Selection of Active Pharmaceutical Ingredients (APIs) and Excipients for Topical Formulations

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Transdermal drug delivery (TDD) is a viable option for systemic delivery of select drugs. It provides advantages, such as avoidance of first-pass metabolism, patients' improved compliance, controlled or sustained release, and decreased side effects. This article focuses on transdermal delivery via application of a topical, semisolid formulation in the form of a gel, lotion, or cream. The authors discuss physicochemical criteria for selection of APIs and excipients for this type of delivery.

A significant challenge in using TDD resides in the issue of permeation of drugs through the skin. Many researchers have written about chemical permeation enhancement and other methods for enhancing delivery. A recent review on advanced physical techniques used for enhancing delivery of drugs includes discussions on structurally based, electrically based, velocity based and other physically based techniques that enhance permeation [1].

Another area of research focuses on transdermal delivery of peptides and proteins. Since they have higher molecular weights compared to chemical APIs and are hydrophilic in nature, they cannot passively permeate across the skin because the stratum corneum allows transport only of small lipophilic APIs. A recently published review of enhancement techniques included chemical enhancers, iontophoresis, microneedles, electroporation, sonophoresis, thermal ablation, laser ablation, radiofrequency ablation, and noninvasive jet injectors that aid in the delivery of proteins by overcoming the skin barrier [2]. Kalluri and Banga's review describes various techniques and discusses mechanisms, sterility requirements, and commercial development associated with these types of products.

Nanotechnology also is an area of intense research and has been applied successfully for transdermal delivery. For both dermal and transdermal delivery, approaches in the field of nanosized particulate systems include nanosized microemulsions, vesicular systems, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and polymeric nanoparticles [3].

This article focuses on topical formulations for transdermal delivery. The first section discusses physicochemical criteria for selection of APIs that are suitable. A discussion of excipients follows, including design of experiments for formulation development and in-vitro release testing to evaluate the formulations.

Selection of APIs

This section provides general and simple guidelines for selecting APIs suitable to transdermal delivery using topical formulations. They are based on a simple set of metrics derived from molecular properties, desired plasma levels, and pharmacokinetic parameters. The starting point for a simple pharmacokinetic (one compartment) system is a ratio of the steady-state transdermal input to the elimination output. The steady-state transdermal input is the product of A, the area of application, and J_s, the steady state flux. The elimination output is the product of V, the volume of distribution, and k_e, an elimination-rate constant. The steady-state transdermal input divided by the elimination output gives the steady-state plasma level C_p, as shown in Equation 1 [4].

Equation 1: $C_p = AJ_s/Vk_e$

Thus, if a formulation scientist knows the desired plasma level and the pharmacokinetic parameters and can estimate J_s, he or she can determine if C_p can be achieved with a reasonable area of applica-

tion on the skin surface. Cooper used Equation 1 and a J_S from in-vitro skin-penetration studies to predict, with reasonable accuracy, the surface area required to deliver systemic levels of indomethacin from topical application of a gel [5].

Assuming that the formulation scientist knows the desired blood level and pharmacokinetic parameters, an estimate of J_S requires use either of molecular parameters or results from in-vitro experiments. The remainder of this section is devoted to estimating J_S from molecular parameters.

For simplicity, consider J_S to be the product of S, the solubility of the drug in the lipids of the stratum corneum, and P_{SC}, the permeability of the stratum corneum (Equation 2).

Equation 2: $J_S = SP_{SC}$

Wang, Kasting, and Nitsche have developed very sophisticated models for predicting permeability [6 to 8]. Their models are beyond the scope of this analysis, which will employ a much simpler model to determine if transdermal delivery is possible or out of the question.

In this simplest model, the formulation scientist can view permeability as the quotient of D, the diffusion coefficient of the stratum corneum, divided by h, its effective thickness. Kasting, Smith, and Cooper developed a model for D based only on the molecular volume of a drug (or on its molecular weight since volume scales reasonably well with molecular weight) [9, 10]. The scientists estimated solubility using ideal solution theory, which assumes the drug is similar to the lipids. For a series of molecules of substituents on benzoic acid (basically all the same size), Cooper graphed a linear result for steady-state flux (J_S), as found through in-vitro skin-penetration studies, versus isopropyl myristate, which represents ideal solubility [11]. Equation 3 shows the equation for ideal solubility used in the study.

