# Novel Acrylate Adhesives for Transdermal Drug Delivery

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**In this article, the authors discuss novel acrylate adhesive polymers developed for use in transdermal drug delivery systems. They analyze the solubility and adhesive performances of adhesives that incorporate either hydroxyethyl acrylate (HEA) or pyrrolidonoethyl acrylate (PyEA) as a polar monomer to control drug solubility. A graft macromer is used to control adhesive performance. Testing of transdermal patches in human skin panel studies suggests that the macromer component may help reduce cold flow at the edges of the patch and also may reduce irritation.**

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Transdermal drug delivery (TDD) patches are designed to deliver a therapeutically effective amount of drug across a patient's skin. Transdermal patches typically involve a liquid, gel, solid matrix, or pressure-sensitive adhesive carrier into which the drug is incorporated. The earliest TDD systems were reservoir-type devices that used membranes to control the rate of drug release. Today, a drug is more commonly dispersed or dissolved in a pressure-sensitive adhesive (PSA) matrix.

A specific transdermal patch optimally should include a number of properties, and designing an effective transdermal patch often involves finding a suitable balance of these properties because they can be mutually exclusive. A primary consideration is that a patch should provide a sufficient skin flux of drug yet still be produced in a manageable size. In addition to ensuring the correct rate of drug delivery, a patch must contain an adequate amount of drug so that it does not become depleted before the end of the designated dosage period, which is typically 1–7 days. A patch also should sufficiently control the rate of delivery to avoid any overdosing resulting from normal use, and it must maintain the chemical stability of the drug and the physical stability of the patch itself to perform reliably after aging. Because it is affixed to an external part of the body for extended periods of time, a patch should be nonirritating to the skin in regard to chemical sensitivity, chemical irritation, and mechanical irritation.

From a patient-acceptance perspective, a patch should be comfortable, unobtrusive, and easy to manufacture. Patient acceptance is largely responsible for making drug-in-adhesive (DIA) TDD systems a preferred drug delivery form. The typical components of a DIA system are the backing material, the adhesive, the excipients, the drug, and a release liner. The choice or design of adhesive is critical because it will have a strong effect on a patch's drug release, stability, and wear properties (1,2). The most common adhesives used for TDD systems are acrylates, silicones, and polyisobutylenes. Silicones and polyisobutylene PSAs contain fairly limited properties, whereas acrylates can be tailored to achieve a wide range of performance in regard to various drugs, excipients, and particular product requirements.

This article describes novel acrylate adhesives developed for transdermal use that are a part of 3M's Latitude transdermal systems. The basis of these adhesives is the use of an acrylate-based polymer that incorporates a polar monomer to control drug solubility and a graft macromer to control adhesive performance.

