

# Innovations in Transdermal Drug Delivery: Formulations and Techniques

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**Abstract:** The transdermal route of drug delivery has attracted researchers due to many biomedical advantages associated with it. However, excellent impervious nature of skin is the greatest challenge that has to be overcome for successfully delivering drug molecules to the systemic circulation by this route. Various formulation approaches used to systemically deliver drug molecules include use of prodrugs/lipophilic analogs, permeation enhancers, sub saturated systems and entrapment into vesicular systems. Further, the adhesive mixture, physical system of the delivery system and release liner influence drug release and its permeation across the skin. In addition, great strides in designing delivery systems for maximizing percutaneous drug permeation without comprising with ease of therapy cannot be neglected in improving functionality of transdermal drug delivery systems. This article deals with the innovations pertaining to formulation and techniques as described in recent patents.

**Keywords:** Transdermal drug delivery, transcutaneous permeation, percutaneous permeation, adhesive, microblades, microporation, electroporation, iontophoresis, sonophoresis, microneedles.

## INTRODUCTION

Innovations in the area of drug delivery are taking place at a much faster pace as compared to the last two decades. Improved patient compliance and effectiveness are inextricable aspects of a new drug delivery system. Transdermal delivery offers several biomedical advantages over conventional routes including avoidance of presystemic and systemic first pass metabolism and controlled release over extended period besides providing a convenient non-invasive and easily terminable means for systemic as well as topical drug delivery [1]. Despite the fact that US FDA approved the first transdermal patch in 1981 [2], this dosage form did not excite the pharmaceutical manufacturers to a great extent. Further, mega-pharmaceutical mergers in the late 1990s especially of pharmaceutical companies involved in development of transdermal delivery systems resulted in only few companies keen to develop transdermals. Infact, projects incorporating new drug delivery technology mainly aimed at oral route till 2000.

Low turnover rate of transdermal products from pharmaceutical research and development departments could be attributed to the enormous endeavors that were required to be undertaken for overcoming the excellent impervious nature of human skin. Other factors that limited the success of transdermal technology included skin irritation, limitation of dose that could be incorporated in the patch, lag time for drug absorption/ onset of action, variation in drug absorption rate with respect to site of application and failure of adhesiveness. It is with renewed interest for extending patent life, high component of patient acceptance and the rise in non-oral drug delivery systems (pulmonary, inhalations etc.) that pharmaceutical companies became more aggressive in exploring skin as an attractive route for drug delivery.

The market for transdermal devices is currently estimated at US \$ 1.2 billion, approximately 10% of the entire US \$ 28 billion drug delivery market [3]. In addition, transdermal drug delivery market is currently based on only 10 drugs. Hence, pharmaceutical scientists are constantly striving to add new deliverables to the short list of approved transdermal products. Therefore, it becomes interesting to study the strategies being adopted by pharmaceutical scientists in their quest for overcoming the barrier properties of human skin while developing successful transdermal drug delivery systems. This article aims at studying the relatively new patents on transdermal products with a view to explicitly understand the strategies being evolved and put into practice while developing transdermal products.

## ENHANCING DRUG DELIVERY ACROSS SKIN

### I. Formulation Strategies

Overcoming the barrier status of skin is of prime concern for the success of a transdermal patch. A product development scientist often uses permeation enhancer(s) that increase the rate of transfer of drug(s) across the skin. In addition, adequate adhesiveness seems to be essential to ensure intimate contact of the formulation with skin for intended duration. Furthermore, choice of the rate controlling membrane is critical as it controls the release rate of the drug from the formulation.

### Ingredients

#### Adhesives

The use of hormones for preventing ovulation as a means of contraception as well as for female hormone replacement therapy is not new. Transdermal delivery of these hormones is advantageous due to the controlled input it can offer over a long period. However, due to large molecular size, weight and high lipophilicity there is a need to include suitable ingredients for enhancing their permeation across skin.

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Jona *et al.* (2000) patented the combination of different adhesive resins and permeation enhancers for administering 17- deacetyl norgestimate alone or in combination with an estrogen such as ethinyl estradiol to women. The adhesives used were polyacrylate (Duro-Tak 87-2287), polydimethylsiloxane (Silicone 4202) or a combination of Vistanex L100, Vistanex LM-MS-LC and polybutene. The permeation enhancers incorporated for enhancing the permeation of these drugs were thioglycerol, oleic acid, methyl laurate, propylene glycol monolaurate, transcutanol, dibutylsebacate, N, N-dimethyl amide, lauramide diethanolamine, propylene glycoisostearate or AMIFAT (derived from glycerin, oleic acid and 2- pyrrolidone-5-carboxylic acid). A patch comprising 5-layer composite containing backing, adhesive matrix, non-woven polyester layer, adhesive layer and release liner was described for obtaining sustained release of both drugs [4].

Horstmann *et al.* (2000) patented a transdermal therapeutic system having a layered structure for systemic delivery of 17- -estradiol. The system comprised of 17- -estradiol, Cariflex RTM TR 1107 (styrene-isoprene-styrene block copolymer), Staybelite ester 5E (thermoplastic ester resin of colophony derivatives) and viscous paraffin. Precoating the removable protective layer with an adherent layer of fluoropolymers prevented premature precipitation of the active ingredient during storage. This was claimed to be due to lower diffusion coefficient of the drug in the adherent layer as compared to the base materials. The system provided enhanced delivery because it contained oversaturated solution of 17- -estradiol, which did not crystallize on storage [5].

The pressure-sensitive adhesive layer may induce coloration by interacting with the incorporated drug. The use of an azo or organic peroxide compound as polymerization initiator during co-polymerization of acrylic copolymer was found to be effective in preventing the coloration. The formation of 2-mercaptobenzimidazole and/or propyl gallate was claimed to be responsible for this protective effect [6].

Braun (2000) patented transdermal formulations comprising copolymers made from isooctyl acrylate, N-vinyl-2-pyrrolidone and/or 2-hydroxy ethyl acrylate with isopropyl myristate, propylene glycol, oleic acid or lauric acid as permeation enhancers. The delivery device was tested *in vitro* for delivering required amount of lerisetron for the treatment of nausea, emesis, anxiety etc [7]. Tetrahydrocannabinol is known to bind to silicone-based materials. Hence, aluminized polyester and polybutene nonwoven polyester is preferred for use as backing layer. A combination of porous material capable of absorbing tetrahydrocannabinol along with a solution, which is non-solvent for tetrahydrocannabinol, was found to be suitable for controlling its rate of diffusion from transdermal patch [8].

