J. Contr. Rel., 92, 137-146 (2003)

Characterization of Transdermal Solute Transport Induced by Low-Frequency Ultrasound in the Hairless Rat Skin

Mizue Mutoh（武藤香絵）,[1] Hideo Ueda（上田秀雄）,[1] Yasushi Nakamura（中村恭士）,[1] Kotaro Hirayama,[2] Mahito Atobe,[3] Daisuke Kobayashi（小林大介）,[1] Yasunori Morimoto（森本雍憲）[1,4,5]

[1]Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan.
[2]Dai-ichi High Frequency Co., Ltd., 2-17-8 Tonomachi, Kawasaki 210-0821, Japan.
[3]Department of Electronic Chemistry, Tokyo Institute of Technology, Nagatsuta, Yokohama 226-8502, Japan.
[4]Research Institute of TTS Technology, 1-1 Keyakidai, Sakado, Saitama 350-0295, Japan.

Sonophoretic drug transport with low-frequency (41-445 kHz) and low-intensity (60-240 mW/cm^2) ultrasound was characterized using hydrophilic calcein and deuterium oxide (D_2O) as a solvent vehicle in excised hairless rat skin. The excised skin was mounted in vertical diffusion chambers for measurement of skin resistance and sonophoretic transport of calcein and D_2O. The calcein content of the skin was also measured after ultrasound application. When the stratum corneum (sc) side was exposed to ultrasound at an intensity of 60 mW/cm^2 for 30 min, the calcein flux in the sc-to-dermis direction was increased by 22.3-, 6.3-, and 3.8-fold from a baseline of 0.0088 ± 0.0100 nmol/(cm^2・h) at frequencies of 41, 158, and 445 kHz, respectively, without significant changes in skin resistance. The ultrasonically-enhanced fluxes returned to baseline following cessation of the ultrasound application. At 41 kHz, there was a further increase in the magnitude of enhancement and a significant decrease in skin resistance (by 50% of the baseline resistance) on increasing the intensity from 60 to 120 mW/cm^2, whereas no further enhancement was observed at 158 and 445 kHz up to 240 mW/cm^2. Comparison of the calcein content in the skin before, during, and after ultrasound application at 41 kHz, 120 mW/cm^2, was consistent with a transient ultrasonically-induced

increase in calcein flux. In the sonophoretic transport experiments at 41 kHz, 120 mW/cm^2, calcein transport correlated well with D_2O transport. When 41 kHz ultrasound was applied to the sc side at 120 mW/cm^2, the calcein and D_2O fluxes in the sc-to-dermis direction were 13.7- and 5.2-fold higher than those in the dermis-to-sc direction. Similar directionality was also observed in tape-stripped skin, suggesting possible induction of convection in the direction of sound propagation. However, dermal application under the same ultrasound conditions induced neither an increase in calcein and D_2O transport nor a decrease in skin resistance. These results demonstrate that low frequency sonophoresis is a potentially useful technique for controlling transdermal drug transport. Convective solvent flow as well as structural alteration of the skin induced by ultrasound is likely to be responsible for the observed sonophoretic transport enhancement.