permeation across the intact skin is the transepidermal pathway for most compounds. Two permeation routes exist in the stratum corneum: intercellular and intracellular pathways. The intercellular route is the main permeation pathway for most hydrophilic and lipophilic compounds (Moghimi et al. 1998). Due to the hydrophobic nature of the intercellular space and its structural properties, lipophilic (logP 1 to 3) and low-molecular-weight compounds (less than 500 Da in the most ideal state) are more susceptible to permeating this barrier (Gorouhi et al. 2009).

Drug delivery to burned skin encounters challenges when eschar is present. Eschar does not have a stratum corneum, which is an important barrier, but this does not result in the loss of its barrier properties. The barrier performance of eschar is sufficient to inhibit permeation of molecules, especially those of a larger size (Moghimi et al. 2009b, Grice et al. 2017). Unfortunately, opposite to intact skin, there is no well-understood pathway for permeation through eschar. Eschar is a melting pot of proteins and lipids; therefore it might be considered a barrier for both hydrophilic and lipophilic permeants (Jelenko et al. 1967, 1968). Following is an attempt to define more about the nature of eschar by reviewing those works that evaluated the permeation of molecules across it.

Is the eschar a permeable tissue at all? Yes, but like normal skin, it has barrier properties, and permeation through it depends certain variables (Rode et al. 1981, Stefanides et al. 1976, Gray et al. 1991). This property was observed in our group with diazepam, nitroglycerin, clindamycin phosphate, chlorhexidine digluconate, and silver sulfadiazine (Ghaffari et al. 2013, Manafi et al. 2008, Moghimi et al. 2009a, Sharif Makhmal Zadeh et al. 2010)

Using the agar diffusion technique and burn clinical isolates, Stefanides et al. evaluated the penetration of topical antimicrobial agents (e.g., gentamicin sulfate, mafenide acetate, nitrofurazone, povidone-iodine, silver nitrate, and silver sulfadiazine) through human eschar. After placing eschar samples or paper discs (as control) on the surface of agar on the inoculated plates, antimicrobial agents were delivered to the center of the eschar or paper disc individually. The plates were then incubated 24 hours and after that the diameter of the inhibition zone (as a measure of antimicrobial agents' permeability across the eschar) was measured and interpreted. Apart from silver nitrate, which did not penetrate even across the paper disc in an effective amount, the remainder of antimicrobial agents penetrated the eschar and showed activity post-penetration (Stefanides et al. 1976).

Although eschar is a permeable tissue, permeation of some antimicrobials through this tissue is insufficient to achieve therapeutic levels (Herruzo-Cabrera et al. 1992, Ward et al. 1995). It has been suggested that chemical penetration enhancers or physical enhancement methods might be used to alter the barrier performance of the burn eschar, as discussed next. These approaches have been applied to increase the permeation of drug molecules across the intact skin.

### 62.5.1 Improvements by Chemical Penetration Enhancers

Different chemicals such as terpenes, sulphoxides, pyrrolidines, fatty acids, fatty alcohols, azones, alcohols and glycols, surfactants, and so on have been used as penetration enhancers to increase permeation of drugs through different biological barriers such as skin over decades (Williams et al. 2004). Such an approach has also been used to increase the permeation of different agents through burn skin and eschar (Table 62.1 and Figure 62.1). These studies are addressed here, and the effects of chemical penetration enhancers on the barrier properties of eschar are discussed.

Moghimi's group (Manafi et al. 2008) investigated the effects of chemical penetration enhancers on the permeation of chlorhexidine gluconate, silver sulfadiazine, and nitroglycerin across human third-degree burn eschar. Antimicrobial studies using plate method and ex vivo permeation studies using diffusion cells were conducted to evaluate the effects of chemical enhancers on the permeation of these drugs through burn eschar. Different classes of enhancers were used in this study, including those expected to mainly influence the membrane hydration (water, NaCl, glycine, and glycerin), those that seemed to mainly affect the lipid domain fluidity (n-hexane, citral, and ethyl acetate), and finally those that affect both hydration and lipid domain (ethanol, urea, and sodium dodecyl sulfate). Chlorhexidine gluconate and silver sulfadiazine were included in the microbial