Eutectic Systems for Penetration Enhancement

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12.1 Introduction

The skin is an extremely important organ of the body, it forms a highly restrictive barrier between soft human tissues and the external environment, and it maintains body fluid homeostasis. In addition, it protects other internal organs from noxious insults. As a consequence, when breaches in the skin's barrier occur, they are repaired quickly using an effective system of enzymes and immune cells which are within close proximity to the skin surface. If a medical condition requires treatment using the skin as a means of drug administration, this biological context must be understood, the properties of the applied chemical must be characterized, and the site of action of the applied agent must be known in order to facilitate effective clinical therapy.

When a discrepancy exists in the native physicochemical properties displayed by a drug applied to the skin and the desired properties that theoretically allow the agent to passively reach its intended site of action, enhancement strategies may be sought to try and optimize the delivery process (Suhonen et al. 1999). A wide range of percutaneous penetration enhancement strategies have been developed over the last six decades, and presenting a molecule to the skin as a eutectic mixture is one that falls within the category known as chemical enhancement techniques. A eutectic system is most typically a binary system that when mixed exhibits a melting point that is lower

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than either of the component agents (Benson 2005). Studies using several drugs including ibuprofen (Stott et al. 1998), propranolol (Stott et al. 2001), testosterone (Kaplun-Frischoff and Touitou 1997), and lidocaine (Kang et al. 2000), combined with a second component (which may be a drug or excipient) to form a eutectic system, have been shown to enhance drug penetration into the skin compared to control systems containing only the single therapeutic agent. The enhanced permeation into the skin has been attributed to the lower melting point of the combined agents, which has been said to increase the solubility of penetrants in the lipids of the skin's outermost layer, the *stratum corneum* (SC). EMLA cream® (AstraZeneca, UK), a product that displays superior clinical efficacy compared to either prilocaine or lidocaine applied alone (Juhlin et al. 1980), is the oft-cited example used to highlight the utility of the eutectic system approach, but the deliberate formation of these systems remains an underused means to enhance drug delivery into the skin. This could be due to the challenges of formulating a product that contains two important functional molecules. In addition to the regulatory and manufacturing challenges posed by the use of two functional components in a topical formulation, the presence of two important diffusing species, which can enter the body simultaneously, at different rates, renders the production of new eutectic systems problematic.

According to the Higuchi equation (Higuchi 1962), the flux of a compound from a saturated solution is constant, regardless of the saturated concentration in a given vehicle because all saturated solutions have a thermodynamic activity of one (Twist and Zatz 1986). This theory was developed using the context of highly restrictive barriers such as the skin, and it has shown to be a reliable model for a number of therapeutic delivery systems (Davis and Hadgraft 1991; Dias et al. 2007; Iervolino et al. 2001). However, this mathematical model was designed to describe the mass transfer of a single agent. Tracking the movement of two agents across the human skin generates a three-dimensional problem as not only do the molecules have the capacity to change their behavior in a ratio-dependent manner, but they also encounter a series of different diffusional barriers which have the ability to independently influence molecular transport. In the discourse that follows, an attempt has been made to review the experimental studies that have investigated the manner in which agents are transported through hydrophobic barriers when applied as eutectic systems. In addition, using the lidocaine and prilocaine eutectic system as a central theme, what appears to be the most important concepts in this field have been highlighted in an attempt to advance the current understanding of how eutectic systems function to enhance drug delivery into the skin.

12.2 Dual Drug Diffusion

The effects of applying multiple drug molecules on the process of diffusion through membranes can be studied using porous regenerated cellulose membranes (RCM). Regenerated cellulose is an inert material that when formed into a membrane has been shown to provide a diffusion barrier with minimal membrane-drug interactions with non-ionized agents (Reid et al. 2008; Fiala 2008). In addition, it has been found that when the polarity of the application vehicle is well matched to the membrane, the residence time of the applied drug molecules in the membrane is short, drug partitioning is limited, and hence the transport rate can be directly related to the rate of molecular diffusion in the membrane (Reid et al. 2008; Fiala 2008). Using this basis, previous experimental data using RCM has been interpreted to suggest that the simultaneous membrane diffusion of lidocaine and prilocaine can be considered as a competitive process (Fig. 12.1, Fiala et al. 2008).