Rovati *et al.* (2000) used an adhesive mixture prepared by dissolving in ethyl acetate a copolymer obtained by radical polymerization of ethyl hexyl acrylate, vinyl acetate, hydroxy ethyl acrylate and glycidyl methacrylate. A fine suspension of estradiol, norethindrone acetate, octyl dodecanol and aluminium acetylacetonate in methyl ethyl ketone when added to the copolymer solution produced a homo-

genous mass, which was used to prepare a composite medicated patch for transdermal delivery [9].

It is important to note that the permeation of hydrophobic drug (alprazolam) was greater from polymer adhesive blends containing a higher proportion of hydrophilic polymer. On the contrary, permeation of hydrophilic drug (nicardipine hydrochloride) was greater from polymer blends containing higher proportion of hydrophobic polymer. Further, matrixes containing hydrophobic- hydrophilic polymer blends gave substantially higher drug flux as compared to those containing only hydrophilic or hydrophobic polymer [10]. Similarly, *in vitro* permeation of estradiol and norethindrone across human cadaver skin by using different types of pressure-sensitive adhesive systems without permeation enhancer were observed to be comparable to the commercial patches. Higher permeation of drugs from these systems was proposed to be due to the presence of greater thermodynamic activity, which could be achieved with less drug concentration in the absence of permeation enhancer [11].

Oral delivery of tetrahydrocannabinol (THC) has many disadvantages including slow and erratic absorption. Hence, new modes are being tested for delivering therapeutic doses of THC [12]. Transdermal route is preferred as it can provide a steady and sustained delivery of THC. 'Soft' vesicles known as ethosomes formed by addition of high (20-50%) concentration of ethanol patented by Touitou (1996) possessed the advantage that small vesicles could form a reservoir in the skin and a film on skin surface for prolonged delivery [13] after evaporation of solvent.

THC exhibits low skin permeability and strong tendency to bind to tissue and protein thus make its transdermal delivery difficult. A transdermal patch containing 10% of cannabinoid mixture (dispersed in light mineral oil) gelled using silica particles along with a mixture of N, N- dimethyl amide and alcohol ethoxylate (1:1) gave an overall cannabinoid flux of 15  $\mu\text{g}/\text{cm}^2/\text{hr}$  as compared to 0.1  $\mu\text{g}/\text{cm}^2/\text{hr}$  obtained without using permeation enhancers. Higher flux of 25  $\mu\text{g}/\text{cm}^2/\text{hr}$  was obtained when the cannabinoid mixture along with polyoxyaryl ether and vinyl phenol ethoxylate (1:1) were suspended in acrylic adhesive to prepare an adhesive matrix reservoir. This formulation when incorporated in low-density polyethylene open pore form exhibited a flux of 17  $\mu\text{g}/\text{cm}^2/\text{hr}$  across excised human cadaver epidermis [14].

Ethylene vinyl acetate was used for preparing reservoir matrix of drugs including buspirone, melatonin, taerine, testosterone, alprazolam, gestodene and ethinyl estradiol. The incorporation of N-vinyl-2- pyrrolidone in the formulation was claimed to improve the wearability, storage stability and drug utilization of the transdermal device. The amount of N-vinyl-2- pyrrolidone required for enhancing drug permeation and improving stability depended, respectively, on the stability of the enhancer and improvement in stability or wearability with respect to devices not containing poly-N-vinyl amide. Formulations containing N-vinyl-2- pyrrolidone exhibited greater drug permeation across epidermis as compared to those not containing it. Further, the permeation of drugs from transdermal devices containing combination of permeation enhancer and N-vinyl-2-pyrrolidone was higher than that from patches containing only permeation enhancer

or only N-vinyl-2-pyrrolidone indicating a more than additive effect [15].

A transdermal patch containing needle-shaped form of indomethacin in carboxyvinylpolymer gel along with polyoxyethylene sorbitan monooleate, tocopherol acetate and ethyl p-hydroxy benzoate was found to be stable and provided better *in vitro* release as compared to cataplast containing platy form of crystals [16].

A transdermal formulation containing a combination of norethindrone acetate and estradiol hemihydrate in an over saturated state was formulated by including 2.5 to 3.5% w/w of silicone dioxide (Aerosil 380) in the matrix. Drying the medicated laminate at 35-95°C was not able to remove the moisture. However, exposing the laminate to IR lamp for 2 min reduced the moisture content to less than 0.5% w/w thereby, activating the silicone dioxide. The resultant patches gave significantly higher flux of both drugs across human cadaver skin as compared to reference formulation. This unexpected behavior was suggested to be due to absorption of water from the skin by the activated silicone dioxide resulting in decreased solubility of the hormones. This in turn, perhaps provoked an increase in the driving force resulting in better flux of both drugs [17].

In an attempt to extend the delivery from transdermal patches, Hoffmann (2002) obtained a patent for incorporating nicotine depot in the form of non-woven fabric having higher drug concentration than in the matrix. This was laminated on one side with a nicotine-impermeable backing layer consisting of a vapour deposited aluminium layer and a thermoplastic butadiene-acrylonitrile modified acrylonitrile methyl acrylate copolymer. The matrix got enriched with nicotine slowly thus, exhibiting release over extended period [18].

A simple formulation comprising polydimethylsiloxone-oil-based adhesive polymer composition, an absorption enhancer, a volatile silicone and a volatile polar solvent (ethanol and ethyl acetate) was claimed to be easily applied to the skin using a brush. This formulation was capable of delivering lipophilic active ingredients including cholecalciferol, calcitonin, oestradiol propionate, prednisone, 17-estradiol and medroxyprogesterone acetate transdermally after evaporation of the solvent from the applied formulation [19].

Song *et al.* (2004) patented the manufacturing method of transdermal drug delivery system of diclofenac diethyl ammonium. Unlike previous systems, the release liner was first coated with a mixture containing non-ionic surfactant, acrylate adhesive and diclofenac diethyl ammonium. Separately, the backing membrane was coated with acrylate adhesive. Another adhesive layer was formed on top of release film by coating with acrylate adhesive. Then, an adhesion solution prepared by mixing solution of a terpene, dissolution promoter and gelling agent was coated through a nozzle on this layer. Finally, the backing membrane was laminated onto the upper surface of the dried volatile absorption enhancer layer. Menthol, propylene glycol, glycerin, isopropyl alcohol, triacetin, glyceryl mono-oleate, glyceryl mono-laureate and sorbitan mono-oleate were found

to exhibit superior compatibility and synergistic effect on permeation of diclofenac when used in combination [20].

