup inside the traditional USP 2 apparatus), where in situ UV-Vis probes were positioned inside the dialysis cartridges for continuous monitoring of the drug concentration during release [5]. The proposed IVRT set-up along with other state-of-the-art physicochemical characterization techniques, such as cryo-scanning electron microscopy, laser diffraction and confocal microscopy, were used to reveal the underlying mechanism of drug release from multivesicular liposomes (MVLs). The FDA researchers have chosen to work with MVLs containing bupivacaine, because it possesses a unique design that is distinct from other types of lipid-based vesicles like unilamellar or multilamellar liposomes. In addition to its unique physicochemical properties, MVLs also exhibit complex drug release characteristics, creating challenges to the design and development of appropriate *in vitro* release testing methods. The set-up described in this paper allowed the FDA researchers to analyze the sequence and mechanisms of the drug release from MVLs. They have shown that the bupivacaine release from MVLs exhibits a characteristic tri-phase profile: an initial burst release, a lag phase, and a secondary release. Combining the release data with the observed (exterior/inner) morphological changes, the FDA researchers discussed a potential bupivacaine release mechanism from MVLs, where lipid erosion and drug diffusion dominate at different stages of release. They further identified conditions which may influence each of the three phases of drug release.

It is not an easy task to establish reproducible, robust and discriminatory *in vitro* drug release testing methods for liposome formulations. This research advances the understanding on MVL-based formulations and offers a roadmap to guide the formulation and/or process development in MVLs, as well as other similar liposome formulations. The IVRT method reported in this paper may be further optimized to serve as a tool to improve product quality or to support bioequivalence between a generic MVL product and a reference listed drug. Each drug has its unique physicochemical properties, and thus, its mechanisms of release from MVLs may be different, but the same approach can be used to study the drug release mechanisms. Furthermore, the approach in the study can also be adapted to evaluate other complex drug products, such as micro/nano polymeric particles and conventional liposomes.

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