Engineering Drug Nanoparticle Structure and Function for Bioavailability Enhancement

by

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ABSTRACT

Formulating hydrophobic small molecule therapeutics is a critical challenge in pharmaceutical processing. Nearly 90% of drug candidates are hydrophobic, yet these molecules exhibit low bioavailability that limits therapeutic efficacy. Several engineered formulation approaches have been developed to enable bioavailability, among which nanosizing drug particles is one of the most successful. By reducing drug particulate size from the micro-scale to nano-scale, this approach achieves faster dissolution, higher apparent thermodynamic solubility, and enhanced membrane permeability in the gastrointestinal tract. Despite the promise of nanoformulation, processing drug nanoparticles remains challenging. Conventional top-down media milling is time- and energy-intensive, can destroy crystal structure, and risks contaminating drug products with trace heavy metals or ceramics. Bottom-up methods have emerged as an alternative, directly assembling nanosized drug nanoparticles via precipitation or evaporation. The Doyle Group has developed a bottom-up nanoemulsion templating approach, in which lipophilic drugs dissolved in an organic carrier are emulsified in an aqueous polymer solution, gelled to immobilize drug-loaded nanodroplets, and dried to simultaneously template and encapsulate solid drug nanoparticles within a polymer matrix. Prior work demonstrated this process for two model hydrophobic molecules across several gel systems and form factors. Yet, there are several limitations and challenges with nanoemulsion templating. The influence of process design parameters on the templated nanoparticle morphology remains underexplored. Additionally, the ability to control drug release using the hydrogel structure has also not been established. the applicability to chemically diverse drugs beyond model drug molecules is still untested.

The goal of this thesis is to advance the development of nanoemulsion templating as a platform for the nanoformulation of hydrophobic drugs. To this end, a combination of experiments, molecular simulations, and machine learning are used. The findings in this thesis have general implications for solubility, nanoscale thermodynamics, polymer science, and formulation science. The computational tools presented in this thesis are developed for broad use in the chemical sciences.

First, we adapt nanoemulsion templating in a novel core-shell particle hydrogel system. The core-shell hydrogels are generated using a novel all-aqueous dual gelation, where an orthogonal thermal gelling core and ion-gelling shell are simultaneously generated in a single processing step. This particle platform is a flexible process which enables controllable drug

release. Second, we explore the role of excipients on the templated nanoparticle morphology using molecular dynamics (MD) simulations. Specifically, we evaluated the relationship between surfactant concentration and nanoparticle crystallinity. We simulated the interface between the nanoparticle surface and the excipient matrix, and our results suggest routes for rational control over nanoformulation morphology, a critical drug product attribute. Third, we report the development of fastsolv, a deep learning model for organic solubility prediction, which can accelerate the rate-limiting solvent screening step when adapting nanoemulsion templating for a new drug. Since its deployment, fastsolv has become a widely used tool across the chemical sciences, beyond its motivating use case in this thesis. Fourth, we demonstrate the versatility of nanoemulsion templating by applying it to four chemically diverse drugs (fenofibrate, cannabidiol, clotrimazole, and cholecalciferol) expanding the library of successfully nano-templated drugs from two to five. We also validate the effect of nanosizing on *in vitro* bioavailability, providing a rare quantitative validation of the Ostwald–Freundlich equation. Finally, we synthesize these findings and propose future research to continue the development of this promising process. Overall, this thesis establishes nanoemulsion templating as a robust, flexible, and controllable platform for hydrophobic drug nanoformulation.

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