INTRODUCTION
1. INTRODUCTION

In the past years, drugs have been formulated as ointments, creams or lotions for application to wounded, infected or otherwise traumatized skin surfaces to evince a "local" effect. A more esoteric mode of dosage is to deliver therapeutic agents across intact skin. In the past three decades transdermal drug delivery has moved to a phase of clinical reality beginning with the first scopolamine patches being approved in 1979, to the point where transdermal delivery system delivers a number of drugs.¹ Presently several classes of drugs are under investigation to determine their potential for TDS (trans dermal system) development. The penetration through stratum corneum (SC) is the rate-limiting step for delivery of most of the drugs. Some of the earliest contributions related to transdermal delivery involved understanding the principal permeation barrier in the skin. As early as 1924, Rein hypothesized that the principal resistance to transdermal transport was in a layer of cells joining the stratum corneum to the epidermis.² Blank, 1964, proved the case by stripping experiments in which he removed the stratum corneum from the skin's surface and showed that the rate of water loss from skin increased dramatically once the last cellular layer of the stratum corneum was eliminated.³ Scheuplin's work⁴ established that transdermal penetration was limited by the stratum corneum itself; and this has lead to considerable activity towards different percutaneous penetration enhancement
technologies.\textsuperscript{5} Michaels et al., 1975, did elegant experiments where they examined diffusion coefficients of different drugs through the stratum corneum showing that a number of these drugs had significant permeability.\textsuperscript{6}

There is little question that the skin represents a very important route of delivery in that it can provide an effective means for delivering drugs that are destroyed by the liver when taken orally. The primary pathway of transdermally delivered drugs is paracellular, i.e., around the cells, then through the elastin glue. The glue-like compound, elastin, composed of collagen and hyaluronic acid and other lipids, which occupies the interstices between the cells of the top-most layer of the skin (i.e., the epidermis, including, e.g., stratum corneum, lucidum, granulosum, spinosus) must be dissolved (or otherwise disrupted) in order for a medicament or other active agent, dissolved in a solvent, to transmigrate through viable skin to the subcutaneous tissues where the cutaneous plexi of the capillary net can be reached and/or deeper penetration achieved. When the elastin is dissolved, other agents may then trans-migrate the outer layers, so the body immediately begins to attempt to repair the damage caused by the dissolution.

Diffusivity of a drug molecule is dependent on properties of both the medicament and the medium (carrier). The diffusivity in liquid media in general, tends to decrease with increased molecular volume.

The rate of skin penetration is a function of (1) the diffusion coefficient, (2) the barrier partitioning tendencies, (3) binding affinities and (4) the rate of
metabolism of the medicament by the skin. The Diffusion Coefficient of the medicament is influenced by (1) molecular weight, (2) molecular structure, (3) additives and (4) rate of metabolism of the medicament by the skin. Diffusion is also dependent on the carrier, with diffusivity decreasing with increased molecular volume.

An optimum HLB (hydrophilic lipophilic balance) is required for a medicament to penetrate efficiently. The optimum HLB may be predicted by plotting the log (permeability coefficient) vs. Log\textsubscript{OW} (oil and water partition Coefficient) of the medicament for the stratum corneum and the viable skin. Highly lipophilic drugs bind readily in the viable skin and therefore, dissolution into the blood is minimal. Therefore, highly lipophilic drugs must be shielded to inhibit such binding. Skin metabolizes drugs effectively, so metabolism issues in the skin, such as, enzyme saturation or inhibition, medicament/metabolite fluxes (e.g., how rapidly and completely does the drug metabolize to a different form) should be taken into account. Un-ionized species of medicaments transmigrate more readily. Generally, un-ionized species are two orders of magnitude more permeable than their ionized form.

Thus, the challenge of creating an effective transdermal delivery system would ultimately involve not only having a high enough drug permeability through the stratum corneum, but many other factors including ensuring that the drug delivery system does not irritate the skin, the drug was not unduly metabolized, the drug delivered in this manner bears appropriate
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pharmacokinetics and pharmacodynamics and that the drug was stable in the formulation.

Today there exists a number of transdermal patches for drugs such as scopolamine, nitroglycerin, nicotine, clonidine, fentanyl, estradiol, testosterone, lidocaine, and oxybutinin. Several TDS have been successfully developed and approved by FDA for marketing, e.g., Transderm-NitroTM, EstradermTM, DuragesicTM.7,8

Transdermal clonidine, nitroglycerin and fentanyl patches exhibit fewer adverse effects than conventional oral dosage forms.9 Of particular note has been the value of nicotine patches in preventing smoking and prolonging life. For example, 2 years after being on transdermal nicotine patches for 12 weeks, four times as many patch wearers did not smoke compared to patients who received placebos.10

The current U.S. market for such patches is over $3 billion annually. Depending on the drug, the time of duration of delivery is generally from 1 to 7 days. Patches have been useful in enabling new therapies and in reducing first pass effects. For example, transdermal estradiol patches are used by over a million patients per year in contrast to oral formulations, are not associated with liver damage.

Nonetheless, only a limited number of molecules have been successfully delivered transdermally to date, so various approaches such as chemical enhancers, electricity, ultrasound and microneedles are being explored.
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Iontophoresis has been the primary electrical approach studied and has been shown to provide enhanced transport for some low molecular weight molecules such as pain medications and even decapetides.\textsuperscript{11} It is also being used as a means of extracting substances such as glucose from interstitial fluid.\textsuperscript{12} Electroporation, which involves higher voltage pulses for shorter time periods, has been used to temporarily create pores in the skin and has allowed the delivery of even larger molecules such as heparin and oligonucleotides through human cadaver skin. Ultrasound, particularly at low frequencies, has been shown to greatly enhance the flux of large molecular weight substances through the skin; over five thousand times normal fluxes have been achieved for molecules the size of insulin or larger and ultrasound is currently in clinical trials for delivery of insulin and pain medications.\textsuperscript{13}

The physicochemical properties, potency and pharmacodynamics of the drug need to be appropriate, with high potency (low dose) as a pre-requisite. With respect to other therapeutic areas, the motion-sickness drug, scopolamine is low dose, and has appropriate skin permeation characteristics to enable formulation as a transdermal patch. Peaks and troughs and their associated side effects are obviated by the slow delivery via the transdermal route. The transdermal administration of drug for systemic therapy has thus attracted much attention. The delivery of drugs through the skin for systemic effects may have several advantages over conventional oral and the other invasive methods of drug delivery.\textsuperscript{14}