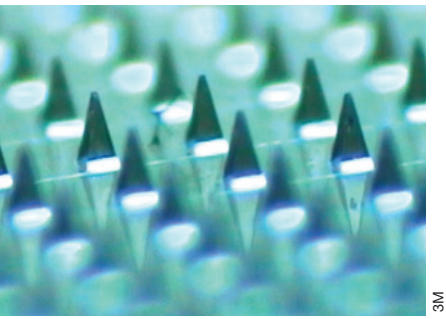
Transdermal Drug Formulation and Process Development

Timothy A. Peterson



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Transdermal drug delivery, a vital technology of increasing interest, offers such benefits as controlled delivery for as long as a week and improved patient convenience and compliance. Although this technology is not applicable for all drugs, recent progress has increased the number of transdermal drug delivery systems that will bring these benefits to patients.

Timothy A. Peterson, MChE, is an advanced-product development specialist at 3M Drug Delivery Systems Division, St. Paul, MN, tapeterson@mmm.com.

A growing number of drugs are being developed and introduced to the market as transdermal patches. Technology is paving the way for broadening the range of drugs that can be administered through the skin. Patients continue to be attracted to the user-friendly attributes of transdermal systems, leading to better compliance with their treatment regimens. However, the advantages of transdermal therapies can be brought to patients only after the development of a well-conceived formulation that integrates such components as adhesives, excipients, a release liner, a backing, and membrane films to achieve optimal system performance.

The development of a transdermal system requires a team of experts with knowledge of pharmaceutics, materials science, engineering, and biology. Assessing the technical compatibility of a drug with transdermal drug delivery technology is the first step. Several models are available that allow a reasonable prediction of skin permeability based on the physicochemical characteristics of the compound (1,2).

The skin permeation rate then can be compared with the required dosage to get an initial read on transdermal feasibility. If further development is warranted, feasibility experiments can be conducted in the lab to confirm skin permeation estimates and evaluate compatibility of the compound with other potential formulation components.

Transdermal system design

Patch design is among the first considerations in developing a transdermal drug. Properties of the drug, the desired delivery profile, and the target patient group determine which design is best for a given application. Every design incorporates four elements: a backing, an adhesive, a release liner, and the drug. In addition, the reservoir and multilaminate designs include a membrane film that controls the rate of delivery from the patch.

In the reservoir-type design, the drug solution is in a liquid reservoir compartment, separated from the release liner by a semipermeable membrane and an adhesive. The matrix design is similar to that of the reservoir, but the drug is instead provided as a semisolid formulation, and there is no membrane layer.

Drug-in-adhesive (DIA) transdermal systems incorporate the drug directly within the skin-contacting adhesive. A multilaminate DIA design adds a membrane between two distinct DIA layers or multiple DIA layers under a single backing. Because of its elegant simplicity and patient preference, DIA is considered state-of-the art in transdermal drug delivery systems design.

The simple appearance of a transdermal drug delivery patch belies the complex development process necessary to produce a therapeutically effective patch. There is no single "recipe" that applies to every transdermal drug delivery product. A well-designed transdermal drug delivery formulation must balance the factors of delivery, adhesion, and skin tolerability using a customized combination of components that complement the drug formulation and yield a commercially viable transdermal drug delivery system.

Selection of the adhesive is among the most important formulation choices because it affects both drug delivery and adhesion of the patch to the skin. It's not easy to adhere materials to human skin. And because some patches are worn as long as seven days, good adhesion throughout the wear period is a significant challenge.

The challenge becomes clear when one considers the dynamic conditions encountered during the wear period: drug and excipient leaving the adhesive matrix and entering the skin, water and oils from the skin interacting with the adhesive, the skin itself hydrating under the patch, and body movements applying stress to the patch in many directions. These conditions, along with the specific interactions between the drug and the adhesive, are often too demanding for an off-the-shelf adhesive. The ability to

customize the adhesive to address these challenges is a key to successful transdermal drug delivery formulation. In addition, the patch must leave no residue when removed and monomer and solvent levels in the adhesive must be limited to avoid skin irritation or systemic toxicity.

