Application of the Aqueous Porous Pathway Model to Quantify the Effect of Sodium Lauryl Sulfate on Ultrasound-Induced Skin Structural Perturbation

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ABSTRACT: This study investigated the effect of sodium lauryl sulfate (SLS) on skin structural perturbation when utilized simultaneously with low-frequency sonophoresis (LFS). Pig full-thickness skin (FTS) and pig split-thickness skin (STS) treated with LFS/SLS and LFS were analyzed in the context of the aqueous porous pathway model to quantify skin perturbation through changes in skin pore radius and porosity-to-tortuosity ratio (ε/τ). In addition, skin treatment times required to attain specific levels of skin electrical resistivity were analyzed to draw conclusions about the effect of SLS on reproducibility and predictability of skin perturbation. We found that LFS/SLS-treated FTS, LFS/SLS-treated STS, and LFS-treated FTS exhibited similar skin perturbation. However, LFS-treated STS exhibited significantly higher skin perturbation, suggesting greater structural changes to the less robust STS induced by the purely physical enhancement mechanism of LFS. Evaluation of ε/τ values revealed that LFS/SLS-treated FTS and STS have similar transport pathways, whereas LFS-treated FTS and STS have lower ε/τ values. In addition, LFS/SLS treatment times were much shorter than LFS treatment times for both FTS and STS. Moreover, the simultaneous use of SLS and LFS not only results in synergistic enhancement, as reflected in the shorter skin treatment times, but also in more predictable and reproducible skin perturbation. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:1387–1397, 2011

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INTRODUCTION

Enhancement of skin permeability by the application of ultrasound is referred to as sonophoresis. Although the use of ultrasound for transdermal delivery of therapeutics dates back to the 1950s, extensive research in this area has only taken place in the past two decades.[1,2] In the early years of sonophoresis research, therapeutic frequencies ranging from 1 to 3 MHz were most common.[3–5] However, a significant shift in the methodology and understanding of sonophoresis took place once the switch was made to low-frequency sonophoresis (LFS, utilizing frequencies in the range of 20–100 kHz) because it was possible to achieve even greater skin permeability enhancements compared with therapeutic frequencies.[6] Following this change, research on the mechanisms of LFS showed conclusively that cavitation above the skin, in the aqueous coupling medium, is the primary mechanism of enhancement.[7,8] Much of this initial mechanistic research involving LFS was performed by utilizing pure aqueous media containing no chemical enhancers in the coupling solution.[6–9] However, another breakthrough in the field occurred when it was shown that combining LFS with a chemical enhancer, specifically a surfactant such as sodium lauryl sulfate (SLS), caused a synergistic effect, resulting in orders-of-magnitude improvements in skin permeability enhancement over the application of LFS alone.[10–14] Since that time, the synergistic effect between chemical enhancers (mainly SLS) and LFS has been well documented,[2,10–12,15] although the precise physical mechanisms responsible for the observed synergism are still not well understood. Nearly all previous studies on LFS/SLS synergism have focused primarily on the effect of a simultaneous SLS and LFS treatment to increase skin permeability to different solutes. Although the extent to which LFS/SLS

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enhances skin permeability, relative to LFS alone, is generally well understood, very little is known about how these synergistic enhancers affect the skin structure itself. To date, only a small number of publications have commented on the structural changes in skin treated with LFS/SLS and LFS.[16–18] These studies provided useful microscopy-based insight into the structural changes that occur when LFS/SLS and LFS are applied to the skin. In the present study, the aqueous porous pathway model is implemented to probe changes in skin structural parameters and to draw quantitative conclusions about the role of SLS in inducing skin perturbation.

