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Review

Current Status and Future Prospects of Transdermal Drug Delivery

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INTRODUCTION

The transdermal route of controlled drug delivery is often dismissed as a relatively minor player in modern pharmaceutical sciences. One commonly hears that the skin is too good a barrier to permit the delivery of all but a few compounds, and that transdermal transport is not even worth consideration for the new drugs of the biotechnology industry (1). Is this a fair characterization and, if not, how has this somewhat negative opinion originated? In this article, we will discuss that: (i) transdermal delivery has been one of the most successful controlled release technologies to-date in terms of the number of approved products which are on the market; (ii) for drugs of appropriate pharmacology and physical chemistry, the transdermal route is an extremely attractive option; (iii) there exist certain criteria which render the transdermal route completely unfeasible, and that it is a general disservice to pretend that these obstacles can be overcome; and (iv) novel aspects of transdermal technology (noninvasive glucose monitoring, iontophoresis, ultrasound-enhanced delivery) represent new avenues of considerable potential and challenge.

CURRENT STATUS

In the U.S., there are seven approved, systemically-active transdermally-delivered drugs (scopolamine, nitroglycerin, clonidine, estradiol, fentanyl, nicotine and testosterone) for some of which there are multiple approved systems. Given that the first 'patch' was not on the market until the early 1980s, these statistics reflect a rather successful history, particularly in comparison to other non-oral routes of novel drug administration (2). After all, how many comparable nasally-delivered, or inhaled, or implanted, or liposomal-based systems, for example, are presently available to the consumer? There is no question that transdermal administration has entered the public's consciousness: the concept of a "patch" is generally acknowledged and accepted. It is true that, following the approval of the first nitroglycerin systems, there were outrageous claims made about the future of transdermal delivery (e.g., "by the 21st Century, we will be taking most drugs in the form of a patch", etc.), claims that were (and remain) completely ridiculous. As will be discussed below, the delivery of drugs via the skin is subject to some substantial constraints, which limit its general applicability (3). Nevertheless, this route of administration does not deserve the 'bad press' that it sometimes receives. Rather than being criticized for its limited success (which is simply not a true reflection of reality), transdermal delivery can be legitimately called to task for some of the compounds that have found their way onto the market. For example, despite the commercial success of the nitroglycerin patches, it is quite arguable that tolerance-inducing drugs, like the organic nitrates, are contraindicated for slow, essentially zero-order delivery, and that a 'drug input-free' period is necessary for optimal therapeutic efficacy (2,4).

ADVANTAGES AND DRAWBACKS OF TRANSDERMAL DELIVERY

If a drug has a right mix of physical chemistry and pharmacology, transdermal delivery is a remarkably seductive route of administration (3). What comprises the right combination of circumstances? First and foremost, particularly for passive delivery, but also true for enhanced drug absorption, the therapeutic agent must be potent (2). Given that the size of the patch cannot (for practical, economic and cosmetic reasons) exceed, say, 50 cm^2, and given that the barrier function of the skin is the best that the human body possesses, it is not within the capability of existing technology to deliver much more than 50 mg of drug per day (2). Next, and again because of the skin's excellent resistance to drug diffusion, the agent must be effective when delivered slowly over a relatively long time period. Transdermal delivery, even with enhancement, is not going to be truly "pulsatile" like an injection or (for example) pulmonary inhalation. Yes, it is possible to have *faster* input with iontophoresis, but the achievement of a true "bolus" has been rarely demonstrated *in vivo* (see below). Furthermore, to be truly useful and to represent a real therapeutic advance,

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transdermal delivery must confer a real benefit over existing treatment(s). Hence, if the drug has a narrow therapeutic window, is subject to extensive first-pass metabolism when given orally, must be taken several times per day, and causes unpleasant side-effects due to its short half-life, which lead to highly fluctuating plasma levels, then transdermal delivery has much to offer, and these are the drugs that should be attracting our attention (2). Physicochemically, it is now generally accepted that relatively low molecular weight compounds (<500 daltons), of correctly balanced oil and water solubilities (octanol—water partition coefficients between, say, 10 and 1000) and with modest melting points, are likely to have decent passive skin permeabilities (5). However, just because a drug satisfies these non-biological criteria does *not* necessarily make it a good transdermal candidate. Suppose the compound is presently administered orally as a once-a-day tablet with good bioavailability and negligible side-effects; what possible benefit (other than the purely capitalistic) will accrue from the development of a "patch"?