Relating the correlation observed for lidocaine and prilocaine between the normalized drug ratio in the applied bulk solution and the species transport back to the principles of the Higuchi equation allows the reduced diffusion of one agent in the presence of the second to be predicted by the initial composition of the applied saturated solutions using Eq. 12.1, where the rate of transport for an individual molecule (dq/dt) was related to

the membrane surface area (A), the membrane diffusion coefficient (D), the thermodynamic activity (α), the activity coefficient in the membrane (γbar), the diffusion path length (L), and the normalized ratio of the applied agent (N):

$$\frac{\mathrm{d}q}{\mathrm{d}t} = A\frac{ND}{\gamma_{\mathrm{bar}}}\frac{\alpha}{L} \tag{12.1}$$

In the case of lidocaine and prilocaine combinations, the normalized solubility was calculated using Eqs. 12.2 and 12.3, respectively:

$$N_{\mathrm{lido}} = \frac{C_{\mathrm{lido}}}{C_{\mathrm{lido}} + \left(C_{\mathrm{prilo}} \cdot S_{\mathrm{lido}} / S_{\mathrm{prilo}}\right)} \tag{12.2}$$

$$N_{\mathrm{prilo}} = \frac{C_{\mathrm{prilo}}}{C_{\mathrm{prilo}} + \left(C_{\mathrm{lido}} \cdot S_{\mathrm{prilo}} / S_{\mathrm{lido}}\right)} \tag{12.3}$$

where S_{prilo}, S_{lido} was defined as the solubility of prilocaine and lidocaine in individually saturated solutions and C_{prilo}, C_{lido} the concentrations of prilocaine and lidocaine in the application solutions. The self-diffusion coefficient measurements (which do not change upon the mixing of lidocaine and prilocaine at equimolar ratios ~ $7.5 \times 10-6$ cm^2/s) were cited in the paper by Fiala et al. (2008) to suggest the trends in the data were due to a reduction in the capacity of the membrane to allow unhindered diffusion of one compound in the presence of the second and not drug-drug interactions (Nyqvist-Mayer et al. 1986).

12.3 Dual Drug Partitioning

Building the effects of drug partitioning into the dual drug transport process is very important in percutaneous penetration. The partition coefficient (log P) of a molecule is typically measured as a ratio between the affinity for a standard oil phase (often octanol) and water. It can be used to predict the ability of a molecule applied to a hydrophobic barrier to pass into it. In terms of the human skin, if the log P is high for a particular drug, it will move across the first energy barrier created by the water/SC interface and into the outer layers of the skin. However, when a polar vehicle is used to administer a compound to the skin's surface, the hydrophobic SC is sandwiched between two hydrophilic phases. The epidermal tissue underlying the SC contains more water and fewer lipids than the skin's outermost layer, and as a consequence, it is distinctly more hydrophilic than the SC (Scheuplein and Blank 1971). Therefore, even if an agent applied topically to the surface of the skin passes into the SC, its subsequent transport through the tissue into deeper layers may be retarded by a second energy barrier (Williams and Barry 2004). As a consequence, a more detailed understanding of the transport process can be obtained if the effects of partitioning into a confluent barrier from a specific application vehicle are recorded and compared to predicted values using transport models that employ log P rather than relying on the latter alone. Human skin can be used in such studies, but it suffers from the problem of structural breakdown when long equilibration times are required to gain the measurements. Silicone membranes can be a useful alternative to human skin in partitioning experiments. Many types of silicone membranes do not have the same structural stratifications as skin, but they form a continuous hydrophobic barrier that is relatively inert and immiscible with polar solvents. They can be sandwiched between two water phases using a Franz cell setup in vitro; thus, they can generate transport and partitioning data using equivalent experimental parameters.

