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A Review of Ethylene Vinyl Acetate Copolymers in Transdermal Drug Delivery

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I. TRANSDERMAL DRUG DELIVERY TODAY

Transdermal drug delivery (TDD), as the name says, is to deliver the drug molecules through the skin. The idea of TDD is intriguing as the skin structure is designed to be impervious to foreign subjects, including drugs, to protect the internal organs primarily due to the lipid lamellar structure of the stratum corneum.

This protective and impervious nature of the stratum corneum presents the greatest challenges in TDD and narrows the drug selections. The ideal drugs for TDD have good aqueous solubility, low melting point, low molecular weight and appropriate lipophilicity, and pH. Regardless of the stringent requirements, many drugs have been successfully used in TDD. **Table 1** shows a list of some active pharmaceutical ingredients (APIs) which are currently used through transdermal route of administration in commercial products [1-4]. TDD provides unmatched advantages when compared to other routes such as intravenous (IV) and oral. TDD can offer constant drug levels, reduced dose frequency and avoids the first-pass effects of the hepatic metabolism, the GI track, when compared to oral delivery; meanwhile it offers a non-invasive procedure that can be self-administrated when compared to IV delivery. Due to these advantages, TDD has had great commercial successes since it was first introduced. The first commercial TDD system in the US was approved by FDA in the early 80s. In the following decades, the TDD technology extended its applications and had a significant commercial impact. **Figure 1** shows the sales of fentanyl as an example [6, 7]. The solid line in the Figure represents the total sales

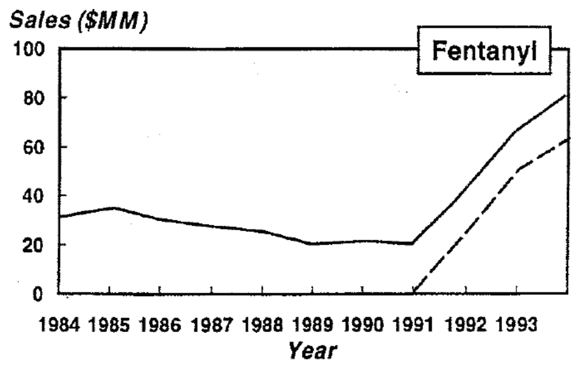


Figure 1. *Sales of fentanyl therapeutic system (solid line: sales of all dosage forms; dashed line: sale of patch form) [6, 7]*

Table 1. *Some commercial active pharmaceutical ingredients for transdermal drug delivery [1-4]*

Active pharmaceutical ingredients	Treatment	TDD form
Capsaicin	Neuropathic pain	Patch
Clonidine	Hypertension	Patch
Diclofenac epolamin	Pain management	Patch
Estradiol	Postmenopausal symptom and osteoporosis	Patch, gel and spray
Ethinyl estradiol and norelgesromin	Contraception	Patch
Fentanyl	Pain management	Patch
Granisetron	Chemotherapy-induced nausea and vomiting	Patch
Lidocaine	Postherpetic neuralgia	Patch
Lidocaine and prilocaine	Local anesthesia	Cream
Lidocaine and tetracaine	Local anesthesia	Patch
Menthol and methyl salicylate	Arthritis pain	Topical liquid
Methylphenidate	Attention-deficit hyperactivity disorder	Patch
Nicotine	Smoking cessation	Patch
Nitroglycerin	Angina pectoris	Patch and ointment
Oxybutynin	Bladder muscle dysfunction	Patch and gel
Rivastigmine	Dementia	Patch
Salicylic acid	Acne treatment	Patch
Scopolamine	Motion sickness	Patch
Selegiline	Depressive disorder	Patch
Testosterone	Hypogonadism	Patch and gel

of all the dosage forms and the dashed line represents the sale in the patch form. It is clear that after the TDD form was introduced to fentanyl, it not only promoted the sales but also dominated the delivery form. Similar impacts have been seen in other drug developments as well [6, 7].

II. INTRODUCTION TO ETHYLENE VINYL ACETATE COPOLYMERS

Along with the business success, the technology in TDD has also been advancing. In the early years of TDD, the developmental pace was slow due to the focus of oral drug delivery technology [9]. In the past 5 years, it has accelerated. **Figure 2** shows the number of patents issued each year resulted from a "transdermal drug delivery" key word body search at uspto.gov after 2000 [8]. The number of issued patent applications was 100 in 2009. By 2014, this number more than tripled to 321. It is a result of a combination of delivery technology and material science developments.