A great challenge that the formulator faces while incorporating drugs possessing plasticizing effect is the failure of adhesive system. Govil *et al.* (2006) observed acceptable shear strength after incorporation of selegeline, a highly plasticizing drug into Gelva 1753 as well as Durotak 87-2516. Similarly, the Polken tack values demonstrated acceptable results. However, while Durotak 87-2194 exhibited cohesive failure and adhesive transfer to skin, Gelva 2655 and 1753 exhibited total adhesive failure. This indicated that no generalization was possible while selecting an adhesive for plasticizing drugs. The inventors used the technique of deprotonating the plasticizing drug to its free base form by using deprotonating agents such as triethanolamine, diethanolamine, ethanolamine, propanolamine, ammonia, polyethylene imine, polydimethyl amino ethyl methacrylate or polyacrylamin. It was observed that for complete deprotonation of the active ingredient, it was essential for the deprotonating agent to possess a  $pK_b$  value at least 0.75 lower than the  $pK_b$  value of the deprotonated form of drug. However, due to low  $pK_b$  and high pH of the deprotonating agents, they were not found to be safe to use. Therefore, an adhesive mixture comprising an acrylic polymeric adhesive which included 60%-80% of C4-C12 alkyl acrylate (2-ethyl hexyl acrylate, butyl acrylate, n-decyl, n-nonyl, 2-ethylhexyl, isooctyl or dodecyl- acrylate, 15%-30% of a C1-C4 alkyl acrylate hardening monomer selected from methyl acrylate, methyl methacrylate, ethyl acrylate, ethyl methacrylate, hydroxyethyl acrylate or hydroxy propyl methacrylate, 1%-20% of functionalizing monomer to facilitate cross-linking selected from acrylic acid, hydroxy ethyl acrylate, methacrylic acid or acrylamide; 0.005%-2.0% w/w of cross-linking agent selected from butyl titanate, polybutyl titanate, aluminium zinc acetate) was found to be suitable for transdermal formulation of highly plasticizing drugs such as selegeline, tetracaine, and chlorpheniramine [21].

Garbe *et al.* (2006) evaluated a series of combinations of pressure sensitive adhesive components for their suitability as transdermal drug delivery devices for oily excipients. A pressure sensitive adhesive matrix requires a balance of viscous and elastic properties that result in a four-fold balance of adhesion, cohesion, stretchiness and elasticity. In order to provide these properties to a pressure sensitive adhesive, the matrix should contain copolymer comprising one or more monomers selected from the group consisting of C4-C10 alkyl acrylates and C4-C10 alkyl methacrylates. It may optionally comprise one or more ethylenically unsaturated monomers co-polymerized with the copolymer. The properties of the matrix are influenced by the presence of oily materials, which may be drug, C8-C22 fatty acids, C8-C22 fatty alcohols, lower alkyl esters of C8-C22 fatty acids or their combination. These acts as 'softener' and raise the compliance value or lower the glass transition temperature of the matrix as compared to the copolymer. However, matrices having substantially high compliance values generally have less than optimal cold flow and have substantial residue on removal from skin. On the other hand, those having substantially lower compliance value are generally stiff and have less than optimal skin contact and adhesion to skin. The highest flux of 0.166  $\mu\text{g}/\text{cm}^2/\text{hr}$  of

levonogestrol was obtained from a matrix containing propylene glycol (15%), methyl laurate (25%), glyceryl monolaurate (2.5%), N, N- dimethyl dodecylamine-N-oxide (1.5%) and 54.5% of 55/40/5 isooctyl acrylate/hydroxy ethyl acrylate/ polymethylmethacrylate macro monomer (Elvacite 1020) copolymer [22].

### Enhancers

For many years, clinical investigators and chemical welfare experts have suggested that substances must exist which could temporarily diminish the impermeability of skin. Such materials, if safe and non-toxic, could be used in dermatology to enhance the permeation rate of drugs and even to treat patients systemically by the dermal route. Such materials appear to increase skin permeability by reducing the diffusional resistance of the stratum corneum, by reversibly damaging it, or by altering its physicochemical nature. The ever-growing research in this area forbids a detailed discussion here. Hence, only few important enhancers that have been mentioned in recent patents that have been taken up in this section.

D'Angelo *et al.* (2000) patented the use of polymeric skin enhancers (polyvinyl pyrrolidone and 1-N-dodecyl azacycloheptan-2-one) for transdermal delivery of high molecular weight drugs calcitonin (3500 daltons) and insulin (6000 daltons), respectively. The drug constituted 15% by weight of the formulation. The multidose transdermal patch assembly included drug impervious support impressed to form a series of compartments. This assembly was found to be advantageous as it allowed customization of medicament to meet specific clinical needs, which was illustrated, with the help of two-day human test (blind study). The transdermal delivery of calcitonin significantly lowered serum calcium levels and increased calcitonin levels. In addition, the rate of delivery was sufficient to achieve therapeutic level. The study revealed that skin permeation could be enhanced by first releasing a skin enhancer so as to modify skin permeability followed by the release of drug active at therapeutic levels [23].

Dittgen *et al.* (2001) described different compositions for transdermal administration, which showed better permeation as compared to known compositions for steroidal hormones. The transdermal therapeutic system consisted of at least one active agent in the form of solid dispersion in combination with at least one destructuring agent (Nicotinamide or urea) and/or at least one structuring agent (lactose) in a common matrix. The flux of testosterone ranged from  $3.1 \pm 1.1 \mu\text{g}/\text{cm}^2/\text{hr}$  to  $11.8 \pm 2.4 \mu\text{g}/\text{cm}^2/\text{hr}$ . The enhancement factors on addition of destructuring/structuring agents were between 1.75 and 3.8 suggesting that adding destructuring agents and/or structuring agents could increase the *in vitro* flux of testosterone. Serum concentration after transdermal application of these patches was 0.04 ng/ml after 1.5 hr and 2.2 ng/ml after 16 hr. After a short lag time of about 2 hr, there was a marked increase in serum concentration, which remained above 1 ng/ml over 20 hr. A continuous decline in serum testosterone concentration was observed after 24 hr of patch application and after its removal [24]. The combination of a monoglyceride permeation enhancer and ethyl palmitate as a co-solvent was found to be effective in enhancing

transdermal flux of a variety of drugs. The enhancer combinations used for different drugs are listed in Table 1.