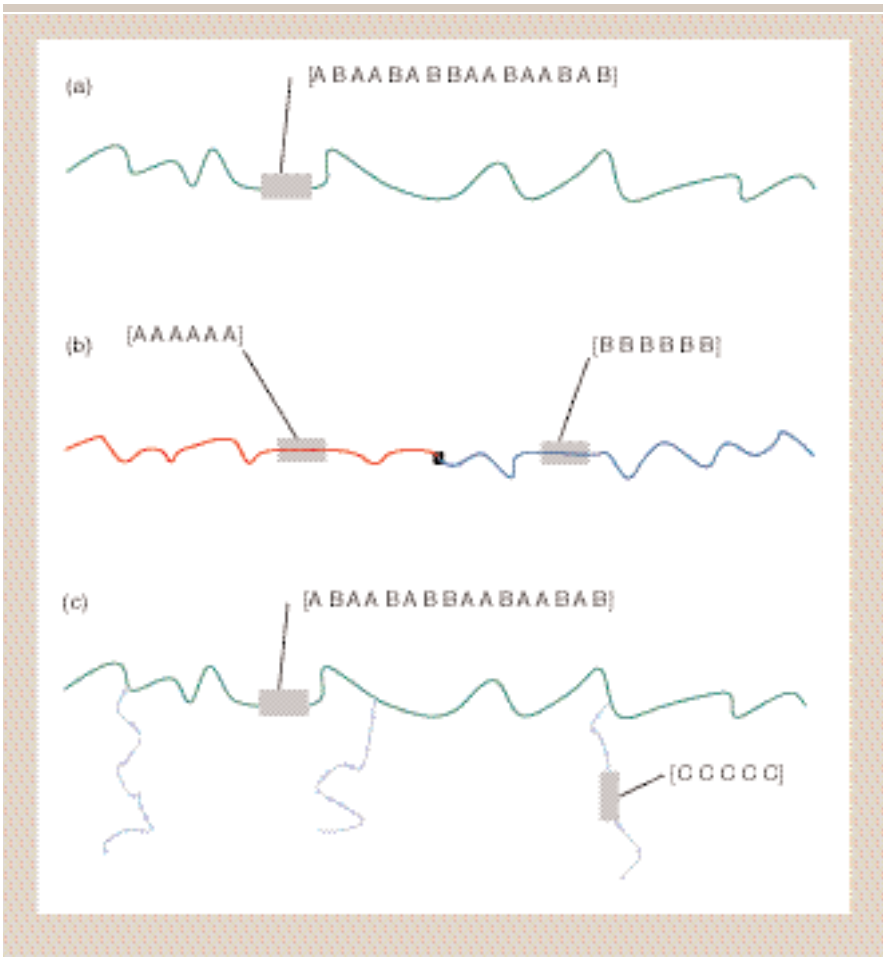


**Figure 1:** (a) A typical acrylate random copolymer. (b) A block copolymer with monomer segregation along the polymer chain. (c) A graft copolymer.

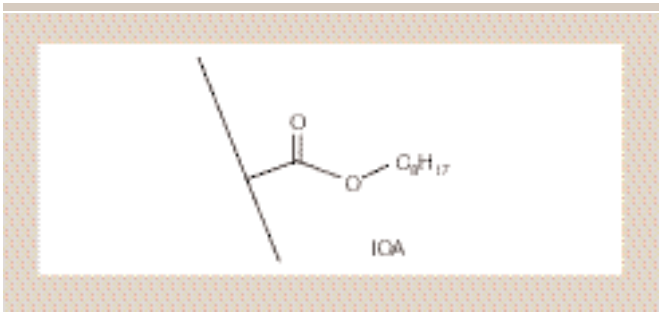


**Figure 2:** A pendant acrylate group attached to a polymer backbone that consists of $CH_2$-CH repeat groups.

## Acrylates

Acrylic or acrylate copolymers have been used commercially as PSA compositions for nearly 50 years (3). An acrylic copolymer that is suitable for use as a PSA must have two main distinguishing characteristics. The first characteristic is that the copolymer will contain a significant fraction of a monomer with a low glass transition temperature ($T_g$). This monomer typically will have a $T_g$ $<-20$ °C, preferably from $-40$ to $-80$ °C. This low $T_g$ monomer gives the PSA its soft, tacky properties.

The second characteristic is that the copolymer will provide reinforcement to the PSA to prevent it from splitting and oozing during use. Several methods for providing this reinforcement can be used such as adding high $T_g$ monomers to the copolymer, adding monomers that cause intermolecular interactions between individual copolymers, covalent cross-linking of the copolymer, and physical cross-linking of the copolymer through graft or block copolymers.

The tacky characteristic of an acrylic copolymer was first described in the 1930s (4); however, the true beginning of commercially useful acrylate PSAs was in the 1950s with the discovery that incorporating a high $T_g$ functional monomer into the acrylic copolymer provided the reinforcement necessary for acceptable PSA performance (5). Reinforcing monomers such as acrylic acid (AA) and acrylamide continue to be widely used today in a variety of PSAs, including in medical and pharmaceutical applications.

Another purpose of incorporating functional monomers into a copolymer is to change the average chemical properties of the copolymer. These chemical properties can affect many performance characteristics of the PSA such as the PSA's ability to wet a surface, its ability to dissolve or complex additives, and the stability of the PSA as well as any additives it may include. In particular, functional monomers can have significant effects on the dissolving or complexing of small-molecule additives such as drugs and pharmaceutical excipients. A classic example of this is the use of *N*-vinylpyrrolidone (NVP) as a reinforcing monomer in an acrylate-based PSA. Because iodine complexes are combined with NVP, these monomers are used in surgical drapes and many other medical applications that require antimicrobial performance (6).