Ethylene vinyl acetate copolymer (EVA) is an important part of the TDD growth. A similar search was done and shown in **Figure 3**. In **Figure 3**, the number of issued patents based on the "transdermal drug delivery" and "EVA" body keywords shows a growth pattern similar to the patents in **Figure 2**. The number increased dramatically in the past couple of years [8].

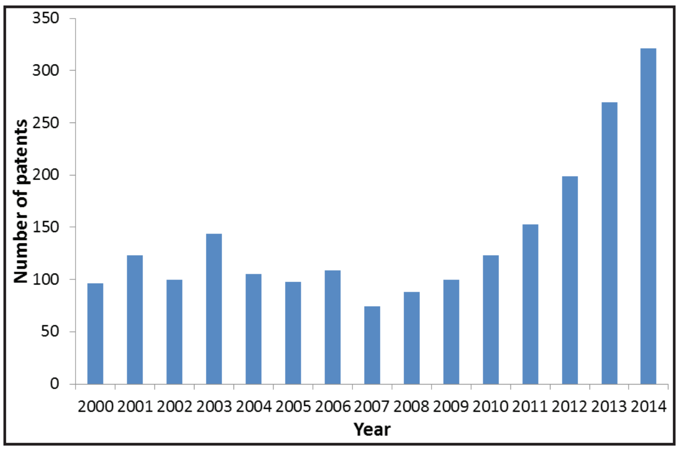


Figure 2. *Number of patents issued each year resulted from a "transdermal drug delivery" key word body search at uspto.gov [8]*

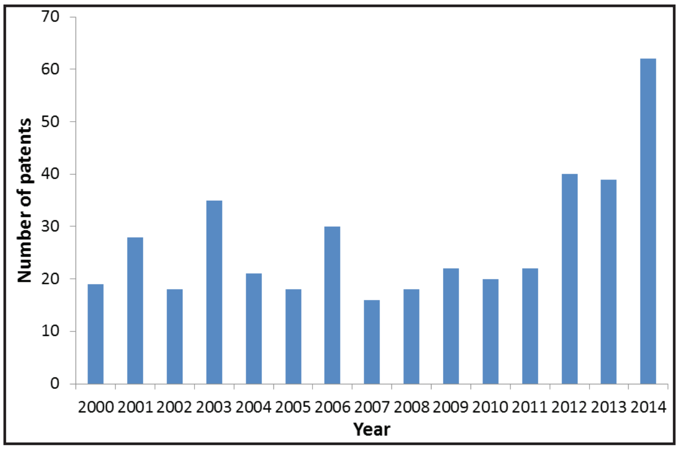
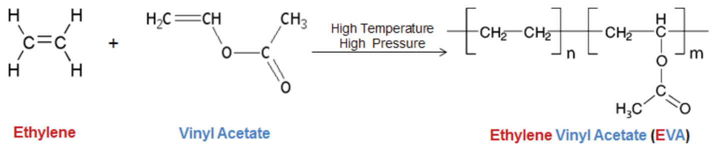


Figure 3. *Number of patents issued each year resulted from a "transdermal drug delivery" & "EVA" key word body search at uspto.gov [8]*

EVA is a copolymer of ethylene monomer and vinyl acetate (VA) monomer produced by free radical polymerization under high temperature and high pressure. Scheme 1 shows the molecular structures.



Scheme 1. *Reaction scheme of ethylene vinyl acetate copolymer polymerization*

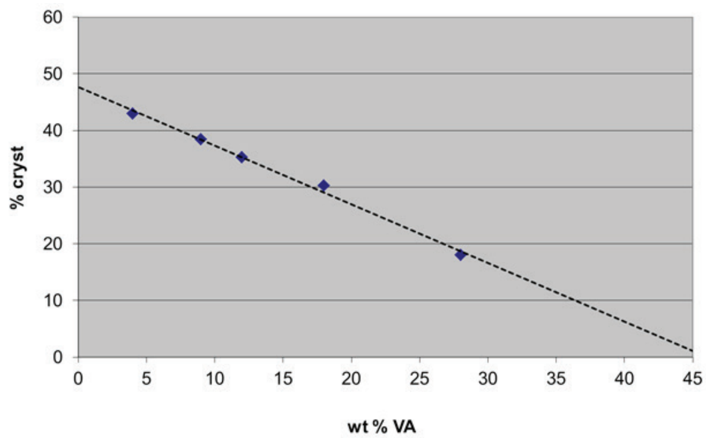


Figure 4. *A correlation between the VA content and the percentage of crystallinity of the EVA [10]*

