Transdermal Penetration Enhancers: Applications, Limitations, and Potential

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Introduction

Delivery of drugs via the skin has many attractions, including increased patient acceptability (noninvasiveness) and avoidance of gastrointestinal disturbances[1] and first-pass metabolism of the drug.[2] The fact that this route is not more widely used is because of the inherent barrier properties of the skin.[3] It is generally difficult to get drugs to cross the skin at a sufficient rate to deliver a therapeutic dose even when the drug is potent. Many different approaches have been taken to overcome the barrier presented by the skin, including mechanical disruption,[4,5] electrical disruption,[6,7] and chemical modification[8,9] of the barrier function. This review will focus on the use of chemicals to alter the penetration rate of drugs across the skin.

Agents capable of modifying the barrier to penetration presented by the skin have been called "penetration enhancers". There is usually a distinction drawn between chemicals that have their effect merely by occlusion of the skin leading to hydration of the skin, which in turn leads to increased permeability and those that interact with either the formulation applied or the skin itself. The former are generally not classified as "penetration enhancers".[10] Much research has been performed to identify penetration enhancers with the aid of in vitro screens,[11,12] and literally hundreds of different chemicals with a wide divergence of chemical structure that are able to modify the penetration characteristics of different drugs and marker compounds into the skin have been identified.[13,14] However, only a small number of these agents have been shown to produce useful enhancement in vivo, only a few have actually been incorporated into products and successfully tested in humans, and, other than previously used ingredients of topical preparations, none has yet been successful in the market place. This review is intended to examine why, despite all this work, we seem to have had very little success to date.

Historical and Current Perspectives

The idea of delivering drugs through the skin is old, as far back as the 16th century B.C., the Ebers Papyrus recommended that the husk of the castor oil plant be crushed in water and placed on an aching head and "the head will be cured at once, as though it had never ached." [15] Today transdermal drug delivery (TDD) is a well-accepted means of delivering many drugs to the systemic circulation, and currently transdermal patch devices are used to treat motion sickness, hypertension, angina, female menopause, severe pain states, nicotine dependence, and male hypogonadism.[16] The advantages of TDD are summarized in Table 1.

Despite all these advantages, a timely warning to formulators was issued by Hadgraft and Guy in 1987,[18] "TDD is not a subject which can be approached simplistically without a thorough understanding of the physicochemical and biological parameters of percutaneous absorption. Researchers who attempt TDD without appreciating this fact do so at their peril."

Our knowledge of these processes has been well reviewed in relation to percutaneous penetration by Barry.[19] Some specific issues that are worth singling out are the variability of the skin both within and between individuals,[20] the importance of metabolism in the viable epidermis as a metabolic barrier,[21] and the role of the immune system in limiting the use of some agents on the skin.[22,23]

The factors influencing the suitability of a drug for TDD are as follows:

⇒ potency of the drug − the daily systemic dose should be ≤20 mg
⇒ molecular size − the drug should have a MW of <500 Daltons
⇒ lipophilicity − the log P should be in the range 1−3
⇒ melting point − should be <200 °C
⇒ hydrogen bonding groups—should be ≤2
⇒ irritation − the drug should not be directly irritant to the skin
⇒ immunogenicity − the drug should not stimulate an immune reaction in the skin

A predictive rule of thumb is that the maximum flux of drug through the skin should decrease by a factor of 5 for an increase of 100 Da in MW, and decrease by a factor of 10 for an increase of 100 °C in melting point.[24]

Enhancement of Delivery

In addition to the potential for enhanced TDD to improve transdermal delivery rate control, the main reason that drug delivery across the skin needs to be enhanced is because of the low permeability of most transdermal candidates across the skin.[25] Traditionally, enhanced TDD has been achieved with patch devices that occlude the skin. Occlusion traps the natural transepidermal moisture of the skin, which increases the water content of the horny layer and swells the membrane, thus compromising its barrier function.[10] Prolonged occlusion of this nature can cause a 10−100-fold increase in drug permeability.[26] However, the tradeoff with these occlusive delivery systems is their propensity to cause local skin irritation.[27]

Physical Enhancement

Although many different physical approaches to enhancing percutaneous absorption have been attempted, the most

