Mechanistic Studies of Ultrasonically-Enhanced Transdermal Drug Delivery

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Abstract

Transdermal drug delivery (TDD), a painless, non-invasive method of drug delivery, is limited to only a handful of drugs due to the low permeability of skin. The application of low frequency ultrasound significantly enhances transdermal transport of a variety of drugs (sonophoresis), most likely through cavitation-related phenomena. It is unclear whether the primary effect of ultrasound is on the skin or on the drug to be delivered. The purpose was to elucidate which of these two possibilities is responsible for sonophoresis.

Introduction

The transdermal route of drug delivery offers a non-invasive and painless alternative to more traditional routes such as injection. However, skin represents a highly impermeable barrier for most drugs, and it is difficult to deliver therapeutically relevant doses. Therefore methods which enhance permeability are needed to broaden TDD’s clinical applicability. Sonophoresis, enhancement of transport due to ultrasound application, is one such method.

Most investigations of sonophoretically-enhanced transdermal drug delivery have focused on the application of ultrasound in the therapeutic frequency range (~ 1 MHz). These investigations have yielded small but statistically significant enhancements in the transport of several model drugs. The enhancements are dramatically increased when, instead of applying ultrasound in the therapeutic range, low frequencies (~ 20 kHz) are used. The inverse relationship between frequency and enhancement of transport is consistent with the hypothesis that cavitation-related events play a key role in sonophoretic mechanisms. This hypothesis has been supported by a number of experimental results. However, which cavitation-related events are primary factors in sonophoretic mechanisms is unclear. This paper reports the results of experiments designed to explore which cavitation-related events are most important for sonophoresis and to decide whether the primary interaction is convection of the drug, or alteration of skin structure.

Materials and Methods

The details of the experimental protocol is described elsewhere. Transport experiments were performed at room temperature using full thickness pig skin, mounted onto a diffusion cell (Crown Glass Co. and Permegear) with the stratum corneum side facing the donor compartment. The receiver compartment was filled with Phosphate Buffered Saline, stirred, and counted using a scintillation counter (model 2000 CA, Packard) and the donor compartment was filled with a solution of radiolabelled mannitol (10 μCi/ml (NEN)). Ultrasound was applied using a sonicator (VCX 400, Sonics and Materials) operating at a frequency of 20 kHz in the pulsed mode (0.1 seconds on, 0.9 seconds off). Ag/AgCl electrodes measured skin electrical conductivity before, during, and after the ultrasound exposure.

Results and Discussion

Figure 1 shows the dependence on intensity of 1) the transport of mannitol, 2) skin conductivity, 3) number of pits on a foil at the position of the skin, and 4) the subharmonic component. It is clearly seen that all four variables display similar dependence on intensity, and that there is a sharp threshold somewhere between 2 W/cm² and 12 W/cm² (values for intensity were derived based on manufacturer’s claims for tip displacement).

Our first objective was to ascertain which type of cavitation - stable or transient - was primarily responsible for the observed transport effects. At low intensities there was a relatively small subharmonic component. At higher intensities higher there was a sharp increase in the subharmonic component.
which was constant over the remainder of the measured range. Thus, the threshold for transient cavitation corresponds to thresholds observed in all of the other parameters evaluated, suggesting that enhanced transport is associated primarily with transient cavitation.

Next, we attempted to determine which transient cavitation-related phenomenon (e.g. shock waves, microjets) contributed to the observed effects. In a simple attempt to quantify the amount of microjetting in our system, we replaced the skin with a piece of aluminum foil, and sonicated under otherwise identical conditions. This yields foils with visible, easily observed pits. There is good agreement between the number of pits counted at each intensity and the corresponding transport data. The radii of the pits were essentially constant for all intensities tested (data not shown). It is important to note that the difference between the surface properties of skin and those of foil make direct conclusions concerning “pitting” of skin impossible. However, the correlation between this curve and transport suggests that microjetting in the donor solution near the skin may mediate enhanced transport.

Microjetting could cause enhanced transport in at least one of two ways. First, it could actively convect drug into the skin, thus acting on the drug itself. On the other hand, it could also act to disorder skin structure, thus creating new pathways through which passive diffusion of drug could occur. The conductivity of the skin is a direct measurement of the skin’s barrier properties. When ultrasound was applied, the skin’s conductance was increased. When ultrasound was turned off, the conductivity dropped slightly, but remained elevated well above control levels throughout the remainder of the experiment. This lends support to the hypothesis that ultrasound affects the barrier properties of the skin. The correlation between conductivity - a measure of structural changes in the skin - and transport supports the hypothesis that changes in the skin’s properties are responsible for enhanced transport.

Conclusions

These results suggest that sonophoresis may enhance transport through a microjet-related phenomenon in which microjets from the donor solution impinge on the skin’s surface, disordering the bilayers of the skin and creating new pathways through which drug may diffuse. Further work is currently underway to test this hypothesis.

Acknowledgements

Financial Support for this work was provided by NIH, BSF, ADA, and JDF.