Use of Physical Enhancers for Gastrointestinal and Transdermal Drug Delivery

By

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Abstract

The research presented in this thesis represents a significant advance in the field of transdermal- and gastrointestinal (GI)-based drug delivery. With regards to the former, previous work has led to a thorough mechanistic understanding of ultrasound (US)-enhanced transdermal drug delivery. Despite these investigations, it was previously not possible to maximize the efficiency of the permeabilization, or to decrease the required treatment time. In this area, this thesis presents work on the use of a new US treatment modality to both maximize the area of skin that is permeabilized and minimize the required treatment time.

This new method involves the simultaneous use of low- (< 100 kHz) and high- (≥ 1 MHz) frequency US. A proof-of-concept of this method is presented in Chapter 2. Specifically, through the use of aluminum foil pitting experiments, the mechanism of enhancement is elucidated, confirming an increase in transient cavitational events. This method is further shown to lead to enhanced delivery of model permeants to porcine skin in vitro.

The new method is further explored in Chapter 3. A physiologically relevant experimental setup, utilizing the receiver chamber of a Franz diffusion cell is developed. With this setup, fundamental studies are carried out to investigate the enhancement in localized transport region (LTR) formation versus the enhancement in the resulting skin permeability in vitro. The most important finding is that the enhancement in permeability is greater than the enhancement in LTR formation, suggesting that dual-frequency US results in more permeable LTRs, in addition to larger LTRs. This phenomenon was not previously realized. Furthermore, the safety of this method is assessed through blinded histological evaluation of skin samples treated both in vitro and in vivo. This investigation demonstrated that dual-frequency US results in no greater histological disruption of the skin than that observed using 20 kHz US alone.

The power of physical enhancers, such as US, is underscored by their ability to permeabilize a tissue layer, such as the skin, which is designed to serve as a barrier. The use of physical enhancers in a tissue that lacks this barrier, such as the GI tract, presents an intriguing opportunity to maximize drug delivery while minimizing treatment times. In Chapters 4 and 5, the use of microneedles
and US to facilitate GI-based drug delivery are explored. Specifically, in Chapter 4, the implementation of an ingestible device containing microneedles is investigated. Studies in pigs demonstrated that microinjections of a model biologic in the GI tract results in superior kinetics compared to traditional subcutaneous injection. A model device containing radially protruding microneedles was also found to be capable of being excreted naturally without any adverse events.

Chapter 5 explores the use of US to facilitate rapid delivery to all tissue types of the GI tract. US are demonstrated to be safe and well tolerated. Further, it is found to enable the delivery of a broad range of permeants with a wide range of molecular weights. The clinical use of such a technology is examined in a model of inflammatory bowel disease, and the tolerability and efficacy of rectal-based drug delivery is studied in both small and large animal models in vivo.

This thesis advances the current understanding of the use of physical enhancers in skin and GI tissue. In the area of transdermal drug delivery, the insights gained here could lead to more clinically viable devices by reducing the required skin treatment time to achieve a certain level of permeabilization. With respect to the GI tract, this thesis advances for the first time the use of physical enhancers, including investigating the mechanism of enhancement and the cellular and histological effects. This should open the door to a previously unexplored line of research. Indeed, this research could lead to improved therapies and expansion of research techniques applied to the GI tract, as well as to new medical devices to enable local rectal delivery and, eventually, oral administration using ingestible devices.

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