Hsu *et al.* (2003) tested the *in vitro* permeation of testosterone across human cadaver skin after application of transdermal formulations containing oleic acid or sodium hydroxide or their combination. The highest permeation of testosterone ( $0.346 \text{ mg}/\text{cm}^2/\text{hr}$ ) was observed from the patch containing combination of oleic acid and sodium hydroxide [26]. Luo *et al.* (2004) discovered that the basic permeation enhancers enhanced the flux of lidocaine without causing skin damage. It was believed that basic solution provided a high pH on skin surface thus, creating channels in the skin for the drug to pass. It was also expected that drug flux could be proportional to the solution strength and duration of exposure. The results revealed that pH of the lidocaine patch increased from 8.86 to 10.87 when the calculated excess NaOH concentration in the patch was increased from 0 to 4.6%. This was accompanied with an increase in the cumulative amount of lidocaine from  $0.428 \text{ mg}/\text{cm}^2$  to  $1.169 \text{ mg}/\text{cm}^2$  passing across human cadaver skin in 24 hr [27]. Perfluoropolyether class of compounds has been found to increase the percutaneous absorption of many drugs including troxerutine, nimesulide, ketoprofen, diclofenac sodium, ibuprofen etc. by 5-20 times [28]. Monoterpene ketones like (-) menthol, (-) menthone, peppermint oil, spearmint oil or mint oil were incorporated in 0.5, 1.0, or 2% w/w concentration into formulations for transdermal delivery of nicotine. The enhancement of nicotine delivery followed the order menthol < menthone < mint oil < peppermint oil < spearmint oil. Spearmint oil, which predominantly contains carvone, yielded the best result [29].

Quite a few recent patents pertain to the use of sodium hydroxide, sodium carbonate, tri potassium phosphate or magnesium oxide for enhancing percutaneous delivery of drugs. Table 2 enlists few recent patents that have utilized these hydroxide-releasing agents. A critical analysis of the reported results suggests an increase in drug permeation with an increase in pH of the formulation. However, neutralization of the hydroxide-releasing agent by the incorporated drug [33] needs to be critically evaluated while formulating such systems. In addition, the deleterious effect due to long term exposure of skin to these hydroxide-releasing agents seems to be of prime concern.

### Type of Formulation

#### Submicron Oil Spheres/Emulsions

Friedman *et al.* (2000) patented submicron oil spheres of diazepam. Submicron globule size in medium chain triglyceride (MCT) oil using lecithin, oleic acid, emulsifying wax, Tween-65 or monotan-68 as oil soluble emulsifier was found to be 120 nm, 150 nm, 5-50 $\mu\text{m}$ , 250 nm or 300 nm, respectively. Similarly, change in the water-soluble emulsifier (Pluronic F-68, Tween-80 or Emulfor EL-620) also led to changes in droplet size. Similar studies were performed for Lidocaine. The data showed that Lidocaine alone in oleaginous base or in regular cream of emulsifying wax (droplet size more than 50 microns) was not effective as local anaesthetic. However, the small droplet size preparation provided local anesthesia and performed better

**Table 1. The Enhancement Ratio of Drugs in Presence of Enhancers as Patented by Beste *et al.* [25]**

Formulation		Ratio of drug flux with enhancer to drug flux without enhancer
Drug	Enhancer system	
Progesterone	EVA 40	1.00
Progesterone	GML/EP/EVA 40	5.67
Progesterone	Polysiloxane	1.00
Progesterone	GML/EP/PVP/Polysiloxane	1.70
Buspirone	EVA 40	1.00
Buspirone	GML/EVA 40	9.19
Buspirone	GML/EP/EVA 40	10.03
Buspirone	GML/EP/PVP/Polysiloxane	3.53
Buspirone	EP/EVA 40	1.28
Buspirone	Polysiloxane	1.00
Estradiol	EVA 40	1.00
Estradiol	GML/EP/EVA 40	2.11
Estradiol	Polysiloxane	1.00
Estradiol	GML/EP/PVP/Polysiloxane	1.38
Oxybutynin base	Polysiloxane	1.00
Oxybutynin base	GML/EP/PVP/Polysiloxane	1.46

EVA 40: Ethylene vinyl acetate; GML: Glycerol monolaurate; EP: Ethyl palmitate; PVP: Poly vinyl pyrrolidone

**Table 2. Summary of the Patents Utilizing Hydroxide-Releasing Agents as Permeation Enhancers in Transdermal Formulations**

Patent No.	Drug	Hydroxide releasing Agent (g)	pH	Flux	Reference no.
US20036562368B2	Oxybutynin	NaOH			[30]
		0.15	-	1747.7 <sup>a</sup>	
		0.25	-	2853.5 <sup>a</sup>	
		0.35	-	2322.8 <sup>a</sup>	
US20036562370B2	Estradiol	NaOH			[31]
		0	7.22	0.22 <sup>a</sup>	
		0.0155	8.75	4.55 <sup>a</sup>	
		0.025	8.90	7.01 <sup>a</sup>	
US20036562370B2	Estradiol	Potassium phosphate tri basic			[31]
		0	6.4	0.6 <sup>b</sup>	
		0.1	8.89	5.6 <sup>b</sup>	
		0.3	10.83	10.2 <sup>b</sup>	
		0.48	9.87	5.3 <sup>b</sup>	

(Table 2) Contd....

Patent No.	Drug	Hydroxide releasing Agent (g)	pH	Flux	Reference no.
US20036562370B2	Estradiol	Sodium carbonate			[31]
		0	7.48	0.3 <sup>b</sup>	
		0.11	9.87	1.4 <sup>b</sup>	
		0.3	10.51	1.0 <sup>b</sup>	
		0.45	10.49	1.4 <sup>b</sup>	
US20036562370B2	Estradiol	Magnesium oxide			[31]
		0	7.48	0.32 <sup>b</sup>	
		0.11	8.95	0.53 <sup>b</sup>	
		0.3	9.66	0.36 <sup>b</sup>	
		0.45	10.28	0.27 <sup>b</sup>	
US20036565879B1	Leuprolide solutions	NaOH			[32]
		0	-	0.52 <sup>a</sup>	
		0.0125	-	3.21 <sup>a</sup>	
		0.0275	-	4.43 <sup>a</sup>	
US20036565879B1	Oxytocin	NaOH (skin pretreated with 4% NaOH for 24 hr)	-	236.8 <sup>a</sup>	[32]
US20036565879B1	Oxytocin	NaOH (skin pretreated with 1% NaOH for 24 hr)	-	30.97 <sup>a</sup>	[32]
US20046719997B2	Phenyl propanolamine HCl	NaOH			[33]
		0	7.33	0.56 <sup>b</sup>	
		0.165	10.08	1.35 <sup>b</sup>	
		0.195	10.16	5.2 <sup>b</sup>	
		0.23	10.83	5.99 <sup>b</sup>	
US20046719997B2	Phenyl propanolamine HCl	Sodium carbonate			[33]
		0	6.54	545.1 <sup>a</sup>	
		0.29	9.81	410.4 <sup>a</sup>	
		0.44	9.86	705.6 <sup>a</sup>	
		0.74	10.17	1147.5 <sup>a</sup>	
US20046719997B2	Phenyl propanolamine HCl	Potassium phosphate tri basic			[33]
		0	6.75	680.5 <sup>a</sup>	
		0.57	9.68	2055.2 <sup>a</sup>	
		0.6	9.62	1762.9 <sup>a</sup>	
		0.66	10.08	2021.1 <sup>a</sup>	

(Table 2) Contd....

