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Enhancing transdermal drug transport with low-frequency ultrasound

The recent completion of the human genome project and advances in molecular biology techniques have enabled the discovery and characterization of many peptides, proteins or polynucleotides as potentially novel drugs. Because these molecules are metabolically labile and undergo extensive enzymatic degradation, they cannot be administered to patients by the traditional oral route. Hence, pharmaceutical scientists have explored alternative modes of administration, such as the transdermal route, for the effective systemic delivery of these compounds.

Transdermal drug delivery offers several advantages over traditional drug delivery systems such as oral delivery and injections: the attractive attributes of transdermal drug delivery include avoidance of first-pass metabolism, elimination of pain that is associated with injection and the opportunity for the sustained release of drugs. However, the efficacy of the transdermal transport of molecules is low because the stratum corneum of the human skin is an effective and selective barrier to chemical permeation [1]. Indeed, the low permeability of the stratum corneum is the key reason that only a small number of low molecular weight drugs are currently administered using this route [2]. In a recent issue of *Drug Discovery Today*, Lavon and Kost [3] provide an excellent and comprehensive overview on the use and mechanism of low-frequency ultrasound to promote the transdermal transport of drugs, which could have applications in drug delivery as well as transdermal monitoring.

The biophysical modes of ultrasonic action on a biological system can be classified into two categories – thermal mechanisms and non-thermal mechanisms [4,5]. The thermal effects of ultrasound, which is directly related to the intensity of the ultrasound, results from the transfer of energy from the vibrating pressure waves to the objects as the waves propagate through the medium. In transdermal applications, this energy is absorbed by the skin, which results in a rise in skin temperature. Although literature supports the observation that increasing temperature leads to enhanced skin permeability [6], recent studies indicate that thermal effects play an insignificant role in promoting transdermal drug transport that is effected using low-frequency ultrasound [7,8]. For example, low-frequency ultrasound (20 KHz at 15 W cm^{-2} for 2 h) caused a 20°C rise in temperature that resulted in 35-fold increase in the level of mannitol delivered across porcine skin *in vitro*. By contrast, when the skin was heated (in the absence of ultrasound) to produce a thermal profile that is comparable to the thermal profile generated by ultrasound, the permeability of mannitol increased by only 25% [8]. These data indicate that the key mechanism responsible for the observed skin permeability is related to the non-thermal effect of ultrasound. Although the mechanism for improved transdermal transport by ultrasound is not well understood and has yet to be characterized fully, a consensus has been reached that acoustic cavitation is responsible for low-frequency sonophoresis.

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Gene expression analysis enriched

The use of DNA microarrays to identify genes that are upregulated or downregulated is a crucial component in