Transport studies using binary mixtures of lidocaine and prilocaine dissolved at different ratios in water (at a pH that retains both agents in the unionized state) have shown that the linear relationship between drug transport and normalized applied concentration observed in the RCM studies (Fig. 12.1) was not conserved when the barrier was switched to silicone (Fig. 12.2). The reason for this was assigned to the changes that occurred during the act of partitioning, which for the confluent silicone membrane, unlike the porous RCM, was predicted to have a significant effect on the transport process (Fiala et al. 2008). The data reported by Fiala et al. (2008) indicated

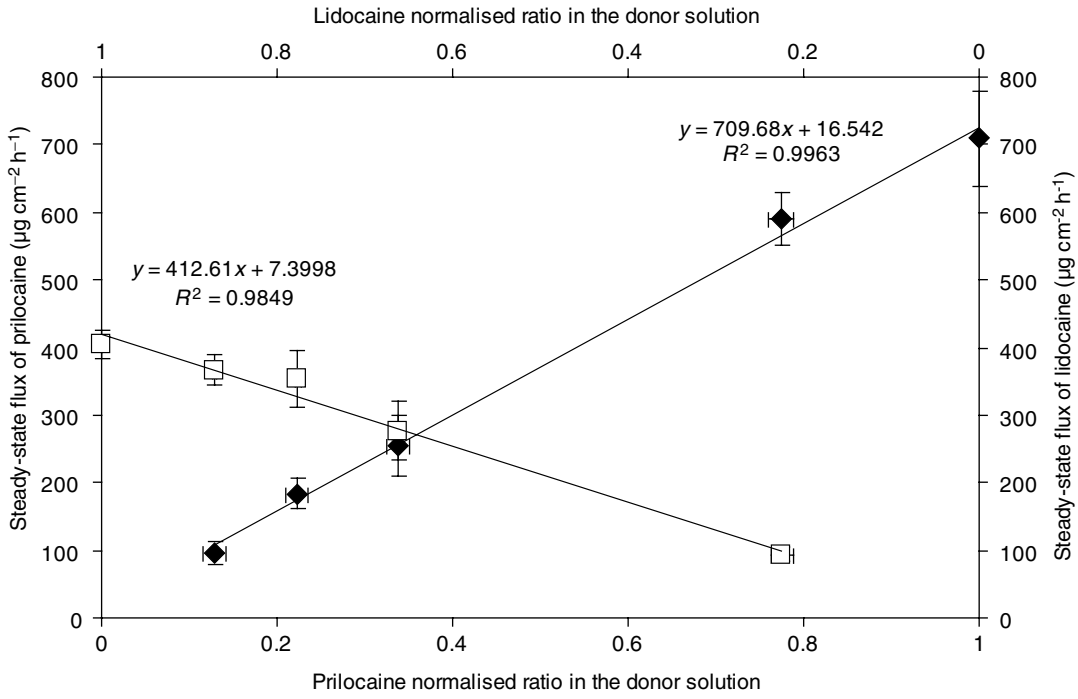

Fig. 12.1 Relationship between the steady-state flux of lidocaine and prilocaine through regenerated cellulose membrane and their solubility-normalized ratio in phosphate buffer solution: prilocaine (♦), lidocaine (□). Each point represents mean ± 1 standard deviation ($n=5$). A linear trend was observed between the steady-state flux of prilocaine and lidocaine and their solubility-normalized ratios in the donor solution and was plotted (represented by *black line*) (Reproduced with permission from Fiala et al. (2008))

that prilocaine partitioning remained unchanged irrespective of the concentration of lidocaine present in the binary drug mixtures, while lidocaine partitioning was enhanced when increasing amounts of prilocaine were present in the applied solutions. The solubility parameters of silicone, lidocaine, and prilocaine are 7.3 (cal $cm^{-3})^{1/2}$, 10.68 (cal $cm^{-3})^{1/2}$ and 11.05 (cal $cm^{-3})^{1/2}$, respectively (Fedors 1974). According to these values, the presence of either prilocaine or lidocaine in the membrane could theoretically alter the solubility parameter of silicone in a manner which may facilitate the passage of the second agent into the barrier when a binary mixture was applied onto its surface. Experimentally, a more efficient partitioning was only observed for lidocaine during the dual drug application process (Fiala et al. 2008). This is difficult to logically explain using the standard transport theories outlined in the literature. Furthermore, the transport data generated by Fiala et al. (2008) suggested that influence of the dual drug application on partitioning was relatively minor in comparison to drug diffusion when an aqueous application vehicle was used. These findings are not in agreement with other published work that has suggested eutectic system enhancement of drug delivery to the skin was mediated through changes in the partitioning process (Benson 2005; Stott et al. 2001). This raises a question as to the particular context in which the previous hypothesis regarding eutectic penetration enhancement was generated and the generality of the conclusions from any of the aforementioned studies.