Patent No.	Drug	Hydroxide releasing Agent (g)	pH	Flux	Reference no.
US20046719997B2	Phenyl propanolamine HCl	Magnesium oxide			[33]
		0	7.89	129.8 <sup>a</sup>	
		0.11	9.6	801.9 <sup>a</sup>	
		0.26	10.09	2533.4 <sup>a</sup>	
		0.5	10.10	1831.4 <sup>a</sup>	
US20046719997B2	Oxybutynin	NaOH			[33]
		0.15	-	1747.7 <sup>a</sup>	
		0.25	-	2853.5 <sup>a</sup>	
		0.35	-	2322.8 <sup>a</sup>	

a:  $\mu\text{g}/\text{cm}^2/24\text{ hr}$ ; b:  $\text{mg}/\text{cm}^2/24\text{ hr}$

than larger droplet size of submicron lidocaine preparation [34].

Chen *et al.* (2004) described the preparation of o/w emulsions for delivering various drugs from transdermal formulations. Different concentrations of Captex 810 D structured triglyceride and polarity modifiers like safflower oil; monoglycerides or acetylated monoglycerides were used along with different concentrations of egg phospholipids. The resulting emulsions had a mean particle size diameter less than 300 nm, 200 nm and 300 nm, respectively [35].

Progesterone emulsions containing soyabean oil, Captex 810 D or glyceryl trioleate as triglycerides and monoglycerides and mono-diglyceride or mono and acetylated monoglycerides as polarity modifiers were observed to possess a mean particle diameter of 150-200 nm. The influence of formulation ingredients on globule size of emulsions is summarized in Table 3.

#### Sub Saturated Reservoir System

Osborne *et al.* (2000) designed a system where the initial equilibrated concentration of nicotine in reservoir and adhesive was below saturation. In addition, the rate-controlling element of the device was substantially impermeable to nicotine. The device was designed with an objective that not more than and preferably less than half of the total nicotine loaded was in the adhesive and rate controlling membrane layers after equilibration and prior to use. This nicotine transdermal delivery device containing 40% nicotine base in 60% rate controlling membrane laminated with a mixture of high molecular weight polyisobutylene and low molecular weight polyisobutylene in ratio of 80:20, 85:15 or 90:10 exhibited good adhesive properties and the *in vitro* release rates were found to be 60  $\mu\text{g}/\text{cm}^2/\text{hr}$ , 70  $\mu\text{g}/\text{cm}^2/\text{hr}$  and 72  $\mu\text{g}/\text{cm}^2/\text{hr}$ , respectively [36].

#### True Solution

Formulations were modified to form a true solution in a complex mixture formed from solvents and solute modifiers in combination with skin stabilizers. This composition was

found to be effective for transdermal delivery of high molecular weight solute (>350 Da) and exhibited delivery rates greater than 0.25  $\text{mg}/\text{cm}^2/24\text{hr}$ .

The invention utilized a mixture of active drug and/or a vasodilator (acetylcholine, amrinone, becyclone fumarate, benzyl nicotinate, cetiedil citrate etc.) to which a permeation enhancer was added. The enhancer did not bind to either active drug ingredient or vasodilator. This eliminated the need for adding polymeric binding agent thus, reducing the total molecular weight of the mixture and enhancing the transcutaneous delivery of active ingredients. Testosterone formulation formulated by this technique showed 10-fold enhanced testosterone level in one hr. Further, devices containing 2.5-mg morphine provided blood levels equivalent to a 10 mg IV dose. Vander Waals forces of the delivery system could be matched to the Vander Waals forces of the total composition so as to maximize the effectiveness. This technique was adopted for transdermal delivery of combination of lorazepam and ibuprofen also. The sum of moles-Vander Waals for delivery system was 2.838 while for delivery system and active ingredients was adjusted to 2.9687 [37].

#### Solution Based Transdermal Delivery System

An efficient transdermal delivery system comprising a vasodilator, an active ingredient (loratidine and ketoprofen) and a permeation enhancer (oleic acid, menthol) was patented. The components were combined in such a manner that dissolved them into solution, eliminating the need for a polymeric binding agent. In this way the total molecular weight of the mixture was diminished and the permeation efficiency of drug molecules was increased [38].

#### Gels

A gel using hydroxy propyl cellulose and ethanol was formulated for transdermal delivery of testosterone. Testosterone loaded in the gel was 21  $\text{mg}/\text{cm}^2$  [39]. Similarly, a hydrogel formulation of fentanyl or sufentanil was prepared using polyvinyl alcohol and resin buffer. The formulated gel had a skin contact area of 2  $\text{cm}^2$  and 0.16  $\text{cm}^2$ , respectively.

**Table 3. The Influence of Formulation Ingredients on Globule Size of Emulsions [35]**

Polyfunctional active ingredient	Oil phase	Polarity modifier	Particle size
Cyclosporin	Captex 810 D	Safflower oil (Long chain triglyceride)	300 nm
Cyclosporin	Captex 810 D	Monoglyceride and acetylated monoglycerides	>200nm
Cyclosporin	Safflower oil	Eastman 9-45	>300nm
Progesterone	Soyabean oil	Eastman 9-45	>200nm
Progesterone	Captex 810 D	Glycerol trioleate and monodiglyceride	>150 nm
Tretinoin	Safflower oil and Triethyl amine (Oil miscible base)	Acetylated monoglyceride, monoglyceride and diglyceride mixture	>100 nm
Tretinoin	Captex 810 D and Triethyl amine	Monoglyceride, monoglyceride and diglyceride mixture	>100nm
Drug free emulsion	Captex 810 D (Structured triglyceride) and soyabean oil (Long chain triglyceride)	Low HLB polyethoxylated vegetable oil	>150 nm
Drug free emulsion	Captex 810 D (Structured triglyceride) and Safflower oil (Long chain triglyceride)	Polyglycerized fatty acid ester	>100 nm
Drug free emulsion	Safflower oil (Long chain triglyceride)	Polyglycerized fatty acid ester	>100 nm
Drug free emulsion	Soyabean oil	Low HLB polyethoxylated fatty acid ester	>100 nm

The approximate weight of gel was 350 mg. This gel was delivered by electrortransport over 20 min in a dosage of 4  $\mu\text{g}$ -5.5  $\mu\text{g}$  [40]. The composition of transdermal formulation patented by Murdock *et al.* (2002) is summarized in Table 4. The workers extended this study to a combination of two active ingredients for the treatment of painful spasticity. Amitriptyline appeared to offer limited pain relief when administered transdermally. The results revealed that the combination of gabapentin with doxepine might offer additional benefit. The addition of guaifenesin to doxepine was proposed to be of particular value in cases of painful spasticity [41].