A very important parameter for EVAs is the copolymer composition or monomer ratio. The high temperature, high pressure radical reaction produces EVAs with various VA contents commonly up to 40% by weight. The polymer properties, such as the melting point, percentage of crystallinity, and polarity, are affected by the copolymer composition. As an example, a correlation between the VA content and the polymer percentage of crystallinity of EVA is shown in **Figure 4** [10]. These properties can further affect secondary properties such as transparency and hardness. Particularly, crystallinity and polarity affect the solubility/diffusivity of small molecules in EVA and compatibility of EVA with other polymers. The secondary properties are critical in building TDD structures where EVA is used in either blends with APIs/additives or multilayer structures [11-14].

EVA has a long and successful history in the medical and pharmaceutical industry. The major R&D and commercial applications are as medical device components and pharmaceutical controlled release excipients in parenteral areas such as intravaginal rings/intrauterine devices [15-17], subcutaneous implants [18-20], ocular implants [21-23], dental products [24-26] and biological deliveries [27, 28]. There is also active R&D work on the potential use of EVA as an oral excipient for controlled release [29-32]. The details of these applications have been previously reviewed in published Celanese white papers [33, 34].

In addition to the areas mentioned above, TDD is another major area where EVA is used in commercial products as functional components and in the development of new drugs [35-38]. Over the years, there have been many different technologies developed to achieve the goal of TDD. These technologies include dermabration [39], electroporation [40, 41], iontophoresis [42, 43], jet injections [44, 45], microneedles [46, 47], spray on patches [48], sonophoresis [49, 50], and transdermal patches [51, 52]. Among these, EVA is heavily used in the construction of transdermal patches. In the following paragraphs, the commercial and developmental use of EVAs in transdermal patches is reviewed.

III. TRANSDERMAL PATCH DESIGNS AND EVA IN COMMERCIAL TRANSDERMAL PATCHES

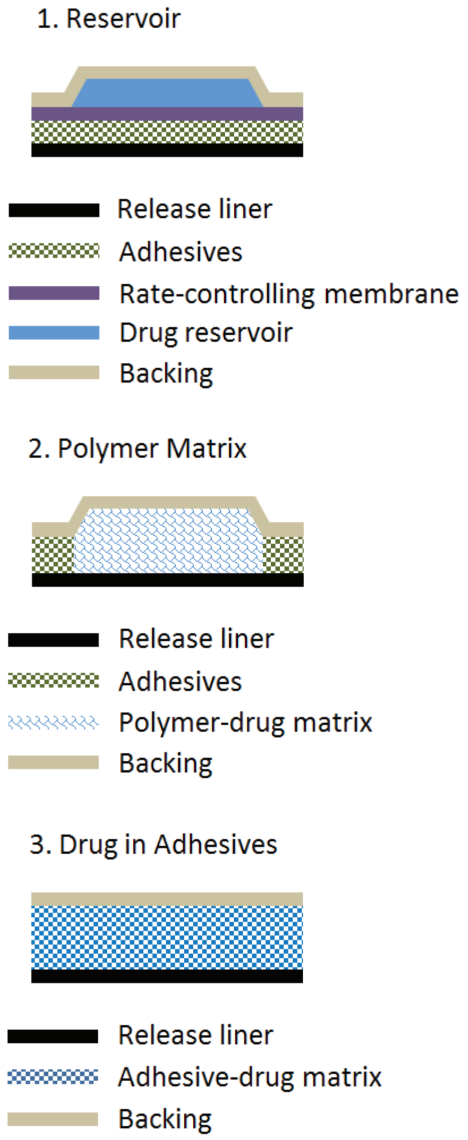


Figure 5. *Cross-section demonstrations of common transdermal patch designs [37, 53, 54]*