Equation 3:

$$S_{ideal} = \rho / [1 - \{1 - \exp[\Delta S_f (T_m - T)/RT]\} M_l / MW]$$

In the equation:

- ρ is the density of the skin lipids
- M_l is the average molecular weight of the lipids
- MW is the molecular weight of the permeant
- T_m is the melting point in Kelvin of the permeant
- ΔS_f is the entropy of fusion of the permeant, which for a large number of permeants was about 16 entropy units

Thus, the melting point of the permeant drives solubility, which decreases about ten-fold for every hundred-degree rise in melting point.

The researchers modeled the diffusion coefficient D and fit it to human in-vitro skin-penetration data as found through Equation 4 for molecular volume v and Equation 5 for molecular weight M.

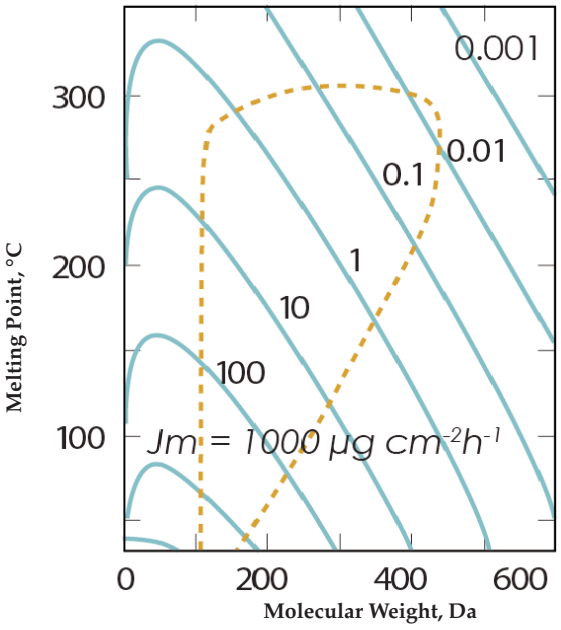
Equation 4: $D = D_0 \exp(-\beta v)$

Equation 5: $D = D'_0 \exp(-\beta' M)$

Figure 1 summarizes these considerations, showing constant, maximum-flux (J_m) contours from saturated vehicles for different melting points and molecular weights. The dashed lines represent the region of the experimental data. Although this figure represents a great simplification of a very complex problem, it provides a very simple way to obtain a ballpark estimate of the maximum flux based on two accessible molecular parameters, the melting point and the molecular weight. Using Figure 1, the scientist needs only to know the melting point and the molecular weight to estimate the maximum steady-state flux.

Figure 1

Maximum Flux as a Function of Melting Point and Molecular Weight



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Selection of Excipients

Formulation excipients often make up over 99 percent of a drug product. Although technically referred to as inactive ingredients, the excipients make up the delivery system in topically applied transdermal products and play a key role in their efficacy [12]. A properly designed formulation should optimize the therapeutic impact of the API, delivering it to the right place at the right time in the right amount.

The development of a topical formulation for transdermal drug delivery is inherently difficult as the skin is specifically designed to act as a barrier to penetration of foreign materials. Many articles and reviews of patch technologies are available in the literature, and this article does not consider them [13, 14]. After the formulation scientist has determined that an API possesses the potential for transdermal delivery, he or she must develop the proper formulation to realize that potential. Very few drugs possess an inherent ability to penetrate the stratum corneum, and the job of excipients then becomes facilitation of the flux of the API through the skin to achieve therapeutic levels.

The molecular physicochemical properties of an API — charge, polarizability, hydrogen bonding, shape, molecular weight, etc. — influence transdermal penetration. In addition, the physical form of the bulk API in the formulation is a critical factor — perhaps one of the main factors — that influences bioavailability. On a macroscopic level, the skin provides an effective physical barrier against particulates; so the physical state of the API has a profound effect on its permeation. The formulation scientist needs to evaluate and track the physicochemical properties of the API in the formulation during development. He or she needs to know if the API is present in a fully solubilized, amorphous, or crystalline state or a combination of the three states. If the API is present as a particulate in the formulation, the particle size distribution (PSD) should be correlated to biological performance to set justifiable specifications. The PSD of the successful formulation should be stable to ensure reproducible bioavailability, and the formulation scientist should track it during storage to ensure that the product has the desired release profile. Also, if the API is in a crystalline state in the formulation, the scientist should know the polymorphic form of the API and track it for stability to ensure that the product is stable for the desired shelf life.