### Prodrugs

A transdermal delivery consisting of prodrug permeable adhesive layer and a prodrug impermeable polymer film was developed. Valeroyl naltrexone and Hep-naltrexone provided higher flux of naltrexone across skin than naltrexone base. Hep-naltrexone prodrug exhibited 8-fold greater permeation as compared to 4-fold greater permeation for Val-naltrexone. The aqueous solubility of prodrug was lower than naltrexone because of lack of free phenolic functional group that promoted aqueous solubility through hydrogen bonding. An increase in octanol/water partition coefficient with the addition of valeryl chain probably resulted in higher permeation of prodrugs [42].

## II. ADVANCED DEVICES

To achieve and to maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin must be overcome before the effective transdermal controlled delivery of drugs can be successfully accomplished. Modification of the conventional device is increa-

singly being attempted for accomplishing the goal of reducing skin's barrier properties and enhancing transdermal permeation of drugs.

### 1. Microblades

Early studies aimed at designing a device for percutaneous drug delivery by overcoming the skin's natural barrier made use of microprojections [43]. The need for such a device existed because it was hypothesized that once a drug penetrated through stratum corneum with the aid of the device, permeation through the remaining layers could proceed readily. The apparatus basically consists of a cutter having a plurality of microprotrusions having a height chosen with respect to the layer of skin that is to be disrupted and a 'stop' for preventing the apparatus from penetrating the skin beyond a predetermined distance.

Godshall (2002) designed a bed of microprotrusions attached to a drug reservoir from where the drug can move to adjacent disruptions. An area between microprotrusions acted as a penetration 'stop' that prevented the permeation of skin by microprotrusions to a depth greater than the height of microprotrusions. A silicon substrate was used for fabrication of microprotrusions, on which silicone dioxide was deposited over which photoresist (to mask chlorine reactive ion that penetrates silicon substrate) was deposited. It was found that blade lengths of less than 50  $\mu\text{m}$  did not produce microcuts sufficient to provide required degree of diffusion and blade lengths of more than 175  $\mu\text{m}$  were painful to the patient [44].

As advancement to the basic technique, a microblade device along with negative pressure was patented for the percutaneous sampling of an agent. The device was designed

**Table 4. Transcutaneous Absorption of Various Drugs Formulated into Lecithin-Organogel Systems [41]**

Active ingredient (mg/ml)	Ingredients*	Dose/day (mg)	Time when blood was withdrawn (days)	Blood serum level (ng/ml)	Reference level (ng/ml)	Remarks
Paroxetine HCl (20)	Etoxydiglycol	40	210	0	49 ± 0.26	Poor absorption/ lab error.
Sertraline (15)	-	100	19	5	30 ± 200 mg/ml	Limited absorption/ lab error
Fluoxetine HCl (10)	Ethyl alcohol, Isopropyl myristate	20	7	45	-	Patient benefit
Carbamazepine (150)	Etoxydiglycol	400	120	4.6	4-10µg/ml	Good absorption, No GI side effects and clinical improvement
Carbamazepine (150)	Etoxydiglycol	200	60	10.8	4-10µg/ml	Excellent absorption, No GI side effects and clinical improvement
Bupropion (15)	Water	100	44	> 0.5	10-30	Poor absorption, lab error, patient non compliance

\* Pluronic F-127 gel and soya lecithin were present in different amounts in all formulations.

to optionally include a drug-sensing element. The angle of leading edge was kept between 10°-40° or the convex/ concave shaped microblades were used. It was concluded that curving of microblade's tips outside the plane of microblade provided better anchoring [45]. Another device comprising of a piercing member having plurality of microblades with 25-400µm length and provision for applying partial vacuum in the range of 0.1-0.8 atm over a period of about 2-30 sec was designed for piercing the stratum corneum for body fluid withdrawal [46]. A similar device consisting of a sheet member having plurality of microprotrusions and a rigid support contacting and extending across the sheet member for transmitting an applied force evenly across the length and width of the sheet. The microprotrusions were found to penetrate up to a depth of about 500 µm [47]. The use of electrotransport, osmosis or pressure along with protrusions for withdrawing body fluids via a hydrogel medium increased the permeation of decapeptide over the transport period as compared to an ordinary electrotransport device [48].

## 2. Microneedles

A gel filled compartment fitted with micro needles was found to be capable of opening the skin permeation pathways up to a depth of 150 µ when applied with pressure [49]. The microneedle drug delivery device fabricated by Prausnitz *et al.* (2003) included plunger/syringe/pump for compressing the reservoir to drive the drug from reservoir through the microneedles. A sealing mechanism was also incorporated to contain the drug in one or more reservoirs until it was ready to be delivered. It further included a rate control mechanism to regulate rate and extent of drug delivery and an adhesive thus, immobilizing the microneedles during its insertion into the skin [50].

A device for enhancing the delivery of drug through abraded skin utilized iontophoresis. The microneedles had a blunt, flat tip and a length sufficient to penetrate the stratum corneum without piercing the stratum corneum. The degree of topical anaesthesia was measured after one hr application and was repeated every 10 min for another hour. The results showed that lidocaine produced total anaesthesia when applied to abraded site as compared to about 65% for unabraded site. Further, enhancement was about 3-fold for the 100 micron abraders and about 7-fold for the 200 microns abraders suggesting the role of length of abraders in enhancing drug delivery through skin [51].

## 3. Needleless Syringe

This device features an elongate, tubular duct having a lumen for delivering the particles towards the target tissue. The device has a membrane which is ruptured by gas pressure to generate a supersonic gas flow in which therapeutic agent is injected. Bellhouse *et al.* (2001) injected insulin particles (10 µ diameter) at an initial velocity of 750 m/sec into the skin and the penetration depth before the particles come to rest within the skin was about 200 µm whereas, for 20µ diameter particles injected with 1500 m/sec velocity, the particles were found to penetrate to a depth of 480 µm. However, injection of DNA-coated tungsten carrier particles into maize cells required size reduction of particles. Coated particles of 1 µm diameter injected at a velocity of 500 m/sec into maize cells penetrated to a depth of 200 µm [52]. Bellhouse *et al.* (2001) used helium in the device whereas, the device invented by Nat *et al.* (2006) utilized carbon monoxide, helium, nitrogen or air. Topical lidocaine anaesthesia produced by this method increased till 5 min and then decreased gradually over next 25 min [53].

#### 4. Increase in Local Temperature

Local increase in temperature increases blood flow and in turn, rate of permeation/transport of active substance into the skin increases. This technique has the advantage of not employing a chemical, is non-invasive and hence, does not require activation of self-repair mechanism by the skin.