There are three common transdermal patch designs as illustrated in **Figure 5** [37, 53, 54]. The three designs are reservoir, polymer matrix and drug-in-adhesives. In the reservoir design (**Figure 5**, 1), the drug reservoir is enclosed by an impermeable backing layer and a rate-controlling membrane which is semi-permeable to the APIs. The compounds in the reservoir diffuse through the membrane as well as the adhesives layer, which requires the adhesives to be physiochemically compatible with the APIs and does not affect the drug delivery rate. When compared to the reservoir design, the polymer-drug matrix directly makes contact with the skin after the release liner is removed in the polymer matrix design (**Figure 5**, 2). In this case, the polymers in the matrix are the key components serving the controlled release function. With pre-compounded drugs and polymers, the APIs are delivered directly from the matrix to the skin with the adhesives forming a peripheral ring around the matrix to hold the patch in place. The third design is the drug in adhesives (DIA) design (**Figure 5**, 3) where the single adhesive layer provides the drug deliver functions as well as adhesion to the skin. The adhesive-drug matrix is very similar to the polymer-drug matrix other than it offers adhesive properties. The adhesive-drug matrix is required to control the rate of delivery, provide pressure sensitive adhesive properties and maintain long term compatibility with the APIs during the production, storage and application periods. In some cases, there are two layers of adhesives that may or may not be separated by a rate-controlling membrane within the adhesive-drug matrix to make a multilayer DIA structure [54, 55].

It is very important to note that there is no clear boundary between any two of the three designs. The same material can be used in different layers in different designs. To avoid confusion, the discussion in this paper focuses on the EVA usage in the functional layers instead of the designs.

EVA is commonly in the adhesive-drug matrix, rate-controlling membrane and the backing layers. **Table 2** summarizes selected commercial transdermal patches using EVA as functional components.

Table 2. *Selective commercial use of EVA in transdermal patches [5, 14, 37, 55-59]*

Product	Trademark Owner	API	Type	Where EVA is used
Climara®	Bayer Pharma	Estradiol	DIA	Backing
Estraderm®	Novartis Corporation	Estradiol	Reservoir	Backing and rate-control membrane
Nicoderm®	Aventis Holdings, Inc.	Nicotine	DIA	Backing and adhesives-drug matrix
Transderm-Nitro®	Ciba-Geigy Corporation (registrant)	Nitroglycerin	Reservoir	Rate-control membrane
Vivelle®	Novartis Corporation	Estradiol	DIA	Backing and adhesives-drug matrix

i. USE OF EVA IN THE ADHESIVE-DRUG MATRIX

EVAs have extremely wide applications in the adhesive industry as hot melt adhesives and pressure sensitive hot melt adhesives. Combined with their long history of providing controlled release functions in the pharmaceutical areas, it is natural to use EVA in the adhesive-drug matrix of the transdermal patches. In addition to the basic requirement of tackiness, the adhesive in the matrix also needs to provide flexibility, structure strength and long term compatibility with the APIs, penetration enhancers and other functional additives such as stabilizer and plasticizers. EVAs with 28 – 61 % VA have been frequently reported to be suitable to transdermally deliver a wide variety of APIs and particularly good results have been obtained from 40% VA EVA [60, 61]. To produce the matrix, the solvent casting procedure is very commonly used. The EVA is dissolved in chlorinated solvents, such as dichloromethane and chloroform. The API(s) and the functional additives are added to the EVA solution and the solution/suspension is cast onto a release surface such as surface treated releasing liners or simply a glass plate. After solvent evaporation, an adhesive-drug matrix can be obtained [62]. In commercial products, the cast procedure described above is also widely used but with some modifications. Even though the adhesive-drug matrix provides some structure strength to maintain the integrity of the layer and prevent it from oozing or flowing, a reinforce layer is often included in the patch design on either side of the adhesive-drug matrix. The reinforce layer provides extra mechanical strength when applying/removing the patch and also provides a better texture feel. It is usually a chemical inert mesh material of nonwoven, woven or knit. In some cases, a bonding layer between the adhesive-drug matrix and the reinforcement could also be introduced.