12.4 Eutectic Combinations

Previous literature has suggested that the skin penetration enhancement effects of eutectic systems can be attributed to superior solubility of the active molecules presented by theses systems in

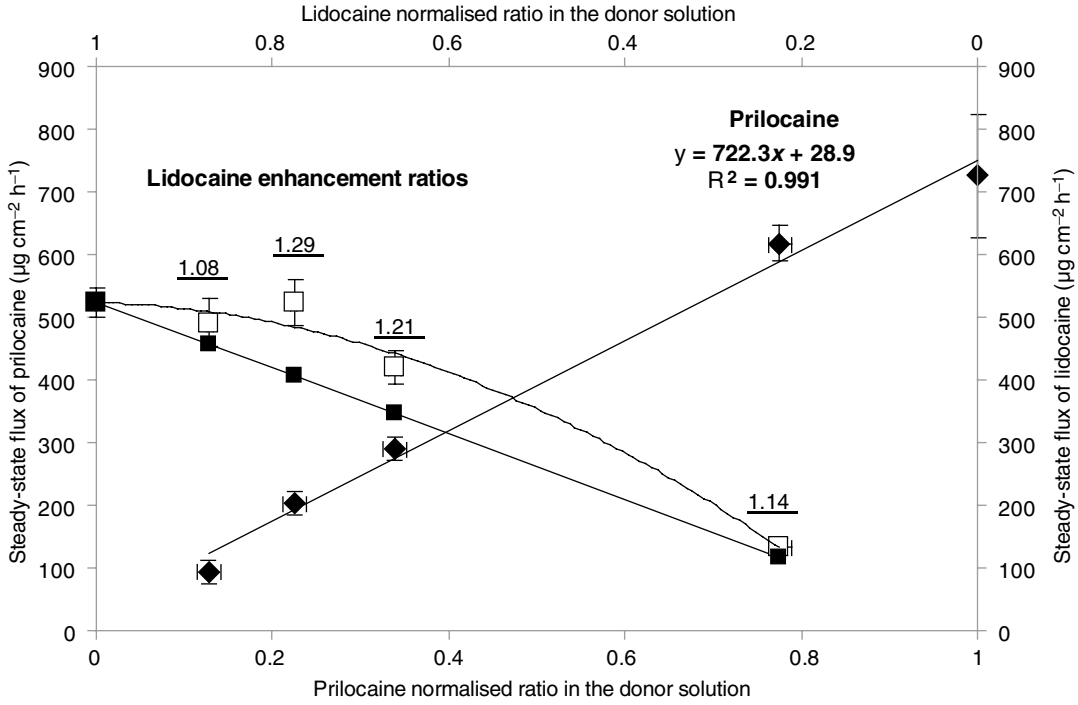

Fig. 12.2 Relationship between the steady-state flux of lidocaine and prilocaine through silicone membrane and their solubility-normalized ratio in phosphate buffer solution: prilocaine (◆), lidocaine (□). Theoretical lidocaine flux (■) was calculated assuming that the diffusion volume was changing as a function of the normalized ratio. Each point represents mean ± 1 standard deviation ($n = 5$). Enhancement ratios of lidocaine were calculated as the ratio of the actual to the theoretical steady-state flux and are indicated by the numbers on the graphs (Reproduced with permission from Fiala et al. (2008))

SC lipids (Alexander et al. 2012; Kaplun-Frischoff and Touitou 1997). This has been linked to the "melting point theory" which suggests that agents with a lower melting point (a key characteristic of all eutectic systems) will often have a greater propensity to associate with solvent molecules (Benson 2005). It has also been suggested in the literature that once the agents delivered by eutectic systems are within the skin, the co-localization of the diffusing species aids barrier penetration by interacting and modifying the skin structure (Watanabe et al. 2009; Woolfson et al. 2000). The facilitation of transport by eutectic systems through drug-skin interaction seems logical from both the perspective of increasing drug partitioning into the barrier and facilitating the movement of drugs through the barrier as such effects seem to be similar in nature to when the skin barrier is heated (Stott et al. 1998). According to Wood et al. (2012), heating the skin has a greater consequential effect on the process of drug partitioning compared to drug diffusion, but a similar conclusion is difficult to substantiate for eutectic systems. Both Pugh et al. (1996) and Fiala (2008) suggest that eutectic systems may have a negative influence on drug diffusion due to species competition and interaction in the solution state. This raises a question as to how, in the context of a topical formulation applied to the surface of the skin, the issues of competitive transport, molecular interactions, and facilitative partitioning function to generate the final transport rate generated from different eutectic systems. In an attempt to provide a critique on this matter, there is a need to highlight the specific details of how the various hypotheses surrounding the eutectic systems have been derived.