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Table 1—Advantages of TDD

- provides constant blood levels in the plasma for drugs with a narrow therapeutic window, thus minimizing the risk of toxic side effects or lack of efficacy
- avoids first-pass metabolism in the gastrointestinal tract and liver, which allows drugs with poor oral bioavailability and/or short biological half-lives to be administered at most, once a day, and which can result in improved patient compliance[17]
- the problems of the gastrointestinal environment, such as chemical degradation of the drug and gastric irritation, are avoided
- removing the transdermal drug reservoir from the stratum corneum can easily terminate drug input
- provides a noninvasive alternative to parenteral, subcutaneous, and intramuscular injections
- suitable for patients who are unconscious or vomiting

notable approaches are iontophoresis,[6] ultrasound (sonophoresis),[4] and electroporation.[7] None of these enhancement methods is passive in that they require the input of energy to achieve their effects. To date, these methods show most promise for TDD systems that incorporate a large drug reservoir on the surface of the skin, and that need to deliver very large molecular weight compounds in the kiloDalton range.[16]

Supersaturation

The thermodynamic activity of a drug can be increased by employing supersaturated systems that give rise to unusually high thermodynamic potentials; this effect was first shown in a volatile:nonvolatile vehicle by Coldman et al.[28] However, topical vehicles relying on supersaturation have the major limitation of formulation instability, both prior to and during application to the skin, unless the formulation can be stabilized with antinucleant and anti-crystal-growth agents.[29]

For example, Kondo et al.[30] used supersaturation to enhance the transdermal delivery of nifedipine in rats. The bulk vehicle was stabilized with polymers and this formulation formed an appreciable mass on the surface of the skin. The vehicle remained on the surface of the skin for a prolonged period (many hours). Therefore, although Kondo et al.[30] advocated the use of a metered spray to deliver these formulations, in reality it would be impossible to obtain a nonocclusive TDD system with a short application time and cosmetic acceptability and still maintain a clinically useful transdermal penetration enhancement.

Metabolic or Biochemical Enhancers

Chemicals that provoke biochemical and metabolic events within the skin can potentially be used to alter skin permeability. For example, these types of enhancers can reduce the barrier properties of the skin by either inhibiting enzymes responsible for the synthesis of specific stratum corneum lipids during stratum corneum repair[31] or by promoting the metabolism of existing skin lipids that are responsible for skin barrier function.[32] Although promising, both of these approaches need to undergo further investigation in vivo of their enhancement effects and their potential to produce skin irritation. It should be noted that chemical penetration enhancers may also provoke unwanted reactionary biochemical and metabolic events within the skin that could alter skin permeability,[16,33] however this is not their aim.

Chemical Penetration Enhancers

Ideally, the goal of dermal penetration enhancement is for the accelerant to reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells.[10,34] The properties proposed for an ideal penetration enhancer are shown in Table 2.

Over the last 15 years, a tremendous amount of work has been directed toward the search for specific chemicals, or combinations of chemicals, that can act as penetration enhancers.[9,35] The bulk of this work has been carried out by pharmaceutical companies that regard the results of their work as proprietary. Consequently, much of the cited literature is found in patents[13] as well as the usual pharmaceutical science literature.[14]

Table 2—Properties of an Ideal Penetration Enhancer[10]

- pharmacologically inert
- nontoxic, nonirritating, and nonallergenic
- rapid onset of action; predictable and suitable duration of action for the drug used
- following removal of the enhancer, the stratum corneum should immediately and fully recover its normal barrier property
- the barrier function of the skin should decrease in one direction only, and efflux of endogenous materials should not occur
- chemically and physically compatible with the delivery system
- readily incorporated into the delivery system
- inexpensive and cosmetically acceptable

Despite the large amount of work performed and the large number of different chemical entities identified, few have made it to the market place because of the following reasons.

1. The Applicability of the Method used to Demonstrate Enhancement—Most of the investigations involve in vitro penetration studies using a variety of membranes.[12,36] The follies of these methods have recently been pointed out by Barry.[37] Although attempts are currently being made to develop a generally accepted standardized methodology for in vitro testing,[11] there is still a large extrapolation to be made from performance in vitro to use in a clinical setting.

2. Incorporation of the Enhancer into a Doseform that is Acceptable to the User While Retaining the Activity of the Enhancer—When developing topical preparations for optimum bioavailability it is necessary to formulate them to ensure that the drug has the maximum tendency to leave the vehicle and partition into the skin. The driving force behind diffusive transport is a gradient in the chemical potential,[38] which is the continuous function (not the concentration) across interfaces. The presence of enhancers, which often will have good solvent properties, can decrease the chemical potential. The formulator needs to balance the solubility, and therefore the ability to use high concentrations of drug in a formulation, with the need to increase the chemical potential. These difficulties were realized early in the evaluation of laurocapram (Azone) where it was shown that incorporation of laurocapram into a commercially available cream containing fluocinolone acetonide did not increase vasoconstrictor activity, whereas simply incorporation of the steroid with 2% laurocapram in ethanol resulted in strong outperformance of the cream.[39]