A disadvantage, however, to the general concept of incorporating functional monomers to adjust chemical properties is that the functional monomers also can have a strong effect on the physical properties of the copolymer, especially its ability to provide reinforcement. This effect limits the amount of functional monomer that can be incorporated because excessive reinforcement will cause a loss of the soft, tacky properties that are necessary in a PSA. Therefore, although an acrylate-based PSA containing NVP can be made, increasing the amount of NVP produces material that behaves more like polyvinylpyrrolidone (PVP), which is a powder and has no PSA properties of its own.

## Block or graft copolymers

Block or graft copolymers also have a long history of use in the

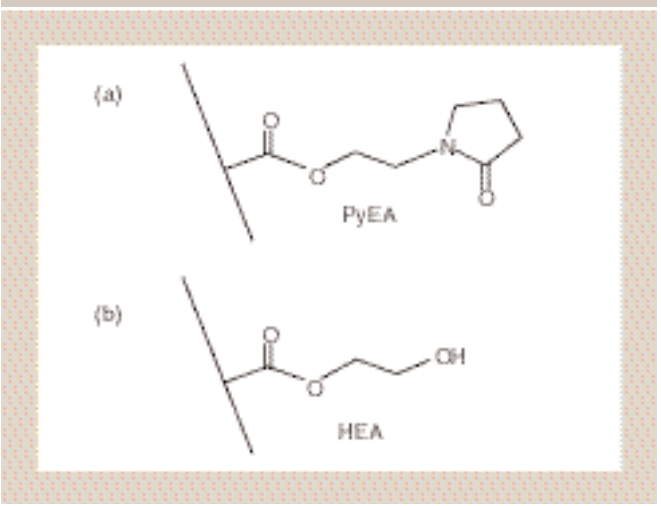


**Figure 3:** Functionalized pendant acrylate groups. (a) Pyrrolidonoethyl acrylate (PyEA). (b) Hyroxyethyl acrylate (HEA).

production of PSAs. The first and most widely used graft copolymers were the styrenic block copolymers, which were developed in the 1950s (7). Block copolymers differ from ordinary copolymers (e.g., the acrylates typically used for medical PSAs) in that the different monomers in the polymer chain (or backbone) are segregated from each other instead of being randomly dispersed along the backbone (see Figure 1a).

Monomer segregation can take place along the backbone (see Figure 1b) or in the form of grafts (see Figure 1c). Although differences between the two types of block copolymers exist, the general mechanism of their performance is the same. Different portions of the polymer want to separate from each other, but because they are covalently connected, they cannot separate on a macroscopic scale. Instead, the blocks or grafts will begin to aggregate in microscopic domains, and if the blocks or grafts have a high $T_g$ value, these microscopic domains will act as physical cross-links for the low $T_g$ polymer chains.

In theory, almost any type of graft can be used for reinforcement as long as the value of $T_g$ is above room (or use) temperature. Poly(methyl methacrylate) (PMMA) and polystyrene are most commonly used for acrylate adhesive reinforcement. In particular, PMMA grafts are very useful for TDD adhesives because they have a high $T_g$ value and differ enough from the acrylate backbone monomers to provide reinforcement, yet they still are fairly similar to the acrylate backbone in chemical character.

## Acrylate graft copolymers for TDD

The ability to obtain a wide range of TDD performance for acrylate graft copolymers lies in the ability to change physical properties such as adhesion and chemical properties such as drug solubility independently from each other. The type and amount of graft copolymer as well as the molecular weight of the entire polymer control the physical properties. The type and amount of functional monomers included in the polymer backbone control the chemical properties.