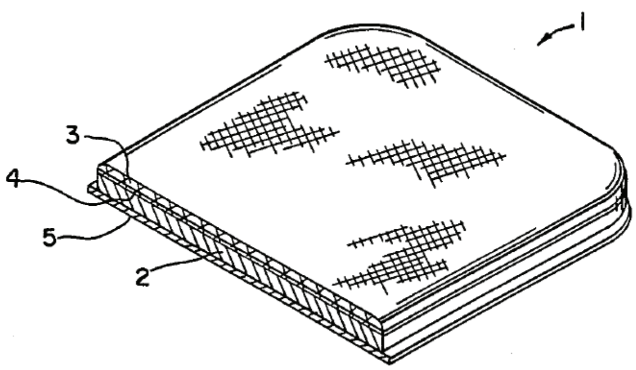


Figure 6. *A claimed design of a transdermal drug-in-adhesive patch [57]*

To give an example, **Figure 6** is the design claim of the patent for the commercial product Testoderm® [57]. In this DIA structure, the patch (1) is composed of four different layers. These layers are the adhesives-drug matrix layer, the reinforce layer, the bonding layer and the release liner layer (2-5 respectively). Fluorocarbon coated polyester film was used as the release liner layer and a spun-bonded polyester fiber on a silicone-coated polyester film was used as the reinforce layer. The bonding layer can be a polyisobutylene (PIB) mixture or silicon based adhesives. 40% VA EVA was used for in the adhesives-drug matrix. In the focused adhesive-drug (40% VA EVA-testosterone) matrix, the EVA showed great compatibility with the API and achieved the controlled release of the testosterone at a normal daily blood level in the in vivo study [57]. EVA based adhesive-drug matrix has been also successfully used in other commercial TDD products with APIs such as nicotine in Nicoderm® (trademark of Aventis Holdings, Inc.) and estradiol in Vivelle® (trademark of Novartis Corporation) [5, 56, 58].

Even though in the Testoderm® case, no functional small molecular additives were used, EVA has been widely used with a variety of different low molecular weight additives in the transdermal patch industry [63-67]. In a study by Sang Chul Shin and coworkers [62], an EVA adhesive-drug matrix for mexazolam transdermal delivery was investigated. A series of additives were mixed with the EVA adhesive-drug matrix to benefit the mechanical properties, such as reduced brittleness. These additives include actyl tributyl citrate, tributyl citrate, cetyl triethyl citrate, triethyl citrate, diethyl phthalate and di-n-butyl phthalate. It was reported that the additives not only contributed to the mechanical properties but also affected the drug release. In the EVA matrix, the citrates were found to slightly increase the mexazolam release rate while the phthalates dramatically increased the rate.

Penetration enhancers are specifically used to reversibly change the impervious nature of the skin temporarily. In this way, the TDD efficiency is enhanced. Common TDD penetration enhancers for EVA adhesive-drug matrix include essential oils, fatty acids, glycerides, non-ionic surfactants, propylene glycol derivatives, pyrrolidones, and even hydroxides [63-67]. In the patent application by Beste and Hamlin [64], the transdermal delivery of progesterone, buspirone, and estradiol through the EVA based adhesive-drug matrix was evaluated. In this publication, glycerol monolaurate (GML) and ethyl palmitate (EP) were used as penetration enhancers to increase the delivery efficiency of 40% VA EVA (EVA 40) based matrix. The selected results claimed are summarized in **Table 3**. The matrix was manufactured by mixing the components in a brabender type of internal mixer. The finished patch then was mounted on human epidermis samples with periodically replenished receptor solution in the reception chamber. The flux of the APIs was measured by the amount of drug diffused through the epidermis in a unit time per unit area. The tests were run in triplicate on two skin donors. The enhancement ratio in **Table 3** is the ratio of the flux value with the penetration enhancer to the flux value without. For both of the skin samples tested, it is clear that at an enhancer level of 32 wt %, the flux of all three APIs were significantly increased with good reproducibility.

Table 2. *Selective commercial use of EVA in transdermal patches [5, 14, 37, 55-59]*

Adhesive-drug matrix	Penetration enhancers	Composition (weight ratio) (drug: EVA: GML: EP)	Enhancement ratio of the drug flux	
			Skin I	Skin II
EVA 40 – progesterone	GML/EP	5:63:20:12	5.67	6.13
EVA 40 – buspirone	GML/EP	20:48:20:12	10.03	8.15
EVA 40 – estradiol	GML/EP	5:63:20:12	2.05	2.11