SKIN BARRIER FUNCTION

From an evolutionary standpoint, the skin did not develop as an epithelium through which absorption was intended. Quite the reverse: the architecture and biology of the skin is, in large part, directed towards the construction of a highly efficient barrier to the outward loss of water (6–8). The most superficial and least permeable skin layer, the stratum corneum, is a remarkable feat of bioengineering, both from a structural and compositional viewpoint, and provides a uniquely impressive resistance to molecular transport both from and into the body (6–8). This is the reason that transdermal delivery requires potent drugs—one simply cannot transfer very many micrograms of any compound across a small surface area in the period of a few hours. Because the principal function of the skin is to minimize transepidermal water loss, the stratum corneum is a predominantly lipophilic barrier that is particularly impermeable in a passive sense to hydrophilic drugs (including charged species). It follows that enhancing technologies (see below), irrespective of the mechanism involved, are likely to elicit their most significant effects upon compounds which have inherently low permeabilities. However, this observation should not be interpreted specifically with respect to the pathway of molecular penetration: that is, just because an enhancer promotes the transport of a polar compound more than that of a lipophilic moiety does *not* mean that the enhancer acts on a putative "polar" pathway across the skin; in fact, logically, it supports, if anything, the opposite conclusion (namely, that the enhancer reduces the skin's lipophilic barrier, thereby rendering it more permeable to the polar species). The diffusional resistance of the stratum corneum is a challenge that has been accepted by the pharmaceutical scientist and considerable activity has been directed towards percutaneous penetration enhancement technologies (9,10). While the different approaches investigated have met with success, at various levels, in terms of reducing the skin's physical barrier to transport, they have encountered a biological aspect of skin barrier function, namely the inflammatory response, which represents another feature of the tissue's role as a protective sheath for the body. The classic response of the skin to any insult of the barrier is to initiate *in situ* a cascade of biochemical events designed to repair the "damage" (e.g., that caused by delipidization with solvents, tape-stripping, UV irradiation, etc.) (11–13). The sequelae involve not only lipid secretion at the base of the stratum corneum from membrane coating granules (14), but also the release of inflammatory mediators, such as the cytokines TNF-α and IL-1 (15,16). It must be remembered, therefore, that a penetration enhancing technology will, by definition, reduce skin barrier function and must, as a result, trigger a response in the skin which is designed to correct the effect. The accompanying level of irritation will reflect the extent of the perturbation. In a practical sense, this natural response ultimately determines the feasibility and acceptability of the enhancement technology and can influence significantly the form of transdermal product which is developed. Consider the two testosterone systems presently on the market: the first, Testoderm® (Alza Inc., Palo Alto, CA), is a relatively large patch designed to be worn on the shaved scrotal skin of the patient. The application site is relatively permeable, permitting the necessary dose to be absorbed without use of "aggressive" formulation components. The second, Androderm® (Theratech Inc., Salt Lake City, UT), on the other hand, is designed to be worn on almost any body site (e.g., upper arm, chest, etc.), being capable of delivering the target dose through inherently less permeable skin by the incorporation of penetration enhancers in the patch. It follows that development of the latter formulation accepted the higher levels of local inflammation (produced as a result of the absorption of the enhancer) in exchange for a significant (expected) improvement in patient acceptability and compliance.

NEW TECHNOLOGIES

Chemical Enhancers

As can be inferred from the preceding discussion, the new directions in transdermal delivery and the most recent developments center around methodologies to increase molecular transport across the skin. Much effort has been directed towards the search for specific chemicals, or combinations of chemicals, that can act as penetration enhancers (9,10). The trend in recent years has been to identify substances that are categorized as GRAS, rather than the more difficult path of seeking regulatory approval for a newly synthesized enhancer (i.e., new chemical entity). One significant problem of chemical enhancers has been alluded to above: effective enhancers are irritating—the typical combination of an amphoteric moiety with a polar solvent invariably elicits a local skin reaction (9,10). More speculative, at least with respect to applications *in vivo* in man, is a so-called "biochemical enhancer" strategy, in which inhibitors of specific stratum corneum lipid synthetic enzymes are administered (so far, typically pre-permeabilized stratum corneum) to keep the barrier open for longer periods of time (17). The practical utility of this rather clever approach requires further investigation. A second limitation of the use of chemical enhancers concerns the issue of *control*. The reason that enhancement is necessary is that, on average, the skin's permeability to a drug is too low. Typically, between subjects (and even at different sites on the same subject), the variability in permeation can be high; coefficients of variation of ≥50% are not uncommon. The most useful enhancer, therefore, serves two purposes: (1) it increases permeability, and (2) it enables more control to be "allotted" to the delivery system, thereby

reducing inter-subject variability. At this time, there is far more evidence that the former is achieved than the latter; that is, while increased permeability is a general observation, high variability remains. A further limitation with respect to the chemical enhancer field is that most of the information presently available is *in vitro* data obtained in experiments using skin from animal models, some of which are much more sensitive to enhancer perturbation than the human barrier (9,10).

