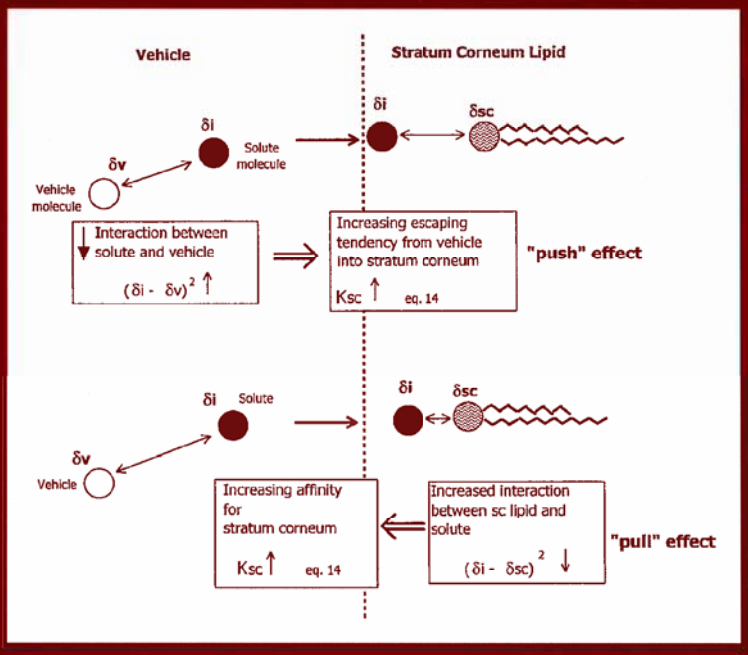
DRUGS AND THE PHARMACEUTICAL SCIENCES VOLUME 119

Dermatological and Transdermal Formulations



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2. Biopharmaceutical Considerations

A fundamental consideration in the development of transdermal therapeutic systems is whether the dermal delivery route can provide the requisite bioavailability for drug effectiveness. This is ultimately determined by the skin-penetration rate of the drug, the potential for metabolism during permeation across the skin, and the biological half-life of the drug. Penetration rates may be modified, if necessary, by the use of penetration enhancers, but drug metabolism and plasma clearance cannot be influenced by any simple means. Although prediction of skin penetration and bioavailability of drugs from transdermal therapeutic systems has been reasonably accurate, there is no doubt that testing of formulated patches in vitro and in vivo will continue to be the most accurate means of evaluating their usefulness.

A wide variety of experimental approaches have been developed for in vitro drug permeability determination through skin, and guidelines have been established to rationalize this aspect of pharmaceutical development (see Chapter 5). In the early stages of product development, skin penetration rates from prototype vehicles and patches are usually determined in vitro using simple diffusion cells and skin from a variety of animals. Although, the use of in vitro systems provides little quantitative information on the transcutaneous metabolism of candidate drugs, a major advantage is that experimental conditions can be controlled precisely so that the only variables are in the prototype formulations. In the latter stages of product development, when quantitative skin permeation data is required, human skin should be the membrane of choice for use in in vitro systems. Although methods are available to improve the sensitivity of in vitro skin penetration measurements (61), it is essential, at this stage, to ensure that account is taken of the inherent variability in human skin permeation.

Factorial design and artificial neural networks have been used in the optimization of transdermal drug delivery formulations using in vitro skin permeation techniques (62–64). For example, Kandimalla et al. (63) optimized a vehicle for the transdermal delivery of melatonin using the response surface method and artificial neural networks. Briefly, three solvents (water, ethanol, and propylene glycol) were examined either as single solvents or binary and ternary mixtures. Measurements of skin flux, lag time, and solubility were made for ten vehicles and compared with values predicted from both a response surface generated from a quartic model and an artificial neural network employing a two-layered back-propagation network with all ten design points in the hidden layer. Predictability of flux using both statistical techniques was good (Table 6), suggesting that such models may be useful in preliminary formulation optimization.

A major drawback of transdermal delivery systems is the potential for localized irritant and allergic cutaneous reactions. At the earlier stages of formulation development, it is, therefore, important to evaluate both drugs and excipients for their potential to cause irritation and sensitization (see Chapters 10 and 11). This is true for all transdermal systems, but especially for those that may stay in place for prolonged periods. The degree of primary and chronic irritation, and the potential to cause contact allergy, photoirritation, and photoallergy should be determined. Normally, the drug and excipients are initially separately evaluated for contact irritation and sensitization in animal models before evaluation in human subjects. It must, however, be emphasized that animal data are often not predictive of the human situation. Evaluation of skin irritation and delayed contact hypersensitivity should

Table 6 Experimental Versus Predicted Flux[a] of Melatonin

Application vehicle[b]	Experimental ($\mu g/cm^2\ h^{-1}$)[c]	ANN Prediction ($\mu g/cm^2\ h^{-1}$)	RSM Prediction ($\mu g/cm^2\ h^{-1}$)
W:E:P (20:60:20)	11.32 ± 0.86	12.17	12.73
W:E (40:60)	10.89 ± 1.36	11.83	11.76
W:P (40:60)	7.54 ± 1.39	6.75	7.50

[a]Flux was predicted on the basis of artificial neural networks (ANN) or response surface methods (RSM).
[b]W, water; E, ethanol; P, propylene glycol.
[c]Data are means ± standard deviation ($n = 3$) and represent flux through rat dorsal skin.
Source: Ref. 63.

always be carried out using the final and complete formulation in human volunteers. Fortunately, most of the observed skin reactions to transdermal systems are transient and mild and disappear within hours of patch removal.

3. Design Considerations

All patch-type transdermal delivery systems developed to date can be described by three basic design principles: drug in adhesive, drug in matrix (usually polymeric), and drug in reservoir (Fig. 6). In the latter the reservoir is separated from the skin by a rate-controlling membrane. Although there are many differences in the design of transdermal delivery systems, several features are common to all systems including the release liner, the pressure-sensitive adhesive and the backing layer, all of which must be compatible for a successful product. For example, if a system is designed in such a way that the drug is intimately mixed with adhesive, or diffuses from a reservoir through the adhesive, the potential for interaction between drug and adhesive, which can lead to either a reduction of adhesive effectiveness, or the formation of a new chemical species, must be fully assessed. Similarly, residual monomers, catalysts, plasticizers, and resins may react to give new chemical species. Additionally, the excipients, including enhancers, or their reaction products, may interfere with adhesive systems. Incompatibilities between the adhesive system and other formulation excipients, although undesirable, may not necessarily be impeding and designs in which the adhesive is remote from the drug delivery area of the system may be developed (see Fig. 6d). There are three critical considerations in the selection of a particular system: adhesion to skin, compatibility with skin, and physical or chemical stability of total formulation and components.

All devices are secured to the skin by a skin-compatible pressure-sensitive adhesive. These adhesives, usually based on silicones, acrylates, or polyisobutylene, can be evaluated by shear-testing and assessment of rheological parameters. Standard rheological tests include creep compliance (which measures the ability of the adhesive to flow into surface irregularities), elastic index (which determines the extent of stretch or deformation as a function of load and time) and recovery following deformation. Skin-adhesion performance is based on several properties, such as initial and long-term adhesion, lift, and residue. The adhesive must be soft enough to ensure initial adhesion, yet have sufficient cohesive strength to remove cleanly, leaving no residue. Because premature lift will interfere with drug delivery, the cohesive and

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