ii. USE OF EVA IN THE RATE-CONTROLLING MEMBRANE

Similar to the control release function that EVA serves in some parental pharmaceutical applications [15, 18], EVA can be used as a rate-controlling membrane in transdermal patches. This membrane is most used in reservoir transdermal patch design which has a long history. In fact, the first FDA approved Transdermal-Scop® (trademark owner: Novartis AG) patch is a reservoir design and uses a porous layer to control the rate [5, 37]. Rate-controlling membrane made of EVA is usually not considered as porous. The mechanism of the rate control is based on the drug diffusion through the EVA where the drug solubility/diffusivity in the EVA and the layer thickness are very important. As a rate-controlling membrane material, EVA offers design flexibility as the copolymer composition can be adjusted to fit requirements. By changing the VA content, percentage of crystallinity and polarity can be tuned. Both of these can be critical to drug solubility and diffusivity in the EVA. Depending on the nature of the drug and the patch system, 5 – 28 % VA EVA has been reported to be used as the membrane material [37, 55, 68].

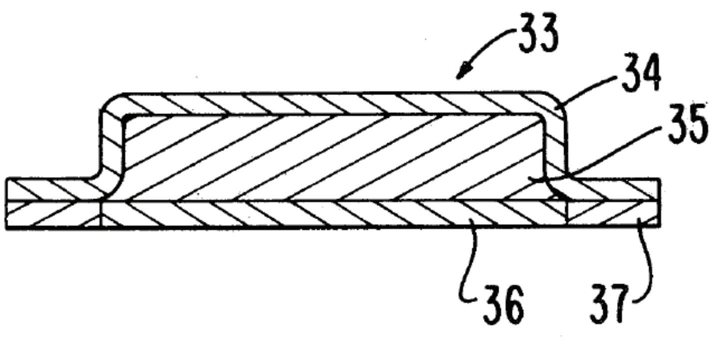


Figure 7. *A claimed reservoir patch design structure with EVA rate-contolling membrane [55]*

One of the commercial products use EVA as the rate-controlling membrane is Estraderm® developed by Alza. In the claimed design (33 as shown in **Figure 7**), the drug reservoir was an estradiol gel with ethanol (35). 34 and 37 shown in Figure 7 were the backing layer and the adhesive layer respectively. 9 % VA EVA film with 50 micron thickness was used as the rate-controlling membrane layer (36). The patch was tested in vitro on a diffusion cell. As a control sample, the estradiol gel was also tested on the same in vitro apparatus. **Figure 8** and **Figure 9** compare the flux values of estradiol and ethanol from the patch (squares) and the gel (triangles). In both Figures, the estradiol and ethanol were released in a controlled way compared to the gel where a burst effect or a very high flux was observed.

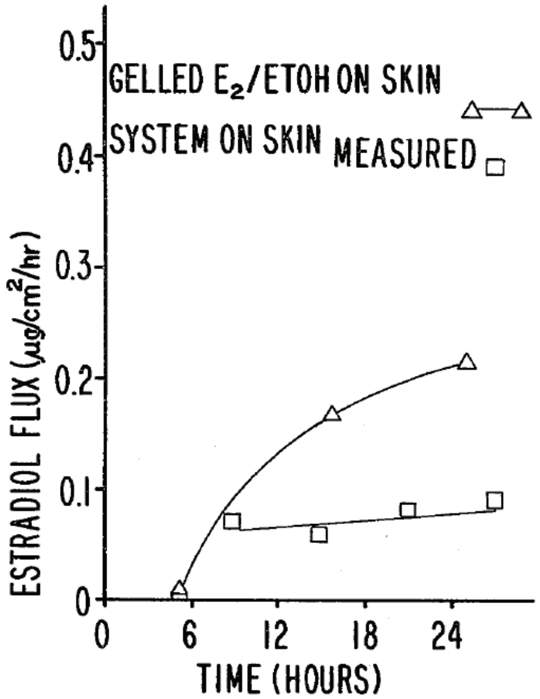


Figure 8. *Estrodiol in vitro flux comparison beween the patch sample and the gel sample on the skin (□ patch on skin; Δ gel on skin) [55]*

