chemical or biological interactions not seen under the control dosing scenario in the absence of absorption modulators.

Recently, our group has continued to develop mathematical models that attempt to account for the observed modulation of a mixture component on the transdermal flux of an applied compound. In most of these QSPR approaches, linear free energy relationships (LFERs) relate a compound K_p to the physical-chemical properties of the penetrating compound. In a mixture LFER model, the physical-chemical properties of the additives which modify the penetrant's absorption (e.g. refractive index, polar surface area, etc.) are now included in the model as a mixture factor (MF).

$$\text{Flux}_{\text{mix}} = K_p \Delta C \times \text{MF}$$

A number of mathematical approaches are used to accomplish this modulation depending on the variables being modeled (e.g. K_p, transdermal flux, or some other pharmacokinetic parameter) (37–43). Differences between these methods also relate to how the physical-chemical properties of both the penetrants and the additives are determined, how the interactions are mathematically modeled, and the complexity of the biological system being studied (e.g. in vivo versus ex vivo skin). In the cases where similar compounds are studied but the biological system is more complex, different MFs may be computed (44). As with any such analysis, the actual compounds being studied, which define the applicable chemical space of the analysis, are also important in that predictions only apply for new compounds (both penetrants and mixture additives) with similar physical-chemical properties. With the continued explosion of the ability to model ever increasingly large data sets, such analyses will continue to be more accurate and predictive of absorption from more complex mixtures.

22.5 CONCLUSION

This brief overview of mixture absorption illustrates the complexity involved when trying to extrapolate single interactions seen with binary mixtures onto absorption from more complex mixtures. However, strategies aimed at quantitating potential interactions in the framework of mechanisms of absorption would seem to be the most promising approach to put order into this complex problem. The data that indicate that measured stratum corneum PC correlates to subsequent absorption through intact skin is encouraging, as it provides an approach to experimentally assessing the effects of complex mixtures on K_p.

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