Stanley *et al.* (2002) developed a transdermal device that employed an oxidation reaction for controlled heating of skin. Heat generating component comprised of a mixture of activated carbon, iron powder, saw dust, sodium chloride and water. Application of heat (42-44°C) for 4 hr was found to be sufficient to decrease the time required for the patch to deliver steady state serum concentration of fentanyl from 14-18 hr to 3-4 hr. A 5-minute application of heating was found to increase serum fentanyl levels by more than 60%, which was sufficient to combat breakthrough pain. Similarly, steady state nicotine concentration sufficient to suppress a baseline nicotine craving was achieved after few hours' application of heat [54]. Another invention reported serum fentanyl concentration to increase very rapidly (within 5-10 min) and significantly (> 75%) following the commencement of heating. The elevated concentration stayed elevated for an extended period of time. Reduction of heating area to half still produced 30% greater mean serum fentanyl concentration [55].

Koch *et al.* (2004) used an effective component Opraflax to increase the local skin temperature and observed an increase in the transdermal absorption rate of morphine base from 5.7 to 26.4% [56]. Zhang *et al.* (2004) patented a heating patch for use with Duragesic (fentanyl) patch at the time of an episode of breakthrough pain to deliver more fentanyl into the systemic circulation. Controlled heat could take care of both baseline pain and episodes of breakthrough pain by employing one single Duragesic RTM patch. Similarly, faster delivery of nitroglycerine, sufentanil, nicotine, insulin, dexamethasone or testosterone was achievable by using controlled heating patch. Further, the onset of analgesia in a patch containing an eutectic mixture of lidocaine and tetracaine was reduced by about 60% as compared to that obtained without heating [57].

#### 5. Mechanical Vibrations

Mechanical vibrations may be used for increasing drug absorption through skin. Bernabei (2004) used electrical pulses to increase the absorption of substances in conjunction with mechanical vibrations. The frequency and phase of electrical and mechanical vibrations were synchronized in order to increase the absorption effect. A syringe containing a permeation enhancer along with the drug is simultaneously actuated with electrical pulses to move the drug. The drug is passed through a tube and then into a groove surrounding a central electrode of the array of electrodes disposed on the plate. Abrasion of the skin to remove 100 µm layer followed by application of the technique resulted in prompt drug permeation. The frequency of electrical pulses applied were in the range of 2500-3000 Hz, with peak voltage of 160 V. Electrical resistance of 100-500 Kohm was provided to avoid high voltages when the array of electrodes were not applied to the skin. An electrical CDC motor was employed to provide an eccentric motion, which generated vibrations on

the vibrating plate. In addition, the use of vacuum pump generated a suction effect on skin and provided a massaging effect on the skin [58].

This technique was modified to utilize two solution absorbing pads which were electrically insulated from each other and each of them were in electrical contact with one or more of electrodes on probe head. One of the pads was soaked in drug and other with a conductive physiological solution. Load impedance of 1 Kohm-10 Kohm, peak voltage of 10 V-100 V, peak current of 10 mA with a pulse of 220 microsecond were used. The burst rate was found to range between 40 Hz to 100 Hz [59].

#### 6. Ultrasound

Physiotherapists used ultrasound to treat patients with local musculoskeletal inflammation using topically applied steroids [60]. More recently, ultrasound was explored for chemical activation of drugs for treatment of cancers (sonodynamic therapy). Further, ultrasound energy was reported to enhance effects of thrombolytic agents such as urokinase [61]. Previous attempts to use high frequency ultrasound (~1 MHz and ~1-3 W/cm<sup>2</sup>) to enhance transdermal drug delivery produced inconsistent results and were found to vary significantly from drug to drug [62-64]. Pulsed ultrasound at 1 MHz was reported to increase transdermal absorption of indomethacin from an ointment in rats [65]. Further, the combined use of chemical enhancers and ultrasound (1 MHz, 1.4 W/cm<sup>2</sup>) met with some success [66].

The recent inventions aim at minimizing loss of energy and focussing the ultrasound beam for better drug permeation enhancement. An ultrasound beam having a focal diameter is channeled into a beam having smaller diameter without substantial loss of energy. Ultrasound has been shown to enhance transdermal transport of low molecular weight drugs (<500 daltons) across human skin. Greater transdermal transport by this method is attributed to cavitation induced either inside or outside the skin. In addition, oscillations of cavitation bubbles result in significant water permeation into disordered lipid regions and lead to the formation of aqueous channels in the intercellular lipids of stratum corneum. Ultrasound channeling or focusing transdermal transport enhancement induced by ultrasound increases with increasing ultrasound pressure amplitude. However, application of high ultrasound amplitudes is prohibited due to discomfort associated with it. Row *et al.* (2002) employed a concave mirror, phased array of transducers or a chamber having specially designed walls to channel and focus the beam. The transducers were connected to an electrical signal (piezo, ceramic or polymer) generator and amplifier, which provided driving and controlling mechanism for the transducer. The exterior walls could be polymeric or metallic. The material of interior walls reflected (plexiglass, non-deforming metal) acoustic energy, and the cavity had a shape of truncated cone or horn shaped with a large opening and a small opening. Cavity was filled with coupling medium (water, saline, alcohol, surfactants), which transmitted ultrasound. An adhesive layer on the bottom of chamber was used to attach the chamber to the skin. The chamber could be optionally connected to a vacuum pump

through a port that opened into coupling medium or included electrodes for application of electric current as an additional mechanism for transport enhancement [67].

Similar device was fabricated by Mitragotri *et al.* (2003), which produced homogenous cavitations in skin [68]. McDaniel (2006) removed outer layer of skin by wiping with acetone and then with enzyme before exposure to ultrasound. The preferred low frequency range ultrasound was between 25 K Hz to 3 M Hz at about 0.5-2.0 W/cm<sup>2</sup> (continuous or pulsed, using about 20-25% duty cycle if pulsed), and a treatment time of 5 to 10 min for higher frequency ultrasound, the parameters were 3 MHz to 16 MHz at 0.2 to 1.0 W/cm<sup>2</sup> for 1-20 min [69].