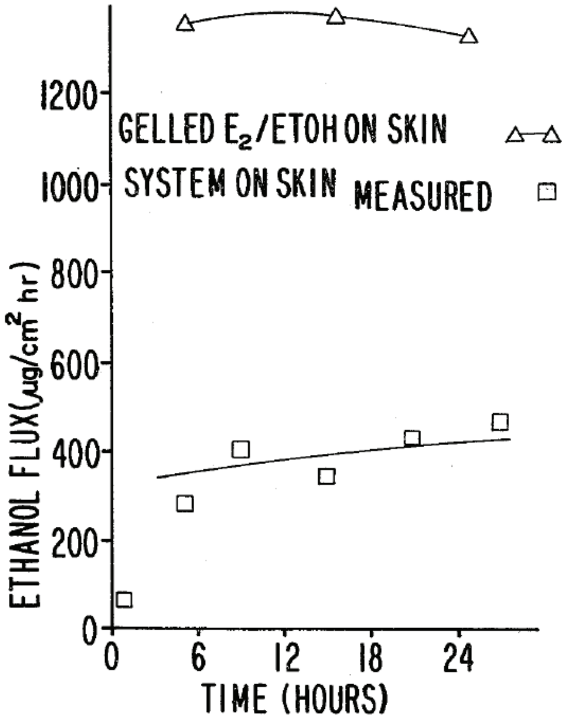


Figure 9. *Ethanol in vitro flux comparison beween the patch sample and the gel sample on the skin (□ patch on skin; Δ gel on skin) [55]*

iii. USE OF EVA IN THE IMPERMEABLE BACKING

The backing layer is designed to prevent the API from being delivered to the undesired side of the patch. When constructing the packing layer of a transdermal patch, the first requirement is the impermeability to the API. Although varying the VA content can alter the permeability of the EVA to the API, being a material used in rate-controlling membrane and drug matrix, EVA is not the best option for a barrier layer. However, it is frequently used in the impermeable backing in a single layer or multilayer structure to provide other functionalities that need to be balanced with impermeability [14, 37]. These functions include compatibility, breathability, conformability (low modulus thus high flexibility), and the ability to heat seal.

IV. EVA WITH DEVELOPMENTAL TRANSDERMAL DRUGS

As described in the previous paragraphs, EVA serves an important role in the commercial transdermal patch products with approved APIs. Because of these commercial successes, it is being used in developmental work with new transdermal drug by researchers across the globe. Table 4 summarizes selected drugs that have been reported to be transdermally studied in an EVA containing system in patents or journal articles. Here are some examples. Focused on an EVA matrix, researchers at CJ Corporation have been systematically studying the transdermal delivery of a wide variety of new TDD APIs including loxoprofen, torasemide, hydrochlorothiazide, glimepiride, pranoprofen, quinupramine ect. [11, 12, 62, 69-75]. Choi and coworkers [76] designed and prepared a DIA transdermal patch using EVA in the adhesive-drug matrix to deliver donepezil for treatment of Alzheimer's disease symptoms such as dementia. The patch was found to have excellent skin adhesion and long term continuous drug release. Reddy and Satyanandam [77] investigated the transdermal delivery of diltiazem. A 40% VA EVA was used in the matrix along with comparing groups using ethyl acrylate/methyl methacrylate/methacrylic acid ester copolymers. When compared to the other polymers studied, EVA containing system was found to be more stable and non-irritant/non-sensitizing to skin [77].

Table 4. *Selected APIs in transdermal patch development using EVA*

API	Treatment	EVA function	Ref
Acyclovir	Herpes virus infections	Adhesive-drug matrix	[57]
Atenolol	Hypertension	Adhesive-drug matrix	[70]
Buspirone	Anxiety	Adhesive-drug matrix	[64]
Diltiazem	Hypertension and angina	Adhesive-drug matrix	[77]
Donepezil	Alzheimer's disease	Rate controlling membrane	[76]
Glimepiride	Diabetes	Adhesive-drug matrix	[12]
Glibenclamide	Diabetes	Rate controlling membrane	[78]
Hydrochlorothiazide	Edema	Adhesive-drug matrix	[71]
Mexazolam	Anxiety	Adhesive-drug matrix	[62]
Nitroglycerin	Angina pectoris	Adhesive-drug matrix	[58]
Oxybutynin	Incontinence	Adhesive-drug matrix	[64]
Pranopofen	Inflammation	Adhesive-drug matrix	[79]
Progesterone	Hormone therapy	Adhesive-drug matrix	[64]
Quinupramine	Depression	Adhesive-drug matrix	[72]
Torasemide	Edema	Adhesive-drug matrix	[11]
Triprolidine	Flu symptoms	Rate controlling membrane	[73, 74]
Loxoprofen	Inflammation	Adhesive-drug matrix	[75]

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