The key to this approach is to have one or more low $T_g$ monomers that can be used to adjust the chemical properties without significantly affecting the physical properties. Most

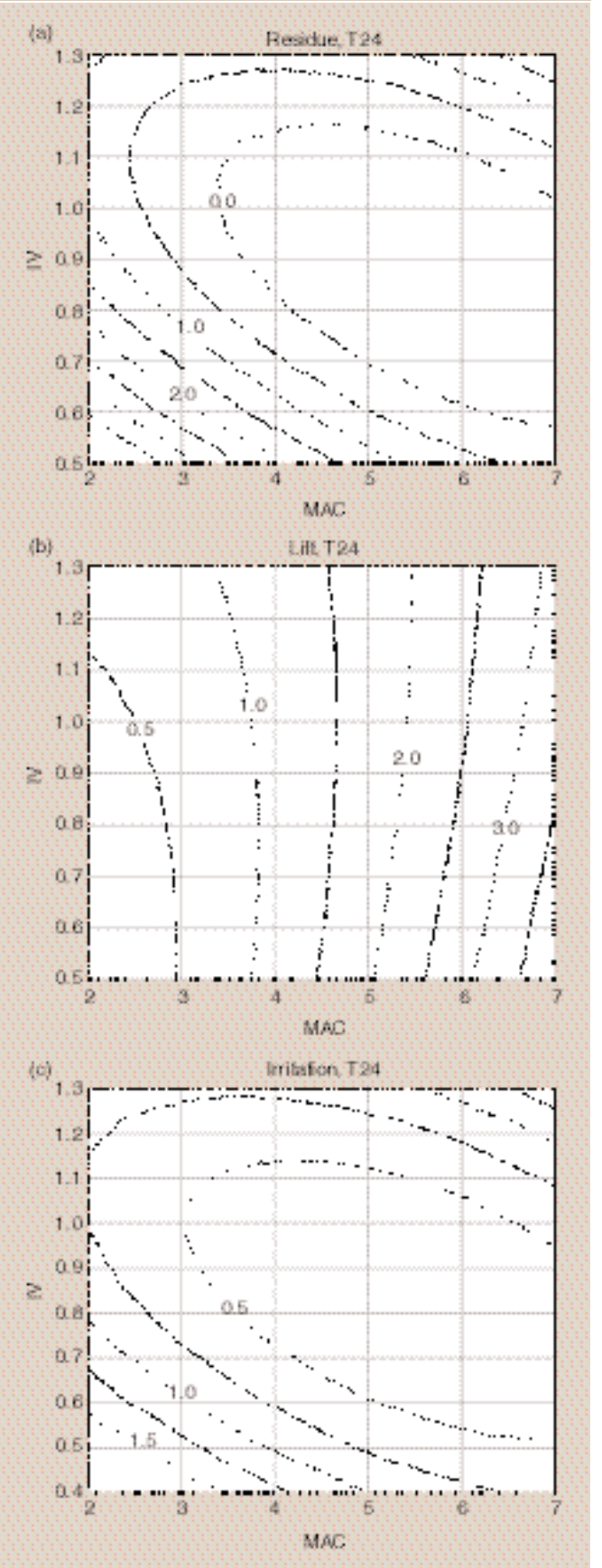


**Figure 4:** (a) Residue, (b) lift, and (c) irritation results in a range of macromer concentrations and adhesive inherent viscosities. T24 is a measurement taken after 24 h of wear. MAC is % macromer in copolymer.