One model that relates melting point to SC solubility was proposed in the 1980s by Kasting et al. who suggested a relationship between transdermal

flux and melting point of the drug based on the concept of ideal solution state chemistry (Kasting et al. 1987). Using this model, the ideal solubility of a drug (S_{ideal} assuming thermodynamic ideality in terms of intermolecular interactions) in the skin lipids can be obtained using Eq. 12.4:

$$S_{ideal} = \frac{\rho}{1-\left\{1-\exp\left[\frac{\Delta S_f}{RT}\left(T_m - T\right)\right]\right\}\frac{M_1}{M_w}} \tag{12.4}$$

where ρ is the density of the skin lipids, M_1 is their average molecular weight, M_w is the molecular weight, T_m is the melting point in degrees Kelvin, and ΔS_f is the entropy of fusion of the drug. The ideal solubility was then used to predict a maximum flux, J_m (Eq. 12.5):

$$\log\left(J_m / S_{ideal}\right) = 1.80 - \left(0.0216 / 2.303\right) M_w \tag{12.5}$$

where M_w is the molecular weight. ΔS_f shows limited change as a function of melting point, but S_{ideal} increases exponentially with decreasing melting point for any given molecular weight, and this relationship is thought to drive flux across the skin, which would also theoretically increase exponentially. Touitou et al. (1994) used melting temperatures as indices to predict the relative transdermal fluxes of a series of enantiomeric eutectic mixtures. Solubility, expressed as solute mole fraction (X) in a given solvent, was related to the melting temperature (T_m) and the enthalpy of fusion (ΔH) using Eq. 12.6:

$$\ln X = -\frac{\Delta H}{R}\left(\frac{T_m - T}{T \cdot T_m}\right) \tag{12.6}$$

From this calculation, the maximum fluxes of one pure enantiomer ($J_{max,\,s}$) compared to the racemic mix ($J_{max,\,rs}$) were predicted (Eq. 12.7):

$$\ln\frac{J_{max,s}}{J_{max,rs}} = \ln\frac{X_{max,s}}{X_{max,rs}} = \frac{\Delta H_{rs}\left(T_{m,rs} - T\right)}{R \cdot T_{m,rs} \cdot T} - \frac{\Delta H_s\left(T_{m,s} - T\right)}{R \cdot T_{m,s} \cdot T} \tag{12.7}$$

Stott et al. (2001) generated data to suggest that the Touitou model (Eq. 12.7) was in good agreement with the skin permeation behavior of a beta-blocker eutectic system and from this concluded that the compound's melting point was an important factor in eutectic system enhancement effects. However, there are two critical details noted by Stott et al. (2001) that do not appear in some of the subsequent work that cites this study. First, Stott et al. (2001) showed that the correlation between melting point reduction and drug flux enhancement using Eq. 12.7 required normalizing to take account of the physicochemical properties of the compounds. This process of normalization involved generating an enhancement ratio against a standard chemical in the data set and effectively negated any effects of the eutectic combination on drug diffusion. Second, Stott et al. (2001) attempted to use the eutectic systems in their pure form, that is, without the addition of solvent molecules. Hence, the relationship between melting point and drug flux in Stott's work was particular in this context, i.e., the data was derived in the absence of a traditional semisolid delivery vehicle and when diffusion effects were negated through a process of mathematical "normalization."

