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A novel thermo-mechanical system enhanced transdermal delivery of hydrophilic active agents by fractional ablation

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ABSTRACT

The Tixel is a novel device based on a thermo-mechanical ablation technology that combines a sophisticated motion and a temperature control. The fractional technology is used to transfer a very precise thermal energy to the skin thereby creating an array of microchannels, accompanying by no signs of pain or inconvenience. This study aimed to evaluate the effect of the Tixel on the skin permeability of three hydrophilic molecular models: verapamil hydrochloride, diclofenac sodium, and magnesium ascorbyl phosphate. Tixel's gold-platted stainless steel tip heated to a temperature of 400 °C was applied on skin for 8 ms or 9 ms at a protrusion of 400 μm (the distance in which the tip protrudes beyond the distance gauge). The experiments were carried out partly *in vivo* in humans using a fluorescent dye and a confocal microscopy and partly *in vitro* using porcine skin and a Franz diffusion cell system. The results obtained in this study have shown that (a) no significant collateral damage to the skin tissue and no necrosis or dermal coagulation have been noted, (b) the microchannels remained open and endured for at least 6 h, and (c) the skin permeability of hydrophilic molecules, which poorly penetrate the lipophilic stratum corneum barrier, was significantly enhanced by using Tixel's pretreatment.

1. Introduction

Transdermal drug delivery has been well-established as a potentially advantageous alternative for many therapeutically active compounds to the parenteral and oral routes. The adverse effects due to fluctuations in plasma drug levels, the high portion of hepatic first-pass metabolism (or other factors leading a low bioavailability), as well as a short biological half-life have been important reasons to intensively explore ways how to circumvent the skin barrier. The highly lipophilic nature of the skin provides the main barrier for influx of drugs and environmental chemicals into the body. The lipophilic properties are related to the outermost keratinizing layer, the stratum corneum (10–20 μm thickness), which is impermeable to most therapeutically active compounds, in particular high-molecular weight, hydrophilic or charged substances. Nonetheless, the advantages of transdermal drug delivery have motivated intensive research activity for the purpose of circumventing the skin barrier with optimal solutions (Barry, 2001; Davis et al., 2002). Various methods have been studied, such as those based on chemical enhancers (Walters, 1989; Smith and Maibach, 1995; Ben-Shabat et al., 2007), or those rely on physical techniques including microneedles (Henry et al., 1998; McAllister et al., 2000), iontophoresis (Singh et al., 1999; Marro et al., 2001; Guy et al., 2001 Sintov and Brandys-Sitton, 2006), electroporation (Prausnitz et al., 1993; Riviere et al., 1995; Vanbever et al., 1994, 1996; Prausnitz, 1999; Hu et al., 2000), ultrasound (Ogra et al., 2008), as well as a diversity of thermal ablation techniques (Sintov et al., 2003; Park et al., 2008; Bachhav et al., 2010, 2013; Lee et al., 2011). Thermal ablation for transdermal drug delivery has included lasers (Bachhav et al., 2010, 2013), radiofrequency (Sintov et al., 2003), or superheated steam (Lee et al., 2011) devices. A pioneering work by Park et al. (2008) has shown, by screening a broad range of temperatures (25°–315 °C) and durations (100 ms–5 s), that skin permeability strongly depends on the temperature and less on the duration of heating so even shorter durations (i.e., on a microsecond timescale) might be sufficient. Lee et al. (2011) later developed a microdevice that ejects superheated steam during only 100 μs at the skin surface, demonstrating a selective removal of stratum corneum of cadaver skin without significant collateral damage to the inner tissue. Recently, a thermo-mechanical ablation (TMAb) technology has been proposed (Lask et al., 2012; Elman et al., 2016), demonstrating

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