Novel Formulations

Although not yet focused on particular transdermal (i.e., for systemic effect) applications, some creative research has been reported in the area of improved formulations for topical (dermatological) drug administration. For example, stabilized, drug-supersaturated vehicles have been prepared and characterized, new microemulsions have been shown capable of large drug loading, and novel polymers with unique attributes (e.g., hyaluronan) are attracting increasing attention. Most energy (and publicity), though, has centered upon liposomal-based delivery systems, for which some remarkable results have been published. The most intriguing, perhaps, is the apparently liposome-mediated transport of recombinant interferon-γ across excised human skin (18). The successful delivery of the protein (>16Kda) to the epidermis was confirmed by a sensitive ELISA, by an anti-viral bioassay and by immunohistochemistry. Mechanistically, however, the role of the liposomes remains unclear. In a number of other experiments, performed in numerous laboratories, the potential for liposomes to "target" topical drugs to follicular structures has been described (e.g., (19)) and the importance of various compositional and dimensional parameters have been discussed. It remains to be seen whether this 'technology' is easily transferable to practical dosage forms and/or to the systemic delivery of drugs via the transdermal route.

Iontophoresis

The drawbacks associated with chemical enhancers, coupled with the fact that they are often not good enough to help with the delivery of the new "biotechnology" drugs (i.e., peptides, small proteins, oligonucleotides, etc.), explains, in large part, the renaissance of interest in iontophoresis that has taken place over the last decade (20). The highly polar, and frequently charged, nature of these compounds has provoked considerable new research into the mechanism and application of electrically-controlled drug delivery through the skin (21). In particular, because of the complicated pharmacology of some of these agents, the potential of iontophoresis to truly *control* the drug input rate is a singular advantage. There is good evidence now that manipulation of the current profile can be used to vary the kinetics and extent of drug absorption (20). The "downside" is that iontophoresis is not necessarily very efficient; that is, of the total charge introduced, only a fraction is translated into drug delivery, the major part being carried by other ions in the circuit (particularly by small highly mobile species, such as Na^+ and Cl^-, moving out of the body) (22). There is an important question of the cost of iontophoresis, therefore, in addition to other concerns (for example) of drug stability in an iontophoretic patch, of the extent of skin metabolism and (as for chemical enhancers) of local irritation. At this time, it is possible to evaluate quite simply the electrochemical stability of a drug and there are techniques that can be used to protect against, or minimize, electrochemical degradation; on the other hand, the degree of (for instance) peptide metabolism in the skin during iontophoretic delivery is not well-characterized. It appears that the irritation associated with active periods of iontophoresis is transient and reversible (23); chronic effects, however, have not been fully investigated. It should be emphasized that the low efficiency of iontophoresis constrains even this quite effective means of enhancement (after all, very large *relative* increases in permeation can be achieved) to potent drugs (20,21). Again, one is not going to deliver hundreds of milligrams a day by this route! Indeed, from the iontophoretic data in the literature, it would appear that insulin is too great a challenge (24)—not that it is undeliverable, rather that the dose required is unfeasibly high. Success in lowering hyperglycemia iontophoretically in small animals is possible (24) because these species do not require very much insulin. Scaling up to a human being quickly reveals that one is going to be (at best) between 10 and 100-fold below the required dose, to even maintain *basal* control of blood sugar levels (24,25). Nevertheless, in our opinion, iontophoretic drug delivery will have its successes—the first drug-device combination (*Iontocaine*, Iomed, Salt Lake City, UT) was, in fact, just recently approved. The initial products will be modest (such as the lidocaine system), but more sophisticated and therapeutically diverse systems can be expected, particularly as the level of regulatory "comfort" increases.

