was due to the action of the propylene glycol within the stratum corneum that provided enhanced minoxidil flux.

Vehicle uptake into the membrane can strongly influence skin permeation. We have shown that the maximum flux across human epidermis for a series of 10 similarly sized phenols with a range of lipophilicities was determined by solute solubility in the stratum corneum [82], which was dependent on the amount of vehicle penetrating into the stratum corneum [83]. The maximum flux and stratum corneum solubilities generally increased with the percentage of propylene glycol in the binary propylene glycol:water solvent system (60%, 40%, or 0%) but that the estimated phenol diffusivities appeared to be vehicle independent. The maximum fluxes were related to vehicle-dependent stratum corneum solubilities, which depended on the amount of vehicle absorbed into the stratum corneum and the amount of phenolic compound dissolved in that absorbed vehicle. In a subsequent study, this was extended to include other polar and lipophilic vehicles (mineral oil, isopropyl myristate) [84]. In this case maximum fluxes for the phenols were similar for mineral oil and water. However, for the isopropyl myristate and propylene glycol:water vehicles, the fluxes were higher for the more polar phenols due to a higher diffusivity and higher solubility in the stratum corneum, respectively. Whereas the maximum flux for the phenols was directly related to solubility in the stratum corneum independent of vehicle, increasing phenol lipophilicity increased and decreased the permeability coefficient for aqueous and lipophilic solvents, respectively. The authors also noted that although the maximum fluxes for phenols with a similar molecular size and varying lipophilicity were comparable between water and mineral oil vehicles, they were higher for the isopropyl myristate and propylene:glycol water vehicles.

Attempts have been made to relate vehicle physicochemical properties and flux across the skin, most importantly by the use of solubility parameters (δ), as described earlier in this chapter. Given the importance of formulation vehicle solvents to skin delivery via both diffusivity and membrane partitioning effects, a means of predicting their effect based on the properties of the permeant and vehicle would be very useful.

17.6.2 Emulsifiers

Surfactants are included in many topical products to solubilize lipophilic ingredients and stabilize emulsion-based formulations. They are generally composed of a lipophilic fatty chain and a hydrophilic head group, a structure that allows them to lower interfacial tension between oil and water, thus stabilizing one phase as dispersed droplets within the other. Surfactants are categorized according to the ionic nature of their head group: anionic (negative charge), cationic (positive charge), nonionic, or zwitterionic (amphoteric: carry both cationic and anionic moieties). As surfactants are common ingredients in topical formulations, their effect on percutaneous absorption has been extensively studied. Anionic (e.g., sodium lauryl sulphate) and cationic surfactants tend to be an irritant, causing transepidermal water loss and damage to the stratum corneum. They can modify the binding of water, possibly through extraction of natural moisturizing factor and/or stratum corneum lipids, leaving the skin dry and brittle. Nonionic surfactants (e.g., poloxamers [Pluronics, Kolliphor], sorbitan esters [Spans], polysorbates Tweens]) are less irritating and are more widely used, but have low direct permeation enhancement activity, though their presence in a formulation may facilitate solubility and permeation.

17.6.3 Viscosity Modification

Topical products are required to spread easily and smoothly on the skin, with good skin retention. This is achieved through modification of the viscosity, with a wide range of polymers available for the purpose, including carbomers (Carbopol), celluloses, and carrageenan. Incorporating viscosity modifiers in a formulation may hinder drug diffusion from the formulation into the skin, but the evidence is controversial. Although the permeability coefficient of estradiol was significantly