Therefore, two important considerations in the design of a transdermal formulation are:

- The physical presentation of the API, either in a solvated, dissolved form or a particulate form or some combination thereof
- The use of formulation components that can alter the stratum corneum to improve transdermal penetration

Scientists have used penetration enhancers for many years and continue to search for the ideal one [1, 2]. Penetration enhancers can function either by altering the skin matrix to loosen the lipid-layer packing or by acting as a solvent for the drug to increase the drug concentration within the skin membrane. The effect of penetration enhancers on the skin must be temporary, and they should be inert, nontoxic, and nonirritating. Many materials can function as penetration enhancers, such as glycols, surfactants, fatty acids and their esters, fatty alcohols, alcohols, sulfoxides, azones, and pyrrolidones. An in-depth discussion of the various penetration enhancers, however, is beyond the scope of this article. Formulation scientists can use the solubility of the API in potential penetration enhancers as a screening mechanism to identify formulation components.

Of course, the physical presentation of the API in the formulation depends on its solubility characteristics in appropriate excipients for topical formulations. A solvated API normally is considered preferable, though scientists should exercise care that the solvating component possesses good skin-penetration characteristics in itself. If it doesn't, the formulation may provide no gradient to drive the API through the skin in meaningful therapeutic levels, and the API may deposit on the skin surface.

As with any delivery format using a solvated drug, scientists should take care that the drug does not recrystallize out of solution uncontrollably during storage or upon application or administration due to contact with bodily surfaces or fluids. Certainly, solubility in a known penetration enhancer is greatly desired. With the advent of many new drugs possessing poor overall solubility, decreasing the particle size as much as possible will increase the surface area greatly. This increase leads to an increased rate of dissolution, thereby maintaining the highest concentration gradient and maximizing the bioavail-

Table 1

Design of Experiments (Custom) for Excipient Compatibility Testing

	Level of Thickener	Type of Emulsifier	Level of Emulsifier	Antimicrobial System	Type of Level of Antimicrobia	Level of Spreading Agent	Spreading Agent	Type of Humectant	Level of Humectant	API Stability	Viscosity	Bioburden
T-1	High	E-1	High	A-2	Low	SA-1	High	H-2	High			
T-1	Low	E-2	High	A-2	High	SA-2	Low	H-1	Low			
T-1	High	E-1	High	A-2	High	SA-1	Low	H-2	Low			
T-2	High	E-2	Low	A-1	High	SA-2	High	H-1	High			
T-2	High	E-1	Low	A-2	Low	SA-2	Low	H-2	High			
T-1	Low	E-1	Low	A-2	High	SA-2	Low	H-2	High			
T-2	Low	E-1	High	A-2	Low	SA-1	High	H-2	Low			
T-2	Low	E-2	High	A-1	Low	SA-2	Low	H-1	High			
T-2	Low	E-1	Low	A-1	Low	SA-2	Low	H-2	High			
T-1	Low	E-2	High	A-1	Low	SA-1	Low	H-2	Low			
T-2	Low	E-2	Low	A-2	Low	SA-1	Low	H-2	High			
T-1	Low	E-1	Low	A-2	High	SA-1	High	H-1	High			
T-1	High	E-2	High	A-2	Low	SA-1	Low	H-1	Low			
T-1	Low	E-1	Low	A-2	Low	SA-1	Low	H-1	Low			
T-1	Low	E-2	Low	A-1	High	SA-2	Low	H-1	High			
T-1	High	E-1	High	A-1	Low	SA-1	High	H-1	Low			
T-2	Low	E-1	Low	A-2	Low	SA-2	High	H-1	High			
T-1	Low	E-1	High	A-1	Low	SA-2	Low	H-2	Low			
T-2	High	E-2	Low	A-1	High	SA-1	High	H-2	Low			
T-2	High	E-2	Low	A-2	Low	SA-1	Low	H-2	Low			
T-2	Low	E-1	High	A-1	Low	SA-1	Low	H-1	Low			
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T-2	High	E-2	Low	A-2	Low	SA-2	Low	H-1	High			
T-2	Low	E-2	High	A-2	High	SA-2	High	H-2	High			
T-1	Low	E-1	Low	A-1	Low	SA-1	High	H-2	Low			
T-2	High	E-2	High	A-1	Low	SA-1	High	H-2	High			
T-2	High	E-1	High	A-1	Low	SA-1	Low	H-2	Low			
T-2	High	E-2	High	A-1	High	SA-1	Low	H-1	Low			
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T-2	High	E-1	Low	A-2	Low	SA-1	High	H-1	Low			
T-1	Low	E-1	High	A-1	High	SA-1	Low	H-2	High			
T-1	High	E-1	Low	A-2	Low	SA-2	High	H-1	Low			
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T-1	High	E-2	High	A-2	Low	SA-2	Low	H-2	High			
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T-2	High	E-1	Low	A-1	Low	SA-2	Low	H-1	Low			
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T-1	High	E-1	Low	A-1	Low	SA-2	Low	H-1	High			
T-2	High	E-1	Low	A-2	High	SA-2	High	H-2	Low			
T-2	High	E-2	High	A-1	High	SA-2	Low	H-2	High			
T-1	Low	E-1	High	A-2	High	SA-2	High	H-2	Low			
T-2	High	E-2	Low	A-2	Low	SA-2	High	H-2	High			
T-1	High	E-2	High	A-1	High	SA-1	High	H-1	High			
T-2	Low	E-1	Low	A-2	High	SA-1	Low	H-2	Low			
T-1	Low	E-2	Low	A-1	High	SA-1	Low	H-1	Low			
T-2	Low	E-1	High	A-1	High	SA-1	High	H-1	High			
T-2	High	E-1	High	A-2	Low	SA-1	Low	H-1	High			
T-1	High	E-2	Low	A-1	High	SA-2	Low	H-2	Low			
T-2	High	E-1	Low	A-1	High	SA-1	Low	H-1	High			
T-2	High	E-1	High	A-1	Low	SA-2	High	H-1	High			