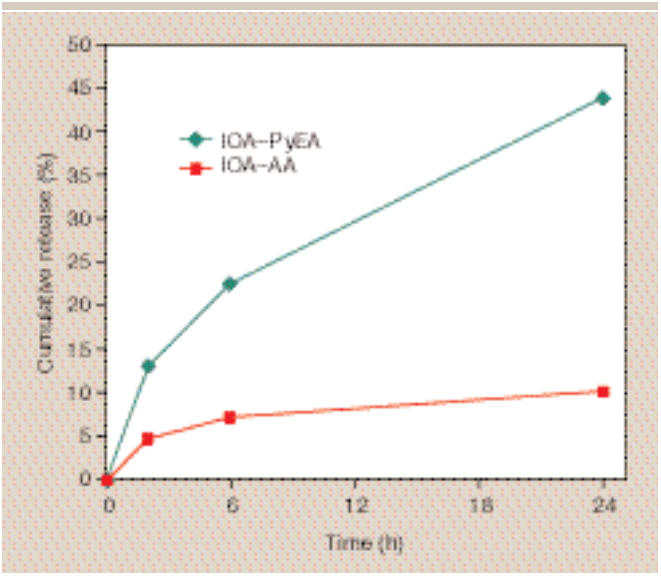


**Figure 5:** Dissolution release rate of atenolol from two acrylate adhesives.

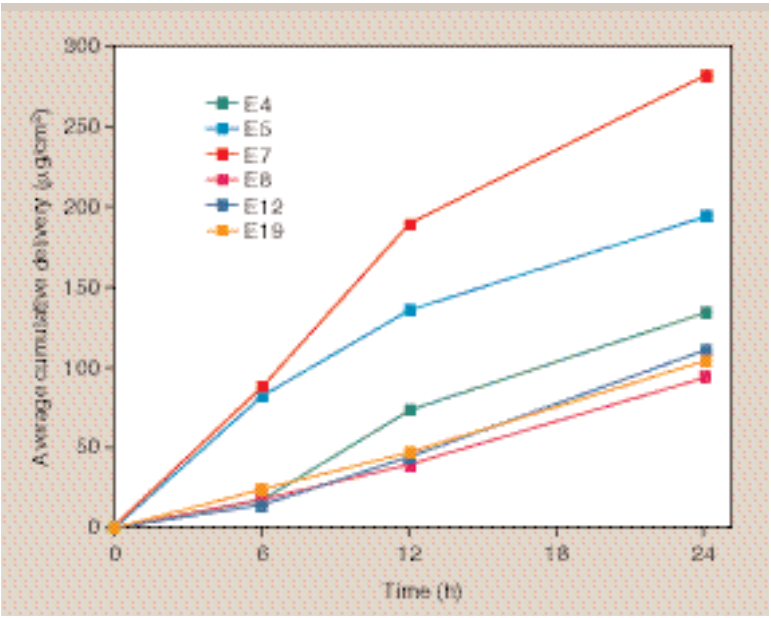


**Figure 6:** Atenolol flux through human cadaver skin for formulations with a PyEA-based adhesive and several penetration enhancers.

**Table I: Solubility for various drugs (in wt %).**

| Drug Used | IOA | IOA–HEA 85/15 | IOA–HEA 60/40 | IOA–PyEA 60/40 |
|---|---|---|---|---|
| Buprenorphine | 3.0–3.2 | 4.5–5.0 | 7.0–8.0 | 5–11 |
| Cyproheptadine | 5–6 | 8–10 | 12–15 | 10–15 |
| Phenobarbital | 3–4 | 4–6 | 8–10 | >15 |
| Testosterone | 0.5 | — | 2 | 4 |
| Captopril | 1–2 | 2–4 | 6–9 | — |
| Haloperidol | 1.0–1.5 | 1.5–2.0 | 2–3 | — |
| Morphine | 0.4–0.6 | 2–3 | 5–6 | — |

acrylate adhesives use either isooctyl acrylate (IOA) or 2-ethylhexyl acrylate (EHA) as the primary (nonfunctional) low $T_g$ monomer. Figure 2 shows one pendant acrylate group attached to a polymer backbone (shown schematically), which consists of $CH_2$-CH repeat groups.

In addition, the adhesives described in the following section incorporate hydroxyethyl acrylate (HEA) or pyrrolidonoethyl acrylate (PyEA). HEA has been used previously in PSAs but not as a major component of a graft acrylate for adjusting chemical properties. PyEA can be incorporated into an acrylic copolymer in significant amounts to adjust the chemical properties without causing large changes to the physical properties that would occur with typical functional monomers. Both of these monomers have low $T_g$ values, and replacement of IOA or EHA with HEA or PyEA in the backbone has a fairly minimal effect on the physical properties of the adhesive. In the pendant group, PyEA has an added amide functionality, and HEA has an added hydroxyl functionality (see Figure 3). These characteristics allow for chemical interactions with most drugs that are more favorable than the interaction between hydrocarbon and drug.

