COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

**Pharmaceutical Sciences Seminar**

Wednesday, March 24, 2021
Join Zoom Meeting
https://umich.zoom.us/j/91361053291
4:00-5:00 pm

# "Reverse Engineering and Optimization of *In Vitro* Release Tests (IVRT) of Liposomal Drug Products"


Presented by:

**Minzhi Yu**
Pharmaceutical Sciences
Ph.D. Candidate



Abstract: Liposomal drug delivery systems have been extensively investigated in the past several decades, leading to the FDA approval of multiple liposomal products. Since the patents of many of these liposomal drug products have expired or will expire in the near future, we have seen an uptick in the number of companies expressing their interest in developing generic liposomal drug products. However, the development of such products is particularly challenging from a technical and a regulatory perspective. The current FDA draft guidance requires thorough formulation characterization for both innovator and generic liposomal drug products. In order to meet these requirements, multiple discriminative analytical methods, including *in vitro* drug release testing (IVRT), have to be developed and validated by sponsoring companies. As it currently stands, there is no compendial *in vitro* drug release test available for liposomal drug products. Therefore, there remains a need to establish robust and discriminative IVRT methods in order to guide formulation development, facilitate quality control and streamline regulatory approval of liposomal products.

The first part of this study aims to examine the commonly used dialysis-based IVRT. One drawback for dialysis IVRT is that dialysis membranes impose significant barrier effects on the drug transport. This delays the appearance of released drug molecules in the sampling compartment, meaning that the apparent drug release results often do not properly reflect the actual drug release kinetics. To address this challenge, we created a two-step approach that includes experimental and mathematical components. Experimentally, we measured the drug diffusion of Doxil® (doxorubicin liposomes) across a dialysis membrane and then applied a mathematical model to predict the drug release from the experimental data measured outside of the dialysis bag. The Doxil® model showed a good agreement between the experimental data and the predicted values. By taking barrier effects of dialysis membranes into consideration, our model can not only enable the proper interpretation of the data from dialysis studies, but also can help to evaluate the appropriateness of applying dialysis methodology to *in vitro* drug release assays.

The second part of this study aims to conduct reverse engineering of Exparel®, a liposomal bupivacaine formulation. Exparel® was developed based on the DepoFoam® technology, where bupivacaine is encapsulated in micro-sized, non-centric multivesicular liposomes (MVLs). Developing generic versions of Exparel® has been challenging due to its complex composition and unique structure. To aid in the development of generic Exparel®, we developed a series of analytical methods to characterize particle size, drug and lipid contents, residual solvents, and pH. We further optimized an *in vitro* drug release assay by tweaking the experimental set-up, dilution factors, and release media. The product characterization and IVRT methods developed in this study are valuable for the development of generic bupivacaine MVLs and other MVL-based products.


For more information on the weekly PharmSci department
Seminar series, please view our website:
https://pharmacy.umich.edu/pharmsci/seminars