creams. Retinol intensity–depth profiles revealed significantly greater penetration of *trans*-retinol from the PG/EtOH vehicle through the SC and into the viable epidermis; this penetration profile was correlated with that of PG alone. In contrast, penetration from capric/caprylic triglycerides was low. The correlation between the retinol and PG skin penetration suggested that PG is an efficient enhancer to promote *trans*-retinol penetration into the viable epidermis.

Mélot et al. (2009) monitored the effect of two penetration enhancers on the delivery of *trans*-retinol through human skin. Three formulations for the combination of 0.3% *trans*-retinol and Myritol 318 were tested: the first one (used as a control) contained no enhancer; the second one contained a lipid fluidizer, oleic acid; and the third contained a lipid extractor octoxynol-9 (Triton X100)—both enhancers were introduced at 1%. These were compared to the very efficient PG/EtOH vehicle. From Raman spectra acquired on the volar forearm of two male volunteers, concentration–depth profiles of *trans*-retinol and Myritol were obtained. Improved delivery of *trans*-retinol was observed with addition of the penetration enhancers in the formulation; oleic acid was found to be more efficient than Triton X100. In the absence of a penetration enhancer, the Raman signal of *trans*-retinol was mainly confined in the first 5 μm within the SC. *Trans*-retinol penetrated into deeper layers of the skin in the presence of each penetration enhancer. Oleic acid yielded penetration to the same depth as the PG/EtOH formulation; however, the amount of *trans*-retinol penetrated into the skin was tenfold higher from the PG/EtOH system. Oleic acid caused a phase separation in SC lipids because it is not miscible with the SC lipids.

Saar et al. (2010) used SRS (Section 55.3) to follow *trans*-retinol skin penetration in a living mouse by tuning the excitation wavelength to the vibration of *trans*-retinol, the C=C stretch at 1596 cm^{-1}. Images showed that penetration of *trans*-retinol occurred through the hair shaft. SRS was also used to image human skin in vivo up to a depth of 50 μm showing the localization of *trans*-retinol around the hair and in the top of the sebaceous gland.

Dos Santos et al. (2019) evaluated the penetration of retinyl acetate and alpha-tocopheryl acetate into young and elderly skin using in vivo CRM. Retinyl acetate (vitamin A acetate)– depth profiles did not differ significantly between the two age groups. Alpha-tocopheryl acetate (vitamin E acetate) penetration in the elderly SC was significantly lower than in the younger skin up to a depth of 12 μm, i.e., half of the SC depth probed. The different effect of age on the penetration of these two compounds is related to intrinsic changes in the skin coupled with the physicochemical parameters of the permeants in elderly skin using in vivo CRM. The authors argued that the decrease in lipid levels in elderly skin, which they observed via ceramide 3–depth profiling, hinders the partitioning of the highly lipophilic compound vitamin E ($\log P = 12.20$, $M_W = 431$ g·mol^{-1}) into the SC compared to vitamin A ($\log P = 9.40$, $M_W = 328$ g·mol^{-1}).

Anesthetic drugs. The penetration of procaine chlorhydrate, a local anesthetic, has been studied by CRM. Lunter and Daniels (2014) investigated the influence of the penetration enhancers propylene glycol and polyoxyethylene (POE)-23-lauryl ether on the penetration of procaine ($\log P = 2.14$, $M_W = 236$ g·mol^{-1}) contained in hydroxypropyl methylcellulose (HPMC)–poloxamer gels in cross-sections of porcine skin. The results of the CRM study were compared to those of a conventional skin penetration experiments in Franz cells. The HPMC–poloxamer gels containing a penetration enhancer and procaine were applied to the skin for 14 hours. The spectral range used for visualization of the procaine distribution in the skin covered the “fingerprint region” between 720 and 1820 cm^{-1}. For the calculation of color-coded images, the peak at 1600 to 1625 cm^{-1}, which results from the υ(C=C) (β NH_2)-scissoring mode, was used to identify procaine in the skin. For semi-quantitative analysis of the procaine content in the skin samples, the procaine peak (1600 to 1625 cm^{-1}) was normalized to the δ (CH_2, CH_3) mode (1430 to 1490 cm^{-1}). This procedure differs from the frequently used normalization to the signal at 2910–2950 cm^{-1} assigned to the υ(CH_3) mode of keratin. No traces of propylene glycol and POE-(23)-lauryl ether were detected in skin. Results indicated that the highest procaine content was found in the SC, corresponding to the highest intensity of the procaine relative peak. Without penetration enhancers, the procaine was detected to a depth of 20 μm. In presence of the propylene glycol, the procaine was also found in the skin up to a depth of 20 μm. With the formulation containing POE-(23)-lauryl ether, Raman imaging