In the case of the lidocaine and prilocaine eutectic system, in vitro transport studies using silicone membrane have shown that prilocaine-rich mixtures demonstrate superior total transport when compared to the 1:1 composition (the latter has the lowest melting point according to Brodin et al. 1984). This data was generated when lidocaine and prilocaine were presented to the membrane in a predominantly unionized state using a pH-modified aqueous solvent (Figs. 12.1 and 12.2). In addition, the TEMPE® spray (Topical Eutectic Mixture for Premature Ejaculation), a product in Phase III development by Plethora Solutions Plc (London, UK), uses a 3:1 lidocaine-to-prilocaine ratio when presenting the compounds as an oil (Henry 1999; Henry and Morales 2003; Henry et al. 2008). These two studies suggest that the melting point theory does not underpin the delivery of molecules from all eutectic systems and that the administration vehicle can have an important influence on the permeation of compounds from eutectic systems. The effects of

the delivery vehicle can be further exemplified through comparison of the data generated in the two papers by Fiala et al. (2008, 2011) in Fig. 12.3.

If the melting point theory cannot be used to adequately describe the transport rate changes observed from the lidocaine and prilocaine system, it would suggest that in the context of a pharmaceutical preparation the means by which eutectic systems enhance transdermal penetration of molecules is a little more complex than first suggested. There have been two additional theoretical concepts that have been proposed to play a role in eutectic system enhancement, these are centered on how the system's chemical potential and association of the drug molecules change when presented as topical formulation.

12.4.1 Chemical Potential

When presented as the pure molten oil, thermal analysis of the lidocaine and prilocaine eutectic system has shown that it can take approximately 7 days, if stored under refrigeration, to reach a state of physical equilibrium, i.e., a constant solid-liquid ratio is attained for the mixtures (Brodin et al. 1984). Chemical analysis of the liquid phase composition at room temperature has confirmed that lidocaine and prilocaine do not attain physical equilibrium after 24 h when mixed at room temperature (Fiala et al. 2011). Previous work has also shown when either prilocaine- or lidocaine-rich ratios of the pure molten oils are prepared at room temperature; a second phase, composed of microparticulate matter, which is presumably non-melted drug product suspended within the eutectic system, can be observed at several ratios of the two drugs (Fiala et al. 2011). It is possible that the suspension formed immediately upon mixing a eutectic system composed of only the two drugs lidocaine and prilocaine may exhibit properties that are similar to a supersaturated solution, in that a state of heightened chemical potential may be temporarily induced. If this was the case, the thermodynamic activity of the molecule in the eutectic mixture that was present in excess may increase transiently and thus generate an unexpectedly high rate of membrane transport. This hypothesis is supported by the observation that eutectic combinations of ibuprofen with terpenes enhanced membrane transport of ibuprofen when a second solid phase existed in the applied molten oil (Stott et al. 1998). If drug flux through human skin was

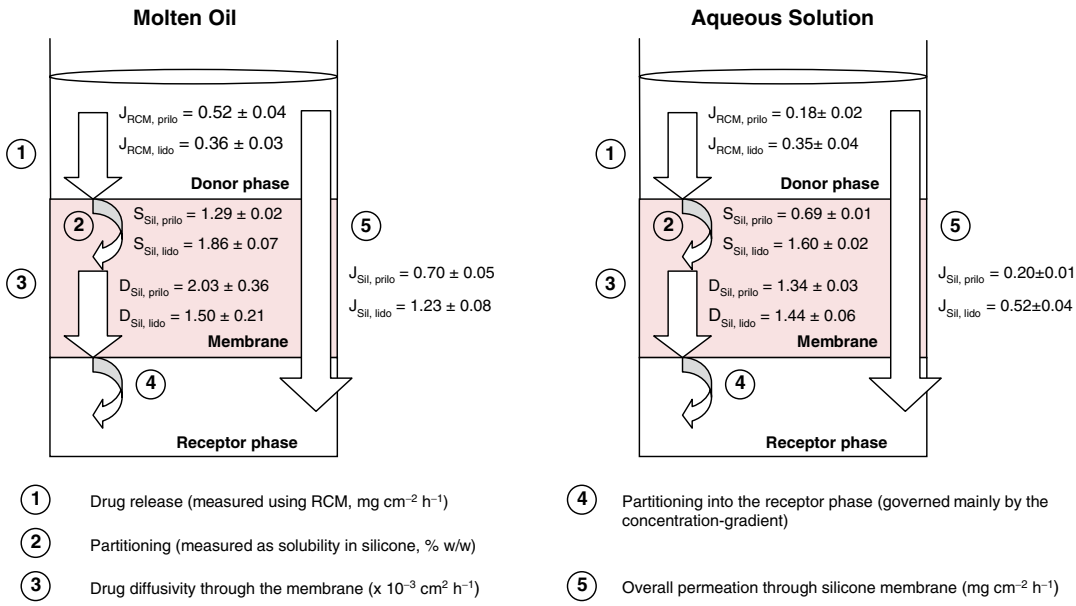

Fig. 12.3 Comparative summary of transport results from a series of studies that used a eutectic prilocaine/lidocaine mixture at a ratio of ca. 2:3 in the form of a molten oil and an aqueous solution