With the above in mind, it is clear that a quantitative study investigating the effect of LFS/SLS on skin structural parameters, compared with that of LFS alone, would provide significant insight on how adding SLS to the LFS coupling medium affects skin perturbation. Furthermore, LFS/SLS combines both physical and chemical enhancement mechanisms, whereas LFS acts solely in a physical manner. It is likely that the mechanical properties of the skin model used may also play an important role in determining the extent of skin perturbation.[9,19,20] Specifically, pig full-thickness skin (FTS), which possesses a full dermal backing, may impart increased mechanical support to the skin in response to the physical perturbation induced by LFS, relative to pig split-thickness skin (STS, dermatomed to 700 μm thickness). In fact, Seto et al.[19] have recently shown that when treating skin with LFS/SLS at 20 kHz, the thickness of the skin plays a significant role in determining the extent of skin perturbation in human skin models (250 μm STS, 700 μm STS, and FTS), whereas in pig skin models, skin thickness does not play a significant role (700 μm STS and FTS). Moreover, the difference in LFS/SLS treatment times for pig and human 700 μm STS led the authors to propose that intrinsic skin differences (e.g., dermal elastic fiber content) may explain the observed differences.[19] In this manuscript, we utilize an approach similar to the one used by Seto et al.[19] to gauge overall skin perturbation. Specifically, we utilize the aqueous porous pathway model to calculate two skin structural parameters: (i) log C, which is related to the average radius of the aqueous skin pores and (ii) the porosity to tortuosity ratio (ε/τ). We compare the structural parameters of skin treated with LFS/SLS and LFS to that of untreated skin (for both FTS and STS) to better understand the effect of SLS on skin structural perturbation and transdermal pathways when utilized in combination with LFS. Furthermore, we also explore the reproducibility and predictability of the LFS/SLS and LFS treatments by comparing: (i) the width of the 95% confidence intervals for the structural parameters calculated, (ii) the correlation coefficient observed between the permeability and the resistivity of skin samples (see Theory section), and (iii) the trends observed in treatment times for skin samples treated to different extents of skin electrical resistivity. Clearly, the reproducibility and predictability of skin permeability enhancement are essential for the successful clinical implementation of this technology.[21,22]

With the above motivation and background in mind, it is important to stress that the study presented here is unique in that it investigates the synergism between LFS and SLS in the context of quantifying skin structural perturbation while utilizing a fixed skin electrical resistivity protocol. It is noteworthy that previous studies have focused primarily on fixed treatment time protocols (typically treating skin samples with LFS for 10 min in the presence and in the absence of SLS).[11,12,15] The present study differs from the previous ones because we treated skin samples with both LFS/SLS and LFS to attain a wide range of skin electrical resistivity levels, allowing treatment times to vary in order to reach those levels. This modification in the treatment protocol is significant because treating skin samples with LFS for a fixed period of time does not ensure that the skin samples are perturbed to any significant extent. Indeed, skin permeability enhancement is usually modest under this type of treatment protocol because LFS application for 10 min results in just a 1.5-fold enhancement in skin electrical resistivity.[12] Note that this is a very small extent of skin electrical resistivity enhancement, considering that skin hydration itself can cause similar extents of enhancement during a 24-h period.[12] Accordingly, in the present study, we require that LFS be applied to attain greater enhancements in skin electrical resistivity, which allows us to better understand the effect of the purely physical enhancement mechanism associated with LFS, relative to the combined physical and chemical enhancement mechanisms associated with LFS/SLS.

Along the lines discussed above, the objectives of the present study are to explain: (i) how the extent of skin perturbation differs between skin samples treated with LFS/SLS and LFS, in the context of the aqueous porous pathway model, (ii) how ε/τ ratios differ between skin samples treated with LFS/SLS and LFS, (iii) how the amount of mechanical support (i.e., the thickness of the dermis in the skin model considered) affects the extent of skin perturbation in samples treated with LFS/SLS and LFS, and (iv) how the reproducibility and predictability of skin permeability enhancement and treatment times of skin samples treated with LFS/SLS compared with those of skin samples treated solely with LFS. Addressing (i)–(iv) will help explain the role of SLS in inducing skin structural perturbation, including the role of SLS in enhancing transdermal transport.