Transdermal drug delivery systems (TDDS) continue to gain market acceptance as preferred methods of drug administration. The success of products that deliver materials such as nicotine for smoking cessation, nitroglycerin for angina, and oestradiol and testosterone for hormone replacement therapy has ensured that the TDDS market is a strong industry segment. Many more drug actives are being formulated for transdermal delivery methods.

As the TDDS market grows, so do the technical and business challenges for specialty adhesives manufacturers. Custom adhesives manufacturers in the pharmaceutical industry must formulate safe, compatible adhesives and must learn to deal with issues not encountered in the manufacture of conventional (nonpharmaceutical or nonmedical) adhesives. To work in a successful partnership with a pharmaceutical company, adhesives manufacturers must have a focused commitment to research and development and lengthy product development cycles (which can be gated by customers’ long-term clinical studies), dedicated manufacturing facilities and quality control functions, and the ability to operate within relevant current good manufacturing practices (CGMPs).

Establishing a partnership
Aside from available or customized technologies, one of the most important aspects in the development of pharmaceutical products is the partnership between an adhesives manufacturer and a pharmaceutical company. This relationship may include the execution of a confidential disclosure agreement. Increasingly, joint (customer–supplier) project plans are being developed that indicate the type of work to be carried out by both companies as well as agreed-upon milestones.

Where practical, adhesives manufacturers are taking on more of the product development process as pharmaceutical companies seek to outsource research, testing, materials qualifications, and many other tasks related to adhesives formulation and production. This means that a plant must operate to relevant pharmaceutical standards by offering CGMP production, quality control, validation, and segregation of processes. Cleanliness and accurate recordkeeping functions such as process docu-
mentation change control, batch traceability, and quality assurance programs are essential and must be reflected in a company’s standard operating procedures. Other important considerations include personnel training, suitable facilities, cleanrooms with controlled access and gowning attire, and equipment such as special heating, ventilation, and air conditioning systems. The adhesives manufacturer also should maintain an open-door policy by having their technical staff work directly with the pharmaceutical company’s scientists and engineers.

Requirements for pressure-sensitive adhesives (PSAs)
The development and production of PSAs for pharmaceutical transdermal drug delivery applications require attention to specific details. The standard functional properties of PSAs — tack, adhesion, release force, and cohesive strength — as well as adhesive formulations with properties such as enhanced drug flux and skin friendliness should be considered.

TDDS require that the adhesive adhere to the skin, which is a highly variable substrate. Further, a PSA must show consistent performance under a broad range of temperatures, humidity levels (including immersion in water during bathing or swimming), and application times (from 24 h for some products to one week for others). The effects of mechanical movement (e.g., stretching) as well as skin irritation and sensitization also must be considered. In addition to having the correct skin-adhesion properties, the adhesive must be extremely stable, consistent from lot to lot, and compatible with the drug.

When developing transdermal adhesive systems, the following also should be considered:
- the drug–adhesive solubility relationship. For a very diverse group of actives (with various molecular-particle sizes), adhesives are expected to allow the maximum amount of drug to penetrate through to the skin. This relationship becomes even more critical when a patch is designed to contain more than one active, each different in molecular size.
- the drug–adhesive compatibility and stability profile, especially during long-term storage. The adhesive must be designed so that it does not react adversely with the drug anytime before the patch expiration date.
- demands of an adhesive system relative to patch design and geometry. Small patch designs can be aesthetically pleasing to the consumer and can save costs during the manufacturing and die-cutting processes.
- quality of wear for an adhesive formulation. This includes adhesion to the skin for the duration of a therapeutic system delivery, which could be as long as seven days, and the cohesive properties of an adhesive to enable the patch to remain fixed on the skin without sliding, especially during long-term wear.

Types of patches
Two types of transdermal patches commonly are used: active and passive. In active patches, external forces are used to assist the drug delivery through the skin (these are discussed briefly in the final section of this article). In passive patches, the drug diffuses into the skin as a result of a gradient in either drug solubility or drug concentration. A permeable membrane, most often the skin, usually controls the rate of drug delivery. The molecular structure of a drug, its solubility, or its potency often determine the effective delivery rate, and some assistance may be required to achieve the desired rate. Passive systems may rely on permeation enhancers that are added to accelerate drug diffusion.

The physical design of conventional passive transdermal patches falls into one of two categories: reservoir or matrix. The reservoir design consists of a reservoir that contains a liquid or solid drug and that typically rests on a rate-controlling permeable membrane that controls the drug delivery rate. The adhesive can be applied directly to the face of the reservoir (see Figure 1) or around the perimeter of the patch (see Figure 2). In a reservoir patch, the drug diffuses through the adhesive; thus, adhesive stability is critical in the presence of the drug.

In a matrix design (see Figure 3), which currently is the more commonly used design for new TDDS, the drug is incorporated into the adhesive. The demands made on the adhesive in this design are even more exacting than those in reservoir systems. Matrix designs require long-term compatibility among the adhesive, the drug, and all excipients in the formulation. In addition, the adhesive must not alter the drug’s potency during extended storage or wear.

