three cyclic terpenes of limonene (a hydrocarbon), eucalyptol (an ether), and α-pinene oxide (an epoxide), and one linear terpene (geraniol; an alcohol). These terpenes have molecular weights of 136 to 154 Da and logP values of 2 to 4.6. The obtained enhancement ratio (ER) values showed that all terpenes, irrespective of their types, increased silver sulfadiazine permeation. Limonene showed the most (ER = 9) and α-pinene oxide had the least (ER = 4.3) enhancement effects on silver sulfadiazine permeation through eschar. ER values of geraniol and eucalyptol were 5.5 and 4.7, respectively. There was a good correlation between Log partition coefficients of terpenes and the effects of terpenes on silver sulfadiazine permeation through eschar. The authors concluded that the main mechanism by which terpenes increased the permeation of silver sulfadiazine through eschar was probably improvement of drug partitioning into the eschar; limonene (logP 4.6) showed the highest effect.

Enzymes have also been investigated as eschar permeation enhancers. Permeation of clindamycin phosphate through hydrated third-degree burn eschar pretreated with trypsin solution (1% w/v) has shown that this protease is capable of reducing eschar barrier performance toward this drug in comparison to untreated (control) samples (Ghaffari et al. 2013), possibly by digesting the protein domains available in the eschar structure. This study has also shown that the enhancement effect of trypsin is time-dependent. The clindamycin phosphate enhancement ratio after trypsin pretreatment was shown to be 1.5 and 2.3 for 4 and 24 hours pretreatment times, respectively. Trypsin treatment of eschar for 24 hours caused perforation of some eschar samples. The authors concluded that protein-acting enhancers might be a reasonable approach for improving eschar permeability.

According to these studies, chemical enhancers are able increase the permeation of hydrophilic and hydrophobic drugs, and their effectiveness depends on the structure and physicochemical properties of both permeants and enhancers.

62.5.2 Improvements by Physical Enhancement Methods

Many physical enhancement methods are available to increase the skin permeation of drug molecules such as sonophoresis, iontophoresis, electroporation, and microneedles (Dragicevic et al. 2018). Here, the studies are reviewed in which the effects of physical enhancement methods on permeation of compounds through burn eschar have been studied.

The effects of cathodic and anodic iontophoresis on permeation of clindamycin phosphate through hydrated third-degree burn eschar were investigated using Franz-type diffusion cells by Moghimi's group (Sharif Makhmal Zadeh 2006). Since the charge of this molecule depends on the degree of protonation of the amine and phosphate groups, the researchers applied two drug solutions with pH values of 5.8 and 8 as the donor phase in their permeation studies. Although anodic iontophoresis at a pH of 5.8 was not effective, permeation of clindamycin phosphate was dramatically increased by applying cathodic iontophoresis, especially at pH of 8 (about fiftyfold increase in flux). Given the pKa of this drug, the researchers believed that in the case of cathodic iontophoresis, electromigration force and in the case of anodic iontophoresis, electroosmosis flow were the main causes of increased permeation of clindamycin phosphate through burn eschar.

In another study conducted by Moghimi's group (Ghaffari 2011), the influences of sonophoresis on the permeation of clindamycin phosphate (clogP: 1.0) and diazepam (clogP: 2.6) (Tetko et al. 2005, VCCLAB 2005) through third-degree eschar were studied using Franz-type diffusion cells. Low-frequency, high-intensity (20 kHz, 4 and 13 w/cm^2) and high-frequency, low-intensity (1MHz, 2 w/cm^2) ultrasound was applied in the permeation studies. Therapeutic ultrasound (high-frequency, low-intensity) failed to increase drug permeation, but low-frequency, high-intensity ultrasound increased the permeation of both drugs through minimal-thickness eschar. Enhancement ratios for clindamycin phosphate and diazepam were 15.4 and 2.76, respectively. Sonophoresis led to perforation in some eschar samples. The authors believed that sonophoresis might be a reasonable approach to increase drug permeation through eschar, especially in thin membranes.