ability of the API. Nanotechnologies for particle-size reduction of poorly soluble compounds continue to be an area of great interest and research [3].

Beyond the active excipients in the formulation — those that serve as penetration enhancers — proper choice of additional excipients is equally important. Other excipients include functional ones, such as thickeners, emulsifiers, and antimicrobial agents, and those included for aesthetic purposes, such as spreading agents, humectants, and detackifiers. They must not only be compatible with the API and fulfill their intended purpose but also must not interfere with the skin penetration of the API. Scientists should always perform excipient-compatibility studies prior to formulation development to determine the stability of the API in the presence of the potential excipients. Design of Experiments (DOE) is a very useful method to perform these studies. With proper set-up and analysis of the resulting data, it not only can limit the number of required sample preparations (compared to preparation of binary mixtures of the API with each excipient) but also can give some indication of second-order interactions. Table 1 gives an example of a DOE.

In this example, the independent parameters include:

- Type (2) and level (2) of thickener
- Type (2) and level (2) of emulsifier
- Type (2) and level (2) of antimicrobial system
- Type (2) and level (2) of spreading agent
- Type (2) and level (2) of humectant

The dependent parameters are the stability, viscosity, and bioburden of the formulation (that is, USP 61 Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests).

This table represents a custom design constructed using JMP software (JMP® 8.0.1, Cary, NC) with the types of excipients being categorical parameters and the levels of excipients being continuous parameters. The table gives the values of the independent parameters as Low and High. The scientist adds the actual values. This design evaluates primary and secondary interactions and consists of 64 runs. Looking at all the parameters, the number of experiments would be 2^n, where n = 10, or 1024 runs in a full factorial design (2 levels of each). As always, for semisolid formulations, scientists should perform excipient-compatibility testing in the wet state to represent actual conditions of use better, with excipients within established and appropriate concentration ranges. Emulsion-based systems can present special challenges in excipient-compatibility testing as a certain number of excipients — water, the oily component, and the emulsifier — need to be universal to each preparation. These systems may require an initial study first to identify a combination of compatible universal components, prior to initiating the full compatibility testing.

Formulation development can commence after demonstration of sufficient compatibility of the API with potential excipients. Each excipient chosen should have a clearly defined and demonstrated function in the formulation, as additional components only increase the potential for adverse interactions. Formulation scientists can develop several initial prototype systems simultaneously for informal assessment of physical stability. Rheology, particle or droplet size, pH, and visual appearance are useful metrics to evaluate basic physical stability. After establishing the physical stability of the prototypes informally, the scientist can employ In-Vitro Release Testing (IVRT) using Franz Cells (Figures 2 and 3) to evaluate the effect of the addition of various permeation enhancers to the prototype formulations.