significantly influenced by the physical equilibration state of the pure oils, this may provide one explanation as to why the TEMPE® and EMLA® systems are formulated using different drug ratios. The former forms a eutectic system only upon its application to the skin, and thus it will most likely not reach a state of solid-liquid equilibrium during clinical use, while the latter is produced from a pre-equilibrated oil mixture free from solid particles. More experimental studies using human skin and a deeper theoretical consideration as to the chemical potential of pure molten oils are needed to understand the influence of physical equilibrium on eutectic enhancement, but it is possible that this could be an important factor in the development of eutectic systems.

12.4.2 Association Complexes

The principal components used to form a eutectic system must interact in their molten state in order to generate their unique melting point-lowering properties. H-bonding interactions are known to be important in the formation of eutectic systems between ibuprofen and terpenes (Stott et al. 1998) as well as between urethane and various polymers (Isama et al. 1993); however, the precise interactions between prilocaine and lidocaine have not been identified. As noted previously, Nyqvist-Mayer et al. (1986) suggested that in aqueous solvents the lidocaine and prilocaine molecules had an equivalent self-diffusion coefficient, and therefore it was deemed that a complex was not formed between the two molecules in an aqueous solvent. In polar vehicles, the molecular interactions could be influenced by the ionization of the molecules, and hence in the work by Fiala et al. (2008), the drug ionization was suppressed in order to reduce the impact of ion-pair formation and/or molecular association. The Nyqvist-Mayer study does not provide the details of drug ionization, and thus it is not clear what microspecies were presented in the test formulations, and this complicates the review of the data in this area. Even if the association of the compounds was considered to occur, there is no spectroscopy evidence to show if this association would be strong enough to form a pure 1:1 complex at equimolar levels of the two drugs or if there would be significant levels of free unassociated drug present in the mixtures. At ratios other than the eutectic, some levels of unassociated molecules are likely to exist, and this provides a complex solution state chemistry landscape where several species are penetrating the membrane and contributing to the total steady-state flux. It is interesting to note that silicone membrane solubility measurements using pure molten lidocaine and prilocaine oils at a ratio of 1:1 showed a higher lidocaine solubility compared to prilocaine, which suggests that either a pure 1:1 mixture does not exist in the donor oil or the silicone-lidocaine interaction is stronger than the 1:1 complex interaction.

For the lidocaine and prilocaine eutectic system, assuming a strong 1:1 complex is formed, an average log *P* for the 1:1 complex can be used with an additive molecule mass in the Potts and Guy (1992) equation to predict the penetration rate of the drugs across the skin when applied as a molten oil (Fig. 12.3). As only two diffusing species are assumed to be present (i.e., free and complexed), the overall permeability can be calculated as the sum of transport of the two species relative to their ratio in the mixture (Eqs. 12.8 and 12.9).

If $R_{\text{prilo}} > R_{\text{lido}}$:

$$K_p = \left[\left(K_{p,\text{comp}}\right)\cdot\left(2R_{\text{lido}}\right)\right] + \left[\left(K_{p,\text{prilo}}\right)\cdot\left(1-2R_{\text{lido}}\right)\right] \tag{12.8}$$

If $R_{\text{lido}} > R_{\text{prilo}}$:

$$K_p = \left[\left(K_{p,\text{comp}}\right)\cdot\left(2R_{\text{prilo}}\right)\right] + \left[\left(K_{p,\text{lido}}\right)\cdot\left(1-2R_{\text{prilo}}\right)\right] \tag{12.9}$$

where R_{prilo} and R_{lido} are prilocaine and lidocaine w/w ratios, respectively; $K_{\text{p, prilo}}$ and $K_{\text{p, lido}}$ are the individual permeability coefficients of prilocaine and lidocaine, respectively; $K_{\text{p, comp}}$ is the permeability coefficient of the complex; and K_{p} is the overall permeability coefficient of the eutectic

