

Pharmaceutical Sciences Seminar Series

Wednesday, December 13, 2023

4:00pm

NCRC Building 10 Research Auditorium

Zoom

“Characterization of Exparel, Understanding of Critical Manufacturing Process Parameters and Investigation of Drug Release Mechanisms *in vitro* and *in vivo*”

Presented by:



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Abstract: Liposomes are some of the most popular drug carriers used for sustained drug release. Traditional liposomes, such as unilamellar vesicles (ULVs) and multilamellar vesicles (MLVs), have been studied extensively and are approved as the carriers for many drug products. A relatively novel type of liposome, known as a multivesicular liposome (MVL), recently sparked interest in the drug delivery community due to its unique structure and drug release characteristics.

Exparel (Pacira Pharmaceuticals, Inc.) is a multivesicular liposomal injectable suspension of bupivacaine capable for a sustained drug release through days to weeks. An assembly of numerous nonconcentric liposomes within a large particle contributes to a unique honeycomb-like structure of multivesicular liposomes (MVLs), allowing for a better drug encapsulation efficiency as well as a longer drug release duration. Exparel was approved by the US Food and Drug Administration (FDA) for the post-surgical local analgesia in 2011, and its label was extended for nerve-block pain relief after shoulder surgeries in 2018. As a long-acting nonopioid drug product, Exparel gained great market success in the past few years, reaching a global sale of \$537 million in 2022. At the same time, its patents either have already or are going to expire soon, making Exparel an appealing target for many generic developers. An Abbreviated New Drug Application (ANDA) for the approval of its generic version in the US was submitted to FDA by eVenus Pharmaceutical Laboratories, Inc. in 2021.

In 2016, the FDA issued a draft product-specific Guidance on Bupivacaine liposomal injection products referencing Exparel, and two years later, FDA issued a guidance for industry on the chemistry, manufacturing and control of liposomal drug products. The draft product-specific guidance emphasized the equivalent product characteristics between a generic bupivacaine liposomal product and the reference listed drug (RLD). However, with its complex formulation and manufacturing process, the generic development for Exparel is challenging. Plus, the instructions were limited and no biowaiver is established yet.

This project aims to bridge the current gaps in developing and regulating the bupivacaine MVL suspension via the investigation of the formulation, manufacturing process, and release mechanisms of Exparel. The formulation was clarified with reverse-engineering of the commercial Exparel. The manufacturing process was studied via identifying the critical production parameters, and lab-scaled production processes were developed accordingly, aiming to make the Q1/Q2 equivalent formulations. The release mechanisms were studied using an optimized implantable cage model developed by Dr. Steve Schwendeman's lab. This project is potential to provide more information about Exparel and other MVL formulations, helping both the generic development and regulation, and eventually, making them more accessible to the physicians and patients.