Figure 2

Franz Diffusion Cell

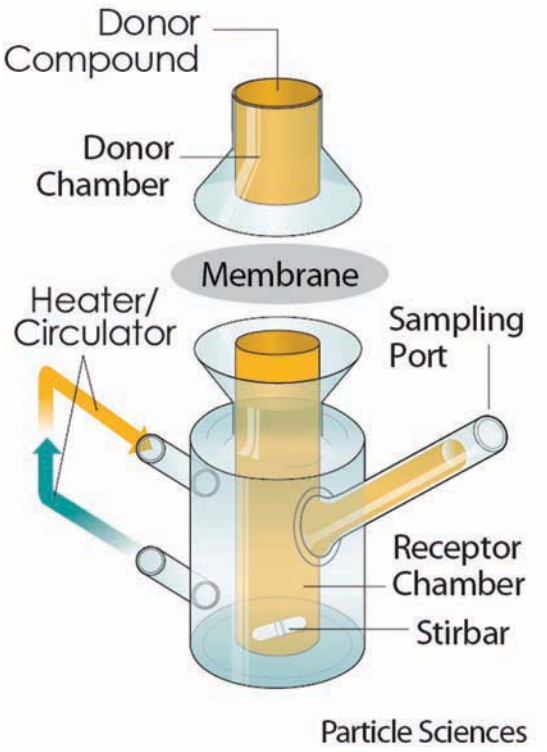

Figure 2

Multi-Station Franz Diffusion Cell System

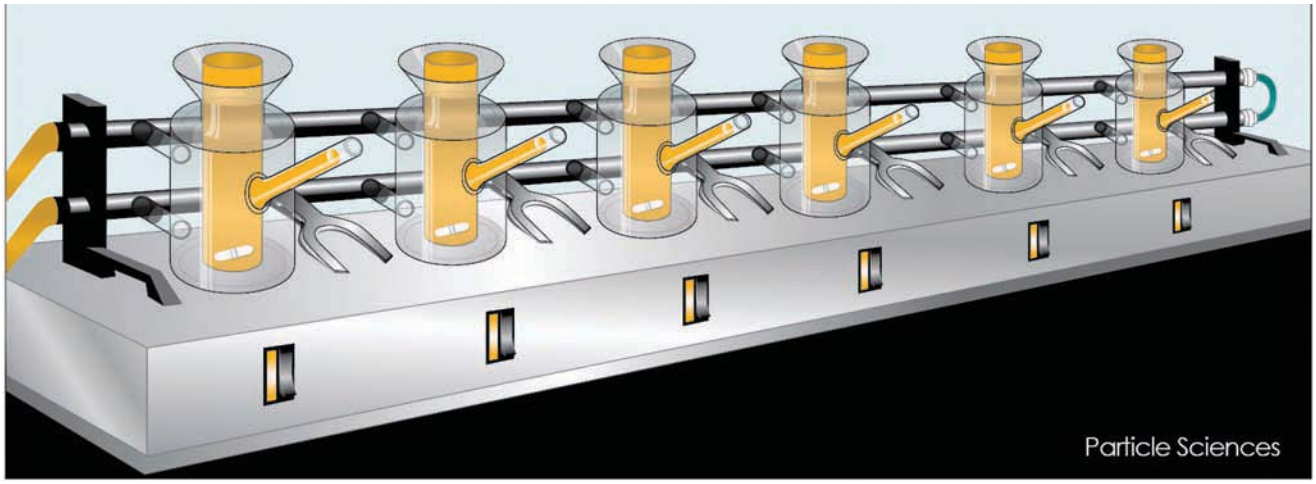

Table 2

Illustrative IVRT Parameters

Diffusion Cell	9-station Franz cell stirrer
Weight of Sample Gel	0.2 – 0.4 g
Membrane	Hydrophilic membrane, 25 mm diameter, 0.45 μm pore size
Receptor Medium	PBS based
Temperature	32°C or 37°C (Vaginal products)
Stirbar Speed	600 rpm
Sampling Aliquot	200 - 400 μL
Sampling Time	0.5, 1, 2, 3, 4, 6 hr

For initial prototype development, membranes for the evaluation may be cadaver skin, murine or porcine skin, or skin construct, or they may be synthetic. IVRT parameters include sample weight, membrane type, receptor media type, temperature, stir-bar speed, sampling aliquot, and sampling time (Table 2). Again, DOE may be a useful tool to evaluate a large number of penetration enhancers as well as combinations and concentrations thereof. After the scientist identifies one or preferably a number of potential penetration-enhancer systems, he or she should re-evaluate the informal stability of the formulations. IVRT also should be part of longer-term stability testing to assure that the skin-penetration behavior of the API in the formulation does not change over time.

Conclusions

This article discusses a simple model for determining if transdermal delivery of an API using topical formulations, such as gels, is possible or out of the question. With knowledge of the melting point and molecular weight, formulation scientists can use the method to estimate the maximum steady-state flux of an API through the skin, thereby determining if the API is viable. The article also discusses selection of excipients for topically applied transdermal formulations, covering the design of experiments for excipient-compatibility testing and in-vitro release testing to evaluate the formulations.

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