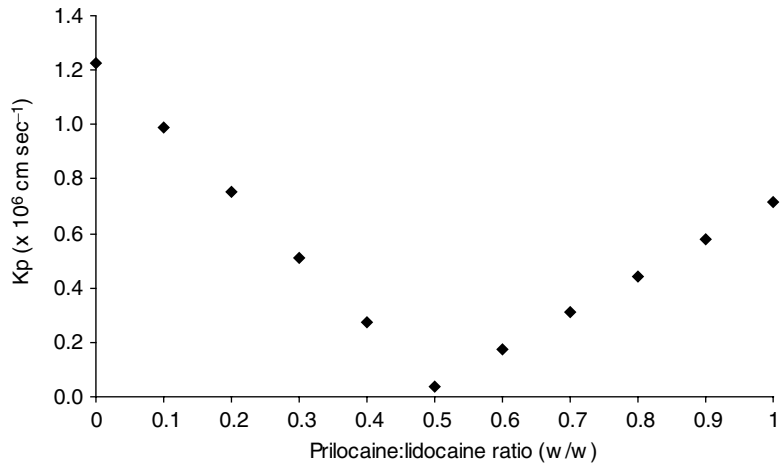

Fig. 12.4 Theoretical K_p values for prilocaine/lidocaine mixtures as calculated using the Potts and Guy equation

mixture. The overall trend of the calculated K_p values (Fig. 12.4) fits well with the competitive transport hypothesis applied to the two anesthetics (Figs. 12.1 and 12.2). However, the Potts and Guy K_p values indicate that when lidocaine was in excess, the free lidocaine molecules drive the total drug permeation to be higher at high lidocaine ratios compared to the high prilocaine ratios. This was not observed practically with the silicone membrane (Fiala et al. 2010), but the Potts and Guy model does support the lidocaine-rich mixture that was employed in the TEMPE® spray. At the time of writing this chapter, there are no publically available data using human skin to suggest the ratio for the TEMPE® system was selected based upon experimental rather than theoretical observations. In addition, the modeling performed in this discourse is extremely simplistic, and again, as stated previously, more transport data using human skin needs to be generated to probe further the issues of complexation. However, what this discussion highlights is that drug-drug complexation must be considered to be a potential factor in the manner in which eutectic systems enhance skin delivery. Furthermore, the strength of the complexes must be measured in the different application vehicles in order for the nature of the permeating species to be identified and allow the systems to be optimized.

Conclusions

Combining two therapeutic agents in a medicine is becoming more attractive to both clinicians and patients as the comorbidity rates continue to increase through the twenty-first century. It would therefore seem sensible to understand how the inclusion of a second agent functions to influence the properties of the first agent in relation to the functional activities of the dosage form. In products that are applied to the skin, if the agents form a eutectic system, current literature suggests that this provides additional advantages as eutectic systems can "enhance the penetration" of topically applied medicines into the skin. The dominant discourse in the literature to this point seems to suggest that a eutectic system reduces the melting point of the drug combination and increases the transport into the skin by facilitating the act of drug partitioning. However, a number of studies, including those which have tested the oft-cited eutectic example of lidocaine and prilocaine, seem to suggest that a direct link between melting point and transport cannot be applied to a number of contexts important to pharmaceutical dosage forms.

The data reviewed in this chapter seems to suggest that the ability to present actives to the skin as a molten oil, without additional formu-

lation excipients, is the special property that underpins eutectic system's induced skin penetration enhancement. When the molten mixture of the lidocaine and prilocaine eutectic system was specifically considered, then a two-phase mixture that was rich in the molecule which penetrates the barrier most effectively was shown to be the most efficient topical formulation and not the system with the lowest melting point. The TEMPE® spray which uses a 3:1 lidocaine-to-prilocaine ratio seems to be a more logical presentation format for these systems compared to a traditional cream, e.g., EMLA®. However, further work needs to be undertaken to understand how the molecules in a eutectic system interact in the molten and solution states and how presentation to the skin affects this in order to advance this very interesting field of research.

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