3. The Need for Delivery of the Enhancer to the Skin and the Maintenance of Skin Concentrations of Enhancer for the Required Time Intervals—Although ethanol can act as a penetration enhancer, and various mechanisms of action have been postulated,[40] in practice its use as a penetration enhancer has relied on the application of a bulk aqueous ethanol vehicle to the skin whereupon the increase in the flux of the drug across the skin is mainly due to a solvent drag effect shown previously.[41] The mechanism of effect relies on the rapid

penetration of the solvent itself and the subsequent drag of the penetrant with it. A necessary corollary of this rapid flux is that the concentrations cannot be prolonged unless there is a reservoir present, thus limiting the applications of this type of enhancer to reservoir-based systems.

Clinical Usefulness

Of all of the potential enhancers identified those that have undergone significant clinical testing are discussed next.

In 1964, Stoughton and Fritsch reported that dimethyl sulfoxide (DMSO) enhanced the percutaneous penetration of various agents.[8] This characteristic was exploited clinically in many different circumstances but it did not lead to significant commercial products partly because of the high concentration needed for an effect and partly because DMSO is unpleasant to use.[42,43] It is interesting to note that after being virtually discarded, DMSO has recently been revived, and topical products containing DMSO with diclofenac are currently undergoing clinical trials.[44]

Laurocapram (Azone) is probably the most widely known chemical enhancer, and it is often used by transdermal research groups because of its good overall enhancing abilities,[45,46] which also makes it a useful basis of comparison for new chemical enhancers. However, because of its potential to irritate the skin,[47−50] laurocapram has failed to gain general clinical acceptance.

Fatty acids and fatty acid esters have been known for some time to enhance penetration. The major attraction of these compounds is that many of these materials are classified as Generally Recognized As Safe (GRAS). For example, Theratech Inc. uses a combination of glyceryl monooleate and lauryl lactate to enhance the diffusion of testosterone across nonscrotal skin in hypogonadal males in the Androderm patch.[51] A major concern is the irritation caused by these agents.[52] In clinical practice, one of the marketers of this product (SmithKline Beecham Pharmaceuticals) suggests the prior application of triamcinolone acetonide to overcome this irritation problem.[53]

There are also attempts to gain regulatory approval for newly synthesized enhancers, such as Macrochem's SEPA enhancer, 2-*n*-nonyl-1,3-dioxolane,[54] and NexMed's NexACT enhancers, alkyl *N*,*N*-dialkyl-substituted amino acetates.[55] Both of these types of agents have already shown good enhancing abilities that are comparable to those of laurocapram.[49, 56−58] Topical gel formulations containing SEPA with ibuprofen or alprostadil are currently in phase II clinical trials in the USA.[59] The NexACT enhancers are undergoing pre-Phase II toxicology studies in the USA, and a Phase III clinical trial in China has been completed for a topical gel formulation of alprostadil.[59] The success of these formulations will probably depend as much on the irritation observed in these trials as on the actual clinical effect.[60]

We have identified some novel GRAS chemical enhancers[61] that are currently used as topical sunscreening agents.[62] The main chemical enhancers in this group are padimate O, octyl salicylate, and octyl methoxycinnamate. As sunscreens, these agents have maximum approved topical concentrations of 8.0, 5.0, and 7.5%, respectively, in the USA, Europe, Japan, and Australia.[62] Over their many years of use as topical sunscreens, these agents have shown a low incidence of local skin reactions.[63]

These compounds have been shown to increase the penetration rate of a range of different drugs across skin from a number of different animal species in vitro.[64−66] We have also shown the enhancing effect of these compounds in vivo using microdialysis in conscious rats to measure the penetration of ibuprofen from topically applied gels.[67] The enhancers in these studies were incorporated into gel formulations suitable for clinical use. The effect of these enhancers in circumstances relevant to clinical use has also been demonstrated in vivo with the hormones estradiol and testosterone applied in the form of a spray to weanling pigs.[68] Significantly higher plasma levels of both of these compounds were found when the enhancer was incorporated into the spray formulations. These enhancers were also used in a small clinical trial in postmenopausal women designed to demonstrate the feasibility of delivery of estradiol via a transdermal spray.[69] The dose form was shown to deliver clinically relevant amounts of estradiol without signs of irritation.

The future will tell whether the enhancers currently under investigation can be formulated into acceptable and nonirritant products. Regardless, the search for new enhancers with ideal properties (Table 2) will continue.

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