Development of a Liposomal Doxorubicin Product Drug Release Assay

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Purpose
A barrier to the rational assessment of generic drug delivery systems for parenterally administered drugs for regulatory purposes is the absence of validated mechanism-based drug release assays that reflect or predict in vivo drug release from the carrier. One such FDA licensed drug carrier is the sterically stabilized liposomal doxorubicin product known as Doxil® (Johnson & Johnson). Our goal is to develop an in vitro release assay that can determine the degree of similarity between Doxil® and generic liposomal doxorubicin.

Methods
We have prepared and characterized a series of 24 different liposomal doxorubicin formulations that span a range of compositions, sizes, source of materials, physical properties, and manufacture processes. The test formulations also include the FDA approved generic Doxil® formulation, Lipodox (Sun Pharma). Some in-house prepared formulations include technologies used in the manufacture of Doxil® and are nearly identical or include modifications making them slightly different from Doxil®. These liposome formulations are compared to the innovator product for drug retention and release characteristics using a single-unit vial-based assay. The variables evaluated for inducing doxorubicin release include time, pH, temperatures, plasma concentration and buffers. Materials used as a sink for released doxorubicin include sulfobutyl cyclodextrin, plasma and hydrophobic beads.

Results
We were able to induce 100% doxorubicin release from liposomal doxorubicin formulations within 8 hours in a manner that distinguishes Doxil from slightly different formulations. The pH of the media has a large effect on the rate of doxorubicin release and also doxorubicin degradation product generation. A pH of 6.0 was optimal for our assays. Addition of ammonium carbonate to the media impacts drug release in a concentration dependent fashion. Hydrophobic beads of 300-1000 microns serve as a very effective sink for released doxorubicin even at a time shorter than our first time point of 1 hour. The release rate and absolute values show high day-to-day reproducibility.

Conclusion
The single-unit vial-based assay described here is able to distinguish the doxorubicin release from liposomal doxorubicin formulations having slightly different characteristics within an 8 h period.

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