The recognized benefits of the transdermal patch (Figure 1) as a viable means of drug delivery is driving the development of new forms of transdermal drug delivery systems (TDDS). These new types can deliver larger compounds such as proteins and small peptides through the stratum corneum. As patches increase in their value and reliability for drug delivery, however, manufacturers face challenges in formulating adhesives that are functional, precise, and safe.

The science of formulating adhesives for TDDS requires a careful balance; that is, the adhesive must deliver functionality while it also provides a safe format. The adhesive must be compatible both with the active pharmaceutical ingredients (APIs) and with the patient’s skin and must deliver a reliable and reproducible therapeutic dose. To deliver precise control and performance, pharmaceutical-grade adhesives today provide highly specialized chemistries designed to overcome unique challenges specific to each application.

Transdermal patches address a range of treatments that is expanding beyond the delivery of compounds with low molecular weights, such as those that provide treatment for short-term conditions like motion sickness, or that provide longer-term therapies, such as hormone replacement. Scientists are developing new patches to treat chronic conditions through the continued use of a daily delivery device. Examples include the first rivastigmine patch for the treatment of Alzheimer’s disease [1] and the rotigotine patch that recently launched in Europe [2] for treatment of some forms of Parkinson’s disease. Fueling this trend are drug manufacturers’ efforts to extend lifecycle applications for solid-dose formats coming off patent protection. Drug developers also are investigating the patch platform as an alternative delivery system for peptide drugs that are vulnerable to proteolytic attack and that tend to undergo aggregation, adsorption, and denaturation [3]. Additionally, the benefits of patches are well-recognized regarding avoidance of unwanted side effects, particularly with compromised populations of patients.

Work to expand the range of use for passive TDDS first began with incorporating chemical penetration enhancers that decrease the barrier resistance of the stratum corneum, to allow delivery of compounds with a higher molecular weight. An adhesive patch may include one or more compounds to increase diff-

Figure 1
fusion, including sulfoxides, alkyl-azones, pyrrolidones, alcohols and alkanols, glycols, surfactants, and terpenes [4]. The increased demand to deliver drug compounds with higher molecular weights, however, has spurred development of active TDDS, including applications using ultrasound, microneedles, and iontophoresis [5]. Whichever type of system the drug developer considers a TDDS to be, passive or active, the products offer companies a unique set of adhesive bonding and dermatologic challenges.

### Drug Compatibility

One of the most significant obstacles to overcome in formulating adhesives for TDDS is the difficulty in maintaining compatibility between the API or medicament and the adhesive’s chemistry to assure that the drug will not change potency. Adhesive manufacturers must offer formulations with carefully selected chemistries that will not react with the API or change its physical properties.

For example, compatibility can become a challenge with acrylate-based adhesives that offer skin-friendly bonding characteristics and that often are a good choice for TDDS. Acrylate-based adhesives may absorb up to 5% of moisture from the skin, which potentially could affect drug bioavailability. Also, the manufacturer needs to eliminate any acrylic-acid monomer in an acrylate-based adhesive to assure that the pH of the adhesive is neutral [5] and that it does not irritate the skin. In iontophoretic drug delivery, pH changes can affect delivery rates; so acrylate-based adhesives must be free of residual acrylic-acid monomer to avoid a potential reaction with the active drug or device components. See Table 1.

Also, compatibility can change as components age; so scientists must perform accelerated and real-time aging studies to ensure that the product maintains its adhesive properties and drug bioavailability during the shelf life of the drug delivery device. If the delivery device requires sterilization, the manufacturer must take measures to ensure that the adhesive will withstand the sterilization procedures and dosage while maintaining its adhesive properties and compatibility with the API.

<table>
<thead>
<tr>
<th>Adhesive Description</th>
<th>Chemistry</th>
<th>Functional Properties for Drug Delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin-friendly PSAs</td>
<td>Acrylic, polyisobutylene, silicone, and hybrid chemistries</td>
<td>Formulations tailored to bond with various skin types and in various environments, for wear times ranging from minutes to days</td>
</tr>
<tr>
<td>Electrically and ionically conductive coatings</td>
<td>Acrylic and polyisobutylene chemistries</td>
<td>Polymer formulations that overcome traditional insulative properties of an adhesive to allow current or ion transport</td>
</tr>
<tr>
<td>Dissolvable films and erodable PSAs</td>
<td>Hydrophilic copolymers</td>
<td>Polymer coatings designed to erode at predetermined rates when in contact with biological fluids</td>
</tr>
<tr>
<td>Ethanol- and enhancer-tolerant coatings</td>
<td>Acrylate chemistry</td>
<td>PSAs that can withstand exposure to enhancer chemicals found in drug delivery systems</td>
</tr>
<tr>
<td>Ultraclean and nonreactive adhesives</td>
<td>Acrylate chemistry</td>
<td>Chemically inert coatings that are compatible with APIs and excipients</td>
</tr>
<tr>
<td>Porous adhesives</td>
<td>Acrylic, rubber, polyurethane chemistries</td>
<td>Coated polymer systems with tailored pore size to allow controlled fluid transfer, with doping used to create biphasic formulations</td>
</tr>
<tr>
<td>Hydrogels and organogels</td>
<td>Hydrophilic polymers and copolymers</td>
<td>Coatings with a high fluid content that form an interface between the skin and a sensing element in device-assisted delivery</td>
</tr>
<tr>
<td>Hybrid PSAs</td>
<td>Rubber and acrylic graft</td>
<td>Polymer matrix that offers high tack and chemical stability</td>
</tr>
<tr>
<td>Molecularly imprinted polymers</td>
<td>Acrylate chemistry</td>
<td>Synthetic polymers for the capture and release of targeted APIs or other chemical moieties</td>
</tr>
</tbody>
</table>
Biocompatibility

Biocompatibility of an adhesive formulation with the skin is a significant concern in the design of any transdermal patch. The adhesive must be nonirritating and free of any residual monomers, leachable components, and reactive materials. Allergic reactions are possible, caused by irritation from and sensitivity to a number of chemical compounds, particularly acrylics and natural, rubber-based adhesives. Adhesive manufacturers address these concerns by modifying formulations to benefit the population of patients while maintaining drug compatibility and the functionality of the patch.

