Advanced Drug Delivery Reviews 65 (2013) 265–277

Contents lists available at SciVerse ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

# Predicting skin permeability from complex vehicles ☆

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ARTICLE INFO

*Article history:*
Accepted 31 January 2012
Available online 10 February 2012

*Keywords:*
Chemical mixtures
Formulations
Percutaneous/dermal absorption
Quantitative structure–permeation relationship (QSPR)
QSAR
Linear free energy relationships (LFER)
Mixture factor
Topical drug delivery enhancers

ABSTRACT

It is now widely accepted that vehicle and formulation components influence the rate and extent of passive chemical absorption through skin. Significant progress, over the last decades, has been made in predicting dermal absorption from a single vehicle; however the effect of a complex, realistic mixture has not received its due attention. Recent studies have aimed to bridge this gap by extending the use of quantitative structure–permeation relationship (QSPR) models based on linear free energy relationships (LFER) to predict dermal absorption from complex mixtures with the inclusion of significant molecular descriptors such as a mixture factor that accounts for the physicochemical properties of the vehicle/mixture components. These models have been compiled and statistically validated using the data generated from in vitro or ex vivo experimental techniques. This review highlights the progress made in predicting skin permeability from complex vehicles.


**Contents**



☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Modeling the human skin barrier — Towards a better understanding of dermal absorption".

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0169-409X/$ – see front matter 
doi:10.1016/j.addr.2012.01.019

## 1. Chemical mixtures

The ability to predict chemical absorption through skin is of great interest to drug developers and risk assessors, alike. Absorption studies that investigate mechanisms and/or the toxicity involved have traditionally been conducted using binary mixtures, that is, a single drug/chemical delivered in a single vehicle. Such studies have demonstrated the significant effects that vehicles may have on chemical absorption [1–5]. However, most topical chemical exposures, whether deliberate or accidental, are rarely in the form of a binary mixture, but often as complex chemical mixtures consisting of penetrants, different vehicles and/or chemical additives. Additional studies on vehicles with additives such as surfactants, alcohols, and solvents have confirmed that their presence may alter the barrier properties of skin [6–9].

This recent research has widened the investigative scope to include the evaluation of vehicles with increasing complexity e.g. ternary mixtures. Examples of these evaluations include the exploration of the effect of ternary mixtures of water, ethanol and/or propylene glycol on the transport of ibuprofen across silicone membranes and skin [10,11], and the transport of testosterone across canine skin [12]. Resultant data indicates enhancement in chemical permeation from mixtures containing propylene glycol and ethanol. Research on the dermal transport of ibuprofen has further been expanded by the incorporation of lipophilic vehicles such as light mineral oil and fractionated coconut oil (Miglyol© 812), both which promote skin permeation [13]. Other research evaluated the effect of phospholipid formulations containing a surfactant on skin permeation of three hydrophilic drugs (methotrexate, acyclovir, idoxuridine) across human skin [14].

More complex commercial formulations of herbicides containing surfactants have also been investigated [15]. Results showed that the three selected herbicides (atrazine, alachor, and triflurain) had significantly greater dermal penetration from the commercially formulated mixture compared to pure compound at the same concentration. Noteworthy, was that the most hydrophobic herbicide had the least penetration but accumulated in the stratum corneum at the greatest rate.

Other studies have provided evidence that suggests that multiple pesticides can interact and form synergistic responses, inducing biological responses far greater than would be predicted. For example, the Gulf War Syndrome was discovered to be the result of interactions of multiple protective chemicals, which were not seen when the individual compounds were tested [16]. Clearly, to improve our understanding and hence to make a better prediction about the consequences of chemicals including their potential interactions, they must be studied in the same complex combinations in which they are applied.

However, only limited work has been done to broadly incorporate the effect of complex mixture interactions [17,18]. Although somewhat a difficult task, the importance of the incorporation of such interactions is becoming more evident with the research progress made in this field. Especially with the abundant presence of complex mixtures in cosmetic and pharmaceutical products, and in occupational and environmental scenarios, the ability to predict absorption is a highly desirable objective.

### 1.1. Pharmaceutics and cosmetics

Although topical administration offers several attractions compared to traditional routes [19], formulation development often requires overcoming the barrier function of the skin [20]. This is often accomplished by the inclusion of specific components that have been as carefully selected as the drug/chemical itself. These added components serve a specific purpose relative to the delivery, stability or activity of the active ingredient [21]. Commonly used components include surfactants, to solubilize lipids within the stratum corneum [22–25], and penetration enhancers, which may increase the diffusion coefficient of drugs in the stratum corneum by disrupting the barrier of the stratum corneum and hence increasing the effective concentration of the drug in the vehicle [26–32]. Penetration enhancers may also improve the partitioning between the formulation and the stratum corneum, or even though less likely by decreasing the skin thickness and providing a “shortcut” through the permeation pathway [27].

In excess of 300 chemicals have been evaluated for their penetration enhancement abilities [33], revealing the modes of action are not always straightforward [27]. Karande and Mitragotri's review [33] demonstrates the employment of synergistic mixtures of chemicals that offer superior skin permeation enhancement, showing that multi-component mixtures of chemicals provide higher skin permeability efficiency than individual chemicals.

Due to the complexity of their actions, penetrations enhancers are typically categorized into chemical groups [33]. Examples include water, which is the most natural penetration enhancer. Water increases the hydration of the stratum corneum and so increases the transdermal flux of a variety of chemicals [34]. Other examples include sulphoxides such as dimethylsulphoxide, which have been shown to promote both hydrophilic and lipophilic chemicals [27]. Effects of dimethylsulphoxide have been shown to be concentration dependent. Generally, concentrations in excess of 60% DMSO are required for optimum enhancement. However, at these high concentrations dimethylsulphoxide can cause erythema and wheals of the stratum corneum and may denature some proteins [27].

Other groups of penetration enhancers include pyrrolidones, alcohols and alkanols, glycols, surfactants and terpenes [27,33]. The addition of these enhancers to a formulation increases its complexity and also the potential for chemical–chemical and skin–chemical interactions to occur.

Recent concerns over the potential increase in toxicity following exposure to complex mixtures of agrochemicals, mosquito repellants and household cleaning products have led to the investigation of penetration retardants. Unlike enhancers, retardants decrease the diffusion of the applied chemical by strengthening the intercellular lipid organization of the stratum corneum. Despite the contrasting behavior, they are often collectively referred to as “penetration modifiers” as both act by modifying the structure of the stratum corneum [35]. Kaushik et al. [36] demonstrated an enhancer becoming a retardant or vice versa depending on the vehicle in which it is applied to the skin. Several other studies have also demonstrated that formulation components clearly influence drug permeation [13,37–39].

The effects of formulation or vehicle on the rate and extent of absorption have been noted to be far greater with topical drug delivery rather than with any other route of administration [40]. This is exemplified by the broad potency range (I–V) of various marketed 0.5% betamethasone dipropionate products [41].

Cosmetic mixtures have an additional esthetic requirement of the vehicle and drug/chemical. Such criteria include visual appearance, odor and residual impression after application, all which influence consumer acceptance and patient compliance [40]. In all topical formulations, other components may also be present for reasons unrelated to dermal penetration, yet may have effects on the stability or chemical partitioning of the formulations that would impact the penetration of the active ingredient.

#### 1.1.1. Nanoparticles

The field of nanoparticle research has progressed over the last dozen years and has seen nanoparticles widely incorporated into cosmetics and household products. Due to their small size, it was speculated that