Packaging the transdermal product

The backing film, release liner, and pouch materials all serve to contain and protect the transdermal drug formulation. The backing protects and contains the formulation throughout the shelf life and during the wear period. The choice of backing material is critical because it influences the delivery profile, adhesion, wearability, and appearance of the patch. Some backings are laminates of several materials (e.g., polyethylene, positron emission tomography, ethylene vinyl acetate) that provide the desired properties. These materials must prevent unwanted absorption of the drug or other excipients. The backing also controls occlusion of the skin or the evaporation of moisture though the patch. The release liner protects the skin-contacting adhesive during storage. It must provide consistent release from the adhesive throughout the shelf life of the product without interacting with the patch's other components.

All currently marketed transdermal products are provided as single-unit pouches. The pouch protects the patch and preserves its stability. Like the release liner, the pouch must not interact with the formulation ingredients. Pouches are typically multilaminates and often include a layer of aluminum foil because of its barrier properties. The inner surface of the pouch material must be sealable.

From the laboratory to the production line

The manufacturing technology of drug-in-adhesive transdermal patches draws heavily upon tape manufacturing processes that have been developed during the past 60 years (3). A solution of adhesive polymer in a solvent is mixed with the active ingredient and any other formulation excipients to form a solution or suspension. The solution is then coated onto a web, usually the product release liner or the backing film. The web is conveyed through a coating station where the solution is applied. Achieving the desired coating uniformity is the overriding objective in the development of transdermal products.

After the coating solution is applied, the web moves into a drying oven where the solvents are removed. The release liner or backing then is laminated to the exposed surface of the dried drug-in-adhesive solution by bringing them together between two rollers under moderate pressure. The web is later cut into patches during a process called *converting*, then packaged and packed in cartons.

Transdermal delivery technology

Recent product approvals and launches continue to increase the

Microneedle enhanced transdermal delivery

One of the most promising developments in transdermal drug delivery has been the emergence of microneedle enhancement technologies, including the microstructured transdermal system (MTS). The microstructure physically disrupts the stratum corneum, the outermost layer of the skin and the greatest barrier to transdermal delivery of most drugs.

By painlessly creating channels through the stratum corneum, the number and type of molecules that can be delivered through the skin is expanded beyond the traditional niche of passive transdermal systems that rely on diffusion of the drug through an intact stratum corneum. Higher molecular weight and more water-soluble drugs, including proteins and peptides, now can be delivered through the skin in therapeutic quantities. Although these systems have yet to reach the market, they are under development and will likely play a role in the growth of the transdermal drug delivery market.

number of commercially available transdermal drug delivery products. Currently, 15 active ingredients are approved for ethical transdermal drug delivery patches across a range of therapeutic categories, including hormone replacement, angina, smoking cessation, pain management, and contraception (recently launched in the United States). Many other products are in late-stage development, including products for attention deficit disorder, incontinence, and Parkinson's disease.

Active delivery systems such as iontophoresis (the use of electrical current to drive charged drugs through the skin) and sonophoresis (the use of ultrasonic energy to disrupt the stratum corneum barrier properties and improve transport through skin) continue to slowly progress toward market. Microneedle enhanced delivery, which incorporates tiny microstructures to painlessly disrupt the stratum corneum, is another approach that has potential to expand the type of molecules that can be delivered transdermally (see sidebar). Microneedle enhancement enables peptide delivery to the systemic circulation and allows targeted delivery of vaccines to the immune responsive cells located within the skin.

New packaging systems are changing the single-unit packaging paradigm. These systems include a dispenser that contains a large supply of patches with a pop-up dispensing mechanism to make patch application easy for patients and to reduce the amount of packaging material. In addition, improvements in transdermal-patch manufacturing technologies are resulting in reduced drug waste and lower manufacturing costs.

References

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