skin lipid after 2 hours of treatment by changes in the lipid peak. The lipid disruption of the skin decreased the barrier effect by SC lipid fluidization and increased the permeability. The results also showed that propylene glycol and oleic acid improved their diffusion and created faster, yet reversible changes of the skin peaks.

55.5.2.1.2 Combination of Penetration Enhancers and Active Substances

As previously mentioned, studies using CRM are useful to evaluate the disruption of the skin barrier by penetration enhancers. Choosing the best possible enhancer to improve the skin absorption of a specific active molecule is an important task in drug formulation design. CRM is helpful to track simultaneously enhancers and active drugs in the skin. The best strategy to enhance cutaneous drug delivery is to combine a drug and an enhancer with similar penetration profiles and distribution patterns. If the fluxes or distribution of both molecules is different, the flux of the active molecule may decrease because of its partial recrystallization in the skin. Several examples are reported next.

55.5.2.1.2.1 Lipophilic drugs **Retinol and derivatives.** The penetration of β-carotene, a lipophilic molecule (log$P$ = 17.62, M_W = 537 g·mol^{-1}) dissolved in DMSO, using CRM was studied by Ashtikar et al. (2013). Three main bands were used to identify β-carotene in the skin, the C=C bound stretching at 1510 and 1153 cm^{-1} and the C-CH_3 bound rocking at 1004 cm^{-1}. Raman analysis showed that β-carotene hardly penetrated the skin; it was essentially found in the first 10 µm of the SC and presented a heterogeneous distribution. This result was quite expected with such a lipophilic molecule that shows poor skin permeability. DMSO may have enhanced the penetration of β-carotene, but this was not proved by the authors.

Trans-retinol is a common antiaging active substance (vitamin A) in cosmetic products. It is frequently used as a hydrophobic model drug in skin absorption experiments (Failloux et al. 2004; Pudney et al. 2007; Mélot et al. 2009). This molecule with a log$P$ = 5.68 mostly remains in the lipid phase of the superficial SC. Raman spectroscopy is an appropriate detection technique, as *trans*-retinol possesses a characteristic peak due to the C=C bond at 1594 cm^{-1} (Mélot et al. 2009) or 1585 cm^{-1} (Förster et al. 2011a), which is well-resolved from other peaks of major skin components (Figure 55.4).

Various types of penetration enhancers for *trans*-retinol were investigated such as glycol, nonionic surfactants, or fatty acids such as oleic acid.

Pudney et al. (2007) compared 0.3% *trans*-retinol applied in a propylene glycol (PG)/ethanol (EtOH) vehicle and in caprylic/capric acid triglyceride (Myritol 318), an oil widely used in skin

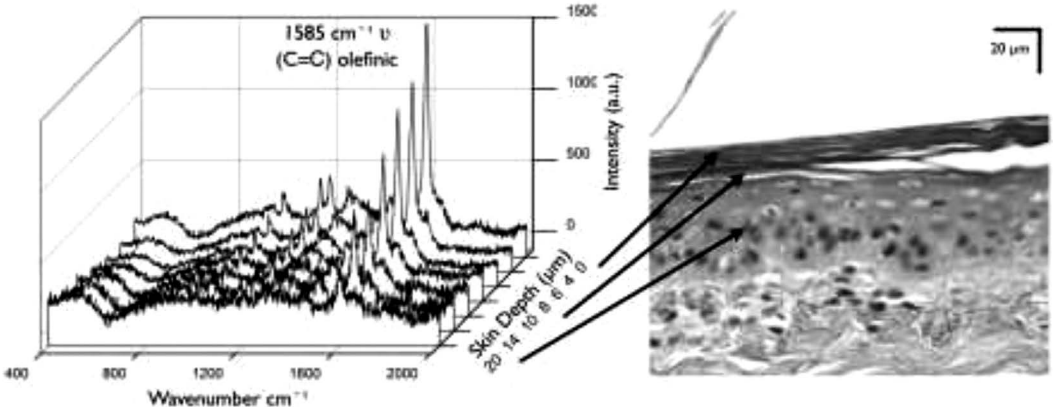

FIGURE 55.4 Raman spectra of pig skin after application of a surfactant solution containing 0.5% *trans*-retinol for 24 hours. The Raman profile was measured at the surface (0 µm) and at 2, 6, 8, 10, 14, and 20 µm skin depth. Arrows indicate skin depths in the image of histological section (magnification of ×40). (From Förster et al. 2011a with permission.)