Electroporation and Sonophoresis

In a more futuristic sense, there are two technologies which are attempting to overcome the most daunting challenges of transdermal drug delivery: that only small doses are deliverable, that rapid absorption is impossible, and that macromolecules cannot be transported through the skin. First, there has been a burst of activity focused on the use of electroporation: i.e., transient high-voltage electrical pulses, to cause rapid permeabilization of the stratum corneum through which large and small peptides, oligonucleotides and other drugs can then pass in significant amount (26). The degree of enhancement achieved *in vitro* is related to the applied voltage, and the number and duration of the pulses, offering the possibility, therefore, of a controllable phenomenon (26). Very little *in vivo* work, however, has been reported and there is almost no information on the skin toxicity associated with the approach (27). Second, there has been a renewal of interest in the use of ultrasound-enhanced drug delivery across the skin. Through the early 1990's there had been numerous studies which showed that high frequency ultrasound (2–10 MHz at ~1 W/cm^2) (28) could produce modest enhancement of simple molecules. It was then demonstrated that low-frequency ultrasound (~100 KHz) at lower power levels could be used to deliver insulin across rabbit skin *in vivo*, resulting in plasma hormone levels that rose significantly during the application period and a concomitant lowering of blood glucose (29). Recently, a parallel reduction of blood sugar has been confirmed in diabetic rats (using an even lower frequency) (30). There was a dose-response both with respect to time of ultrasound application and to the power used. *In vitro* results also indicated significantly enhanced ultrasound-mediated delivery of interferon-γ and erythropoeitin (with molecular weights, respectively, of ~17kDa and ~48kDa). Despite the excitement that these findings have provoked, it is important to maintain an appropriate perspective

until several basic questions are answered with respect (again) to scale-up into man, mechanism of action, "toxicity" in the broadest sense, and economic and technological feasibility. At the time of writing, all of these issues remain open, and the perceptive reader will deduce that a "product" utilizing either of these novel concepts is many years from realization.

Reverse Iontophoresis

Finally, it is appropriate to discuss another new transdermal technology: "reverse iontophoresis"—that is, iontophoresis used not for drug delivery but instead for the relatively noninvasive extraction of "information" from the body for the purpose of classical clinical chemistry. The symmetry of iontophoresis means that current passage causes ions and other molecules to move in *both* directions under both electrodes (20). Thus, with an appropriate level of assay sensitivity, iontophoresis can be used to "sample" an analyte within the body, and to provide potentially, therefore, a key component of a true closed-loop system. The idea has been initially applied, not surprisingly, to glucose monitoring (31). Although glucose is not charged, iontophoresis can dramatically increase the passage of this polar sugar across the skin. This is achieved by electroosmosis (20,21). At neutral pH, the skin is a negatively-charged membrane, permselective to cations. It follows that, on application of an electric field, more charge is carried across the skin by positive ions than by negative ions. In turn, this means that more momentum is transferred to the solvent in the direction of cation movement. This "electroosmosis" results in the fact that polar, yet uncharged, molecules, such as glucose, (which have very low passive permeabilities across the skin) can be effectively "carried" across the barrier at significantly elevated rates. Following *in vitro* and human *in vivo* experiments (32,33), that demonstrated the feasibility of the idea, a recently published study (34) has shown in diabetics that "reverse iontophoresis" has the potential to noninvasively monitor blood glucose levels as efficiently as the currently-used "finger-stick" methodologies. However, it should be understood that this does not mean that the exploitation of this concept is a "slam-dunk". To bring a product to the market requires several key issues to be addressed and solved (31), not the least of which are (a) the development of an "on-board" sensor that can measure small glucose concentrations precisely and reliably, and (b) the ability to calibrate the system so that the glucose measurement at the level of the skin is reflective of blood glucose concentrations even when the system is removed and replaced at a different skin site. Nevertheless, because this technology involves no drug *per se*, and given that it has advanced a considerable distance in a remarkably short period of time, it is reasonable to predict that this use of the transdermal route has a much greater chance of commercial success before the millennium than *any* approach for non-injection insulin delivery.

SUMMARY

The skin evolved to be a protective barrier. It performs this function remarkably well and presents, therefore, a formidable challenge to the drug delivery scientist. Even so, transdermal drug delivery systems are now recognized components of the pharmaceutical "toolbox" for therapeutic application. Indeed, this route of administration is perhaps one of the most successful controlled release technologies available today. To go to the next "level," however, requires that a method be identified by which drug permeability can be reversibly, predictably and controllably enhanced. Several approaches have been investigated and have reached various levels of understanding and practicality. None, though, has yet made the sought-after breakthrough which will direct the field for the next decade or more. Chemical enhancers have been studied most intensively (code for: "there appear to be more problems with chemical enhancement than other approaches"), while iontophoresis moves forward circumspectly, and most excitement associates itself with electroporation and low-frequency ultrasound (code for: "we know least about these technologies"). Interestingly, a 'dark horse', that is, "reverse iontophoresis", is an application that has crept up quietly and now attracts the attention of many a punter (35). But, whatever one's bias or favorite, it is fair to say that (1) the transdermal field has, to-date, performed more than respectably, (2) that it is full of ideas and new directions, and (3) that it will again surprise and confound the skeptics!

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