solvents. Laurocapram enhanced and retarded DEET permeation in propylene glycol and polyethylene glycol 400 (PEG 400), respectively. Dimethyl-N-(2-methoxycarbonyl benzene sulfonyl) iminosulfurane retarded permeation of DEET with ethanol and PEG 400, but not with water or propylene glycol. Mechanistic studies by differential scanning calorimetry and infrared spectroscopy techniques showed that the permeation modifiers that enhanced permeation acted mainly by disruption and fluidization of the lipid bilayers, whereas permeation retardation was mainly through strengthening of the lipid–protein complex and improved organization of the stratum corneum lipids through H-bonding [73].

17.6 FORMULATION COMPOSITION

A typical topical formulation is composed of a number of ingredients that provide a physically stable product with good efficacy, skin feel, and patient acceptance. Common ingredients are:

- Dispersing and/or solubilizing agent (e.g., water, propylene glycol, ethanol)
- Emollient (oil, humectant)
- Emulsifier (most commonly a combination of nonionic surfactants)
- Viscosity modifier (e.g., carbomer, carrageenan, alginates, cellulose derivative)
- Preservatives
- Coloring, fragrance (volatile oils, terpenes)

17.6.1 Solvents and Cosolvents

One of the primary ingredients in a topical formulation is a solubilizing agent, chosen based on the hydrophilic or hydrophobic nature of the permeant. It is common practice to apply the cosolvent method, where two miscible solvents are mixed, to increase solubility in a formulation [10, 74]. For example, the solubility of the lipophilic, active compounds ibuprofen and estradiol in ethanol:water cosolvent mixtures can be increased by 5500-fold and 30-fold relative to their aqueous solubility, respectively, as the amount of ethanol is increased from 0% to 100% [75].

As discussed earlier, many of the solvents and cosolvents used in topical formulations are known to influence the barrier properties of the skin. Ethanol and other small alcohols, such as isopropyl alcohol, are commonly used in topical and personal care formulations (e.g., hydroalcoholic gels) and transdermal patches. They permeate rapidly into the stratum corneum and can enhance the flux of both hydrophilic and lipophilic permeants [76–78]. They are miscible with water and form optimal cosolvent mixtures at particular compositions (e.g., around 60% ethanol:water), above which permeation enhancement declines, most likely due to dehydration of the stratum corneum at high alcohol content. At high concentrations, ethanol may extract intercellular lipids.

The fatty alcohol propylene glycol is a colorless and viscous liquid that is commonly used as a cosolvent in topical formulations at 1% to 10% [79, 80]. It acts in a similar way to ethanol but is a milder solvent that is less likely to extract lipids. A binary mixture of propylene glycol:water was shown to provide a linear enhancement in ibuprofen flux across excised skin with increasing propylene glycol content, with the effect attributed primarily to increased solubility and partitioning of ibuprofen [10]. Propylene glycol has also been shown to act synergistically with other enhancers, including Azone, oleic acid, and terpenes.

Grice and colleagues [81] investigated the influence of ternary combinations of ethanol:propylene glycol:water on minoxidil uptake into appendages, stratum corneum, and through human skin *in vitro*, reporting a change in the transport mechanism of minoxidil over time. At early time points (up to 12 hours), formulations containing the highest ethanol:propylene glycol ratio provided higher minoxidil uptake, which was attributed to the evaporation of volatile ethanol leading to increased minoxidil concentrations in the skin. After 12 hours the maximal flux was obtained from the formulation with the lowest ethanol:propylene glycol ratio, which the authors suggested