Three Generations of Transdermal Drug Delivery

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The skin offers an excellent route to administer medicines into the body, given its large and accessible surface. However, the barrier properties of stratum corneum must be overcome for transdermal delivery, especially of large compounds and large doses (1).

First-generation transdermal delivery methods have relied on selecting drugs with low molecular weight, high lipophilicity and low dose requirements. Such drugs can permeate across skin at therapeutic rates without the need to increase skin permeability (2). Most transdermal patches in clinical use today fall into this category. Drugs for dermatological disorders can often be of larger size and lesser lipophilicity, given the smaller doses needed for local therapy and the often compromised skin barrier associated with the disease state (3). In some cases, prodrugs have been made to optimize drug properties for increased transdermal absorption (4).

The second generation of transdermal delivery methods involves molecular-scale disruption of the skin barrier to increase transdermal transport. Chemical enhancers (5, 6), non-cavitational ultrasound (7) and iontophoresis (8, 9) have been studied extensively and are used as part of a number of approved transdermal drug delivery products. These approaches have been effective to increase skin permeability to small molecule drugs that otherwise have difficulty crossing the skin at therapeutic rates. Their more aggressive application to enable delivery of a broader number of drugs, including macromolecules, has been limited by insufficient targeting of effects to stratum corneum, which causes side effects in deeper tissue.

The third generation of transdermal delivery methods overcomes this limitation by targeting effects to stratum corneum by disrupting the barrier at either the molecular scale or the micron scale. Cavitational ultrasound (10, 11), electroporation (12, 13) and chemical enhancer mixtures (14) cause molecular rearrangements in the stratum corneum to increase skin permeability to small molecules and macromolecules as well. Microneedles (15, 16, 17), thermal ablation (18) and skin abrasion (19) generate micron-scale holes in the stratum corneum to enable administration of a range of compounds, including macromolecules and particles. These methods are mostly in preclinical and clinical research stages.

Overall, the field of transdermal drug delivery has advanced through the first generation of methods that have enabled current patch products, the second generation that broadens the scope of compounds that can be delivered and, most recently, the third generation that promises to enable transdermal delivery of proteins, vaccines and gene-based therapies.

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