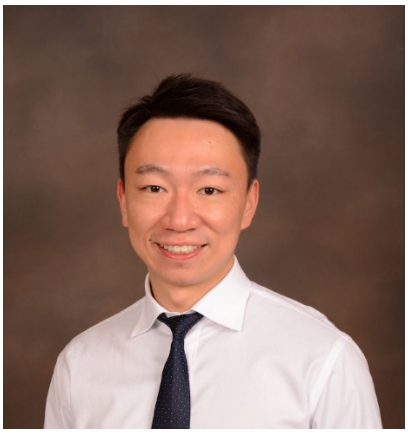
COLLEGE OF PHARMACY
PHARMACEUTICAL SCIENCES
UNIVERSITY OF MICHIGAN

Pharmaceutical Sciences Seminar

Wednesday, December 15, 2021
4:00pm
2548 NUB or Zoom

"Mapping *in vivo* Microclimate pH Distribution in Exenatide-encapsulated PLGA Microspheres"

Presented by:



Justin Hong
Pharmaceutical Sciences
Ph.D. Candidate
(Mentor: Dr. Steven P. Schwendeman)

Abstract: The pH inside the aqueous pores of poly(lactic-co-glycolic acid) (PLGA) microspheres, often termed microclimate pH (μpH), has been widely evaluated *in vitro* and shown to commonly be deleterious to pH-labile encapsulated drug molecules. However, whether the *in vitro* μpH is representative of the actual *in vivo* values has long been remained a largely unresolved issue. Herein we quantitatively mapped, for the first time, the *in vivo* μpH distribution kinetics inside degrading PLGA microspheres by combining two previously validated techniques, a cage implant system and confocal laser scanning microscopy. PLGA (50/50, Mw = 24 – 38 kDa, acid-end capped and ester-capped) microsphere formulations with and without encapsulating exenatide, a pH-labile peptide that is known to be unstable when pH > 4.5, were administered to rats subcutaneously via cage implants for up to 6 weeks. The results were compared with two different *in vitro* conditions. Strikingly, the *in vivo* μpH developed similarly to the low microsphere concentration *in vitro* condition with 1-μm nylon bags but very different from conventional high microsphere concentration sample-and-separate conditions. Improved maintenance of stable external pH in the release media for the former condition may have been one important factor. Stability of exenatide remaining inside microspheres was evaluated by mass spectrometry and found that the peptide was steadily degraded primarily via pH-dependent acylation with a trend that slightly paralleled the changes in μpH. This methodology may be useful to elucidate pH-triggered instability of PLGA encapsulated drugs *in vivo* and for improving *in vivo*-predictive *in vitro* conditions for assessing general PLGA microsphere performance.

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