In a recent draft offering guidance for an extended-release patch, the FDA provides meaningful guidelines for evaluating the performance of transdermal patches regarding safety and bioequivalence. These recommendations now provide a measurable standard for evaluating adhesion and dermal response [7], which are important factors to consider in designing longer-wearing patches and devices.

Proper Moisture

Consumers remove the majority of transdermal patches available today within 24 hours; however, manufacturers are developing extended-wear patches for time periods of up to seven days [8]. To ensure a healthy skin environment for proper dosing, it is important that the adhesives selected for longer-term wear enable the skin to breathe, which prevents over-hydration that potentially could affect drug bioavailability. Longer-wear devices should combine these adhesives with breathable materials such as polyurethane films that offer high moisture-vapor transmission rates and gas-exchange properties to promote a healthy skin site.

Adhesion and Sealing Performance

Good adhesion performance is paramount for prevention of movement or shifting of the patch during the dosing period, and even more so, for delivery of treatments that require a skin-preparation step prior to applying the patch. Any lifting from the skin can affect whether the patch is delivering an effective dose. A number of factors can impact adhesive performance; so the construction must ensure that:

- All component materials are flexible, and the patch comfortably adheres and conforms to a number of application sites.
- Careful consideration of product geometry avoids uplifting of patch edges. Rounded edges are preferable to prevent patch lifting and to avoid irritation at corners. To avoid high concentrations of electrical current that could cause burns, round edges are particularly important in applications that use an electrically conductive adhesive.
- The product maintains proper adhesion during physical activity and normal exposure to moisture, including sweating, showering, or swimming.
- Protective, adhesive-film overlays seal active compounds or highly sensitive electronic components in active transdermal devices and prevent any moisture exposure that potentially could affect bioavailability and performance of the device.

The Balance between Adhesion and Removability

The primary function of the adhesive in TDDS is to secure the patch or device on the patient’s skin for the desired dosing timeframe, thereby assuring reliable and accurate drug transmission, without causing significant irritation. Ease of patch removal after treatment has tended to be a secondary concern but is gaining more attention as TDDS developers consider the special needs of different skin types. Adhesives that are formulated for ease of removal tend to be gel-like in form or softer than other adhesives. Patch developers achieve this characteristic by forming polymer chains that are mobile and can stretch. The challenge then becomes balancing secure skin adhesion and low-trauma removal. The developer must accomplish this balance using a formulation that carefully limits any possible impact upon drug flux through the adhesive.

Skin Types

While manufacturers formulate adhesives to benefit the targeted patient population as a whole for the patch, different skin types present their own unique
bonding challenges. These challenges depend upon a consumer’s health, age, and race and on the moisture-vapor transmission rates, porosity, and oil levels, etc of his or her skin. For example, a manufacturer would design a patch for an older population of patients to be softer in its formulation to address reduced skin elasticity and to provide less trauma to the skin upon removal. A patch designed for a younger population, such as a birth-control patch, would need to take into consideration strong adhesion rates to withstand active lifestyles, movement, and exposure to moisture related to exercise and bathing.

**Careful Thickness Control**

Tight tolerances for control of adhesive and substrate thicknesses from lot to lot are critical for applications where any variations in thickness can have a negative impact upon dosing. For example, scientists have designed some patches with microporjections; that is, an array of drug-treated microneedles — solid metal, hollow metal, or polymer needles — that adhere to the skin with a PSA. The combined thickness of the components of the device controls the depth of penetration of the microneedles for release of the drug into the bloodstream or lymphatic system. If penetration through the skin is too shallow, the user may not receive the proper dose; alternatively, if the needles penetrate too deeply, the user could experience unwanted discomfort and pain.

**Conclusion**

As TDDS continues to deliver patients’ increased compliance by providing predictable and reliable therapeutic dosages without limiting patients’ normal activities, drug manufacturers continue to expand the scope of the drug delivery system. As the scope widens, adhesive manufacturers are responding by developing a range of skin-friendly and API-compatible formulations that withstand the increased exposure to moisture and movement related to a more active population. On the horizon, functionality and fashion may come together as improvements in design make patches appear more seamless and compatible with clothing, all in the name of compliance.

**References**


William Meathrel, PhD, is a senior scientist with Adhesives Research. With over 30 years of experience in product development and applied research, his career has focused on polymers, adhesives, and coatings, and he has secured numerous patents for his work. He holds three degrees from the University of Toronto, including a PhD in organic chemistry, a Master’s of Science in biological chemistry, and a Bachelor’s of Science in chemistry. He also possesses a diploma in Chemical Engineering from the Ryerson Polytechnic University.

Contact Dr Meathrel at Adhesives Research, P.O. Box 100, Glen Rock, PA 17327; E-mail: bmeathrel@arglobal.com or Phone: +1 717 227 3460.