several bands arising from 5-FU within the skin confirmed the hydrolysis of the pro-drug into drug. The difference of spectra recorded for treated and untreated skin disclosed the presence of both pro-5FU and 5-FU at depths of 2, 7, and 12 μm below the SC; the permeation into viable epidermis was not detected. Additionally, image planes of the spatial distribution showed that penetration of both species at 22°C was restricted to the SC, whereas both compounds were distributed throughout the SC and viable epidermis at 34°C, suggesting that hydrolysis was taking place in both the SC and in the viable epidermis. The highest relative amounts of drug with respect to pro-drug were observed in the viable epidermis at depths between 40 and 70 μm from the skin surface.

55.5.2.3 Tracking Formulation Excipients and their Influence on Skin Delivery

Mao et al. (2012) studied the distribution of alkyl chain perdeuterated sodium dodecyl sulfate (SDS-d_{25}) in human and porcine skin by CRM and IR. The band intensities of the CD_2 stretching vibrations were used for analysis of the permeation profiles of SDS-d_{25} in skin. The interaction between SDS and skin was evaluated through the CH_2 and CD_2 stretching frequencies and the amide I and II bands. The results indicated that SDS-d_{25} penetrated both porcine and human skin, with slightly deeper penetration through the SC of porcine skin. The chains of SDS are more ordered inside SC than in SDS micelles, giving evidence of an intercellular lipid penetration pathway for SDS in SC.

Binder et al. (2018) studied the penetration of sulfathiazole sodium (STZ) together with three excipients: sodium laureth sulfate (SLES), sodium dodecyl sulfate (SDS) and DMSO, in porcine skin by CRM and other methods. The penetration profiles of all compounds obtained by CRM and ATR-IR spectroscopy combined with tape stripping were comparable, showing good agreement between the methods. Both techniques showed the penetration depth increased in the order DMSO > SDS > SLES > STZ.

More recently, Binder et al. (2019) investigated the effect of viscosity of hydrogels made of hydroxyethyl cellulose (HEC) or hydroxypropyl methylcellulose (HPMC) on skin penetration of sulphadiazine sodium (SDZ) ($\log P = 0.39$, $M_W = 272$ g·mol^{-1}) by CRM and HPLC analysis. The SDZ was detectable at 1120 and 1600 cm^{-1} bands related to the SO_2 symmetric stretching of the sulfonamide group and a ring-stretching mode, respectively. Highly similar SDZ concentrations were observed in case of all gelled formulations, independently of the gelling agent concentration. This suggests that the specific viscosity of the investigated hydrogels had a subordinate effect on the skin penetration of SDZ. Conversely to drug amounts observed in the tape stripping studies, which were similar to CRM results, the penetration depths observed for SDZ showed a different trend. In fact, the gelling agent concentration seemed to have an influence on the total penetration depth of SDZ. In case of tape stripping, penetration depths between 47% and 78% of total SC thickness were observed. In case of CRM, these values ranged between 90% and 113% of SC thickness. For both hydrogels with HEC and HPMC, penetration depths were reduced as the viscosity of the gels increased. The diffusion of the model drug out of the formulation and into the skin might have been hindered by the high viscosity of the systems and thus resulted in a limited total penetration depth. In conclusion, drug distribution within the skin appeared to be affected by the viscosity of the vehicle. A direct comparison of the results obtained with the CRM and HPLC analysis revealed different absolute drug penetration depths. However, similar trends could be observed despite the varied experimental setup. The authors concluded that moderately enhanced hydrogel viscosity is advisable to allow for convenient dermal application while maintaining satisfactory skin penetration.

Bakonyi et al. (2018) investigated and compared the penetration profiles of four different lidocaine-containing formulations in human skin (hydrogel, oleogel, lyotropic liquid crystal [LLC], and nanostructured lipid carrier [NLC]) by Raman microscopic mapping of the drug. Raman spectra of the lidocaine-free blank formulations and lidocaine-containing formulations were detected in the wavenumber range of 300 to 1700 cm^{-1}. The penetration of lidocaine from the LLC and the NLC reached deeper skin layers and a higher amount of the drug penetrated into