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Kyle D. Fugit, Xiang T. Xiang, Du H. Choi, Sogol Kangarlou, Eva Csuhai, Paul M. Bummer, Bradley D. Anderson

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MECHANISTIC MODEL AND ANALYSIS OF DOXORUBICIN RELEASE FROM LIPOSOMAL FORMULATIONS

Kyle D. Fugit[1], Xiang T.-Xiang[1], Du H. Choi,[2] Sogol Kangarlou[1], Eva Csuhai[3], Paul M. Bummer[1], and Bradley D. Anderson[1*]

[1] Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY 40536

[2] Department of Pharmaceutical Engineering, Inje University, Gimhae-si, Gyeongsangnam-do, South Korea

[3] Division of Natural Sciences and Math, Transylvania University, Lexington, KY 40508

*Corresponding Author:
Prof. Bradley D. Anderson
Department of Pharmaceutical Sciences
College of Pharmacy
A323A ASTeCC Bldg.
University of Kentucky
Lexington, KY 40506
Telephone: 859-218-6536
Fax: 859-257-2489
Email address: bande2@uky.edu

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ABSTRACT:

Reliable and predictive models of drug release kinetics *in vitro* and *in vivo* are still lacking for liposomal formulations. Developing robust, predictive release models requires systematic, quantitative characterization of these complex drug delivery systems with respect to the physicochemical properties governing the driving force for release. These models must also incorporate changes in release due to the dissolution media and methods employed to monitor release. This paper demonstrates the successful development and application of a mathematical mechanistic model capable of predicting doxorubicin (DXR) release kinetics from liposomal formulations resembling the FDA-approved nanoformulation DOXIL® using dynamic dialysis. The model accounts for DXR equilibria (e.g. self-association, precipitation, ionization), the change in intravesicular pH due to ammonia release, and dialysis membrane transport of DXR. The model was tested using a Box-Behnken experimental design in which release conditions including extravesicular pH, ammonia concentration in the release medium, and the dilution of the formulation (i.e. suspension concentration) were varied. Mechanistic model predictions agreed with observed DXR release up to 19 hrs. The predictions were similar to a computer fit of the release data using an empirical model often employed for analyzing data generated from this type of experimental design. Unlike the empirical model, the mechanistic model was also able to provide reasonable predictions of release outside the tested design space. These results illustrate the usefulness of mechanistic modeling to predict drug release from liposomal formulations *in vitro* and its potential for future development of *in vitro - in vivo* correlations for these complex nanoformulations.