Adhesive types used in TDDS
Acrylic, polyisobutylene (PIB), and silicone adhesives have many pharmaceutical applications. Adhesive selection is based on a number of factors, including the patch design and the drug formulation. For applications in which the adhesive is not in direct contact with the drug, additional choices are available in terms of the type of adhesion and skin compatibility. For applications in which the adhesive, the drug, and perhaps en-
hancers are compounded, the selection of a PSA is more complex (e.g., a matrix design).

Adhesives companies generally must customize a PSA to meet the specific requirements of a particular transdermal drug delivery system. Adhesives typically are coated onto films, foils, or fabrics and are available in transfer formats and single- and double-coated laminates.

After determining that an adhesive and a drug are chemically compatible, the key consideration is the rate at which the drug migrates through the adhesive. Acrylics offer a wide range of formulation possibilities for optimizing drug flux, adhesion, and dermatological properties. These materials are readily cross-linked, which can help improve their coadhesive properties where interaction between the drug, enhancers, or solvents would degrade the adhesive. However, excessive cross-linking can harden the adhesive, reduce drug-flow properties, and make skin adhesion difficult. Thus, careful formulation is critical to produce an adhesive with the appropriate balance of flow and cohesive strength and optimize the potential for long-term adhesion to the skin.

PIBs are used widely in TDDS because they can be modified easily for blending and are compatible with many drugs. However, their application is limited because PIBs cannot be cross-linked to improve their properties in the presence of permeation enhancers. Although the formulation latitude is limited to tailoring the cohesive properties of the adhesive, PIBs may be the adhesive of choice for drugs with low solubility and low polarity. Many drugs for transdermal delivery contain amine functional groups, and PIBs are good amino-compatible adhesives.

Silicones, although more costly than acrylics or PIBs, generally offer the highest drug-diffusion rates. It is also easier to modify their adhesive properties, including tack and cohesion. Historically, silicones have had a good biocompatibility record for topical applications, and the low-silanol formulations are also compatible with amino-functional drugs.

Developments in PSAs for TDDS

One of the newest PSA technologies developed for the TDDS market is enhancer-tolerant adhesives. Relatively few drugs can permeate the skin at an efficacious rate. As a result, substantial work has been conducted to identify methods of enhancing drug flux. One such method uses chemical enhancer excipients. These enhancers can be added to any of the components of the delivery system that are in contact with the drug, but the ideal method is when they are compounded directly into the PSA to provide more uniformity. The enhancers permeate through to the skin interface and modulate the skin to increase the permeability of the skin to the drug.

Typical enhancers include high-boiling alcohols, diols, fatty acid esters, oleic acid, and glyceride-based solvents. These materials commonly are added at a concentration of 1–20% (w/w). However, enhancers can pose challenges to PSA developers. The type and amount of enhancer used can have profound effects on the mechanical properties of the adhesive. Enhancers can plasticize the adhesive to the extent that they significantly reduce the skin-bonding capability of the adhesive and make it unsuitable for use. Also, the use of a combination of en-
hancers with a combination of drugs can be difficult. Although a combination of enhancers may improve the rate of diffusion of the various drug chemistries that are acting in parallel, the use of more than one enhancer may be a challenge for the overall performance of the adhesive. To overcome many of the challenges associated with incorporating enhancers in PSAs, enhancer-tolerant adhesives have been developed that can significantly extend drug delivery capabilities.

**New systems in the future of TDDS**

Several exciting active TDDS are on the horizon. Systems that use external stimuli to drive a drug into the skin offer rate-controlled, on-demand delivery of drugs with a large molecular weight that previously were not deliverable by passive transdermal patches. For example, iontophoresis uses a miniature battery to establish an electrical potential between the skin and a conductive adhesive in a TDD patch. A mild electrical current delivers an ionically charged drug into the skin. Presently, reverse iontophoresis is used as a diagnostic tool for blood glucose monitoring by attracting fluid out of the skin so it can be analyzed. Sonophoresis, which uses ultrasound waves, also is being tested. In this technology, a portable device emits sound waves through a patch attached to the device for painless delivery of a drug through the skin. The adhesive used must be able to withstand the effects of the sound waves.

Yet another method is electroporation, which uses electric currents to change the surface properties of the skin, creating channels of low transmission-resistance and thereby accelerating drug delivery.

In addition, buccal or transmucosal patches have been designed to deliver a drug through the mucous membranes in the mouth. This technique allows a much higher drug flux and enables large, high molecular weight drugs to be administered transdermally. The challenge for adhesives manufacturers is to develop an adhesive that adheres to wet surfaces on the interior of the mouth and will not dissolve in an aqueous environment.

In the future, we can expect advances in passive transdermal patches to include

- extended-wear patches with stronger cohesion properties that enable the patch to remain at a fixed point on the skin without movement
- biphasic drug delivery profiles such as time-delayed or time-moderated delivery
- smaller, more aesthetically acceptable patches with increased solubility of the drug in the adhesive for a higher diffusion rate
- generic-drug patches
- combination drug patches such as nicotine with an anti-irritant that delivers more than one drug chemistry, each with a different size molecule and a potentially different therapeutic level.

Adhesives manufacturers that will succeed in the TDDS market will be those that have invested in partnerships with pharmaceutical companies. These companies will require that adhesives manufacturers be involved in the product development process by conducting research, testing, and materials qualification for adhesive formulation and ultimately manufacturing to the relevant pharmaceutical CGMPs.