## Model studies

**Solubility.** Several studies have been conducted using model compounds to characterize these new adhesives. One of the main advantages of these adhesives is their ability to dissolve relatively large amounts of a wide variety of drugs. This characteristic has been reported for HEA-containing adhesives (8). Table I shows the solubility for various drugs (in wt %) for three 3M Latitude adhesives and a nonpolar adhesive containing only IOA.

The solubility results were generated using an accelerated method called crystal seeding to determine drug solubility in adhesives. Using this method, drug and adhesive mixtures are developed with a wide range of drug concentrations then seeded on their surface with pure drug crystal. Solubility is determined by observing growth or dissolution of the seeded drug crystals. Although these values are not always the same as the results that come from actually preparing a patch and observing the adhesive's long-term stability, the comparison of trends is significant.

**Adhesion.** The other main advantage of these adhesives is that they include a macromer to control the rheological behavior of the adhesive (i.e., tack, compliance, and flow). The grafted macromer side chains associate with each other and serve as a method of physical cross-linking among the polymer chains. Testing of transdermal patches in human skin panel studies suggests that the macromer component helps to reduce cold flow at the edges of the patch and reduce irritation.

In addition to several laboratory measurements of the physical properties of these adhesives, adhesion-to-skin performance has been mapped as a function of adhesive molecular weight (measured by inherent viscosity) and the re-

inforcing macromer percentage. Figure 4 shows residue, lift, and irritation results for a range of macromer concentrations and adhesive inherent viscosities. The scorings are based on a visual assessment system with ratings of 1.0 or below indicating good performance. The study used an adhesive with an IOA:PyEA ratio of 6:4 and varying macromer levels. These results were obtained using placebo formulations containing 25% ethyl oleate. Patch constructions used a 3-mil-thick polyethylene backing with a nominal 5-mil-thick adhesive layer.

**Table II: Atenolol solubility in several acrylate adhesives.***

| Adhesive Type | Atenolol Concentration in Adhesive 1% | 3% | 5% |
|---|---|---|---|
| IOA/acrylic acid (AA) 90:10 | O | O | O |
| IOA/PyEA/macromer 68:28:5 | O | O | X |
| IOA/N-vinyl pyrrolidone 90:10 | O | X | X |
| IOA/acrylamide 93:7 | X | X | X |
| IOA/acrylamide/vinyl acetate 75:5:20 | X | X | X |
| IOA/HEA/macromer 59:39:2 | X | X | X |

*O: no crystallization observed
X: crystallization observed

## Formulation example — atenolol

Atenolol is a synthetic, β 1-selective (cardioselective) adreno-receptor blocking agent chemically described as benzenacetamide, 4-(2'-hydroxy-3'-((1-methylethyl) amino) propoxy)-($C_{14}H_{22}N_2O_3$). Absorption of an oral dose in humans is rapid and consistent but incomplete. Approximately 50% of an oral dose is absorbed from the gastrointestinal tract and reaches peak blood levels 2–4 h after ingestion.

As a preliminary step in the development of a transdermal atenolol delivery patch, the solubility of atenolol was determined in several adhesives by a formulation-based method involving preparation of formulations at 1, 3, and 5% drug concentration. Transdermal patches were prepared from these formulations, stored at room temperature and elevated temperature (50 °C), and subsequently monitored for drug crystal growth. After one week, the results indicated the solubility comparisons that are shown in Table II.

On the basis of the preliminary solubility data, IOA–AA and IOA–PyEA–macromer adhesives were chosen for further study. A PMMA macromer (Elvacite 1020, ICI Acrylics, Cordova, TN) was used in the two graft copolymers in this study. Standard dissolution testing was performed to evaluate the ability of these adhesives to release the drug. A dissolution bath (Hanson Research Corp., Chatsworth, CA) was operated under the following conditions:

- paddle speed: 50 RPM
- temperature: 32 °C
- patch size: 30 $cm^2$
- receptor volume: 400 mL
- pull time: 2, 6, and 24 h
- receptor solution: phosphate buffer
- sample volume: 1 mL.

**Table III: Atenolol flux through human cadaver skin for formulations with a PyEA-based adhesive and several penetration enhancers.**

| ID | Benzyl Alcohol (%) | Caprylic Acid (%) | GML (%) | Amine Oxide (%) | Average Cumulative Flux (μg/cm²/h) | Cumulative Drug Penetrating (%) |
|---|---|---|---|---|---|---|
| E1 | 30.0 | — | — | — | 3.2 | 19 |
| E2 | — | 30.0 | — | — | 3.7 | 23 |
| E3 | 27.0 | — | 3.0 | — | 3.0 | 30 |
| E4 | — | 27.0 | 3.0 | — | 5.7 | 25 |
| E5 | 27.0 | — | — | 3.0 | 8.1 | 49 |
| E6 | — | 27.0 | — | 3.0 | 3.4 | 20 |
| E7 | 24.0 | — | 3.0 | 3.0 | 11.8 | 49 |
| E8 | — | 24.0 | 3.0 | 3.0 | 4.0 | 21 |
| E9 | 15.0 | 15.0 | — | — | 2.2 | 21 |
| E10 | 28.5 | — | 1.5 | — | 1.2 | 6 |
| E11 | — | 28.5 | 1.5 | — | 1.4 | 11 |
| E12 | 28.5 | — | — | 1.5 | 4.7 | 23 |
| E13 | — | 28.5 | — | 1.5 | 3.6 | 23 |
| E14 | 13.5 | 13.5 | 3.0 | — | 2.7 | 14 |
| E15 | 13.5 | 13.5 | — | 3.0 | 3.1 | 26 |
| E16 | 12.0 | 12.0 | 3.0 | 3.0 | 3.3 | 26 |
| E17 | 21.0 | 7.5 | 0.75 | 0.75 | 2.4 | 15 |
| E18 | 7.5 | 21.0 | 0.75 | 0.75 | 2.6 | 17 |
| E19 | 18.0 | 7.5 | 2.25 | 2.25 | 4.4 | 32 |
| E20 | 7.5 | 18.0 | 2.25 | 2.25 | 2.8 | 21 |

These tests showed that the delivery rate from the PyEA-based adhesive was much faster than the delivery rate from the AA-based adhesive (see Figure 5). The low percentage of drug released from the IOA–AA adhesive suggests that binding occurred between the atenolol and AA, thereby eliminating the combination from further consideration.

The PyEA-based adhesive was studied with various penetration enhancers that previously had been identified as having potential for enhancement of atenolol delivery. A series of experiments were performed to examine atenolol delivery through human cadaver skin, with the results from one particular mixture design experiment shown in Table III.

Formulations contained 67% of the PyEA adhesive, 3% atenolol, and one or more of the following excipients: benzyl alcohol, caprylic acid, glycerol monolaurate (GML), and *N*, *N*, dimethyldodecylamine-*N*-oxide (amine oxide). Samples were coated onto silicone release liners to provide a dried thickness of ~4 mil (100 μm) and then laminated onto CoTran 9772 (3M

Co., St. Paul, MN) polyolefin backing. In vitro penetration experiments were performed with Franz diffusion cells under the following experimental conditions:

- receptor solution: phosphate buffer
- patch size: 2 $cm^2$
- receptor volume: 10 mL
- time pulls: 6, 12, and 24 h.

Table III shows the formulation concentrations and penetration results. Figure 6 shows the permeation profile for several formulations that provided the highest flux. The permeation profile suggests that benzyl alcohol provided better enhancement than caprylic acid and that the addition of small amounts of amine oxide and/or GML may provide further enhancement. The wide range of permeation rates indicated that transdermal devices with acceptable atenolol delivery rates could be prepared using the IOA–PyEA–macromer adhesive.

## Conclusion

The novel acrylate adhesives developed for 3M's Latitude transdermal systems allow for tailoring of drug solubility through polar monomer content and tailoring of adhesive performance through adjustments in macromer incorporation and adhesive molecular weight. Extensive adhesion-to-skin studies have been performed to provide a process map that can help guide adhesive modification during product development. Because of their mixed polar–nonpolar composition, these adhesives are compatible with a wide variety of drugs, penetration enhancers, and other excipients. They also meet the stringent standards needed for pharmaceutical adhesives, including low skin irritation and a favorable toxicological profile.

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