The patent filed by Kost *et al.* (2001) revealed that the required flux for sonophoretic delivery of insulin to a diabetic patient was 12 units/hr as compared to 12 units thrice a day by parental route. Similar, observation was recorded for -interferon. The transducer operated at frequency range of 20 KHz-100 KHz intensity of 0-20 W/cm<sup>2</sup>, and the application period ranged between 20 sec to 5 min [70]. For glucose extraction and measurement, a glass chamber of 1.5 cm<sup>2</sup> area filled with saline was used. Saline was replaced with sodium lauryl sulphate (1%) after 1 hr and ultrasound (20K Hz, 11µm tip displacement) was pulsed for 5 sec. Ultrasound transducer was activated and a vacuum was applied for 5 min. The average intersubject skin permeability was 1.3x10<sup>-3</sup> cm/hr ( $\pm$  9.6x10<sup>-4</sup>) to 1.8x10<sup>-2</sup> ( $\pm$  1.4x10<sup>-3</sup>) cm/hr. The skin permeability remained high for about 15 hr and decreased to normal by 24 hr. The average transdermal glucose flux after ultrasound application was found to be 25-fold higher than that reported for reverse iontophoresis technique. Further, passive skin permeability of glucose (3x10<sup>4</sup> cm/hr) was reported to be much less than that obtained following ultrasound application (17x10<sup>-2</sup>). This 570-fold increase in glucose permeability was obtained when the frequency tip displacement was 20 KHz and 2 µm, respectively at continuous mode for 10 min [70].

A device comprising a container with an end covered with a porous membrane and containing the drug solution was designed. A submerged tip of ultrasound horn was submerged in drug solution. The membrane was made up of non-woven polypropylene, and bottom surface of membrane was covered with a removable protective film. The membrane had pores ranging in diameter from 10-100 µm. Using frequency of 20 KHz, intensity of 5-55 W/cm<sup>2</sup> and application time of 30 sec-5 min. The apparatus allowed painless and rapid delivery of drugs through skin, and also allowed coupling of ultrasound radiation to a container containing drug solution without dampening ultrasound intensity [71]. Hille *et al.* (2005) patented a technique that employed ultrasound along with skin adherent patch during an initial phase and only patch without ultrasound treatment during subsequent long-term phase. The ultrasonic treatment was carried out using a frequency range between 40 KHz and 0.01-3 W/cm<sup>2</sup> intensity. The data generated revealed a 40-fold increase in absorption within 1 hr by only 15 min treatment with ultrasound [72]. Weimann *et al.* (2005) designed the use of ultrasonic jets for driving drug solution through their ends adjacent to skin and through pores generated by ultrasound treatment. The frequency of

ultrasound radiation ranged between 15 KHz and 1 MHz and the flat distal ended tip comprised of a body having markings indicating amount of drug solution in the container [73].

## 7. Electroporation

A biologically active agent can be introduced into cells by injecting it and applying an electric field to that region. This causes electroporation prior to, simultaneously and/or subsequently to injection of agent. In the first technique, one of the injector was donor electrode and the other injector was the return or counter electrode. The second technique comprised of injectors serving the purpose of donor electrodes. The first technique utilized one injector for applying an electric field to the surface and the other injector was in contact with the tissue and provided electric current in conjunction with one or more electrodes. In the second case, needle free injector introduced a conductive fluid as a jet through an opening in an array electrode, which contained multiple positive and negative electrodes similar to micro-patch electrode. In addition, optionally, the apparatus included a means for controlling the amount of current passing from the device and through the contacted surfaces. The electric field generated pulses of at least 50 V in about 100 µ sec to 100 m sec and the pulses were either monopolar/bipolar. Enhanced permeation of polynucleotides was obtained using this technique [74]. Phipps *et al.* (2005) improved electrotransport drug delivery system for fentanyl and sufentanil. The transdermal electrotransport flux of fentanyl and sufentanil was found to depend on their respective concentration in aqueous solution. As the concentration of fentanyl HCl and sufentanil fell below 11 to 16 mM and 1.7 mM, respectively, the flux also declined significantly, even when the applied electrotransport current remained constant. In addition, hydrogel matrices exhibited little/no tendency to bind silver ions and hence, were preferred matric material for loading halide salts of fentanyl and sufentanil. Applying a current density of 50-150 µA/cm<sup>2</sup> and 150-240 µA/cm<sup>2</sup>, 40 µg of fentanyl and 4.7 µg of sufentanil were delivered across skin [75]. The electrotransport device patented by Southam *et al.* (2006) utilized a silver foil anodic electrode laminated to one surface of the gel. Using a direct current of 200 µA the flux of fentanyl was observed to increase over the first 8 hr after which it remained constant. Further, the flux decreased if the concentration in the device fell below 6 mg/ml. However, application of 240 µA current density for 10 min was observed to deliver 40 µg dose and 80 such doses could be delivered over 24 hr [76].

## 8. Iontophoresis

Iontophoresis involves the application of electromotive force to drive or repel oppositely charged ions through the dermal layers into the area to be treated, either into the surrounding tissues for localized treatment or into the circulatory system for systemic treatment. Positively charged ions are driven into skin at the anode while negatively charged ions are driven into skin at the cathode. Studies have shown increased skin permeation of drugs at anodic/cathodic electrodes regardless of predominant molecular ionic charge [77].

As compared to passive transdermal systems, the active systems like iontophoresis enable higher dosing rates to be achieved. Effenhauser (2000) patented a transdermal system that contained a storage layer for drugs and a transfer-separating layer, which was connected to both reservoir and the patient's skin during administration. In one model, the substances were located in a common storage layer contained in the reservoir. Physical separation occurred during their migration through a separating layer as various substances have different migration rates within it, resulting in sequential administration of substances. In another model, reservoir comprised of at least two physically separated storage layers each of which contained at least one substance. A layer, which physically separated storage layers from each other, was arranged between storage layers [78].

Keller *et al.* (2000) administered dyes/markers/anaesthetics encapsulated within a lipid vesicle, by iontophoresis. Conventional liposome anaesthetic products normally have lag time 30-60 min. However, the lag time of charged liposome anaesthetic products was reduced to 5-10 min. Three liposomal formulations were prepared with different dyes (basic fuchsin, gentian violet and sudan III). Microscopic examination of skin sections after iontophoretic delivery of these liposomes employing electric current of 3-5  $\mu\text{A}$  for 5-10 min revealed slight staining of stratum corneum and epidermis, strong staining in dermis and very high staining in hair follicle region. This was suggested to be due to positive surface charge of the liposomes and the positive electrode of iontophoretic unit. Results of another study revealed that the permeation rate of the liposomes bearing positive surface charge was greater than those bearing negative charge due to effect of positive electrode. In case of positive surface charged lidocaine liposomes the onset of action was 10-20 min, while it was about 40-45 min in case of neutral surface charged liposomes [79].

A conducting silicone matrix incorporating suspension of drug component in ionized and non-ionized phases in an emulsion of a hydrophobic polymer was prepared. In one technique, an aqueous drug suspension was incorporated in a silicone matrix with a silicone surfactant and electrolyte was incorporated into matrix for increasing its conductivity. The drug migrated away from electrode as individual globules and got concentrated on the distal side. This increased the drug concentration distal to the electrode and adjacent to skin thereby, resulting in its enhanced transfer through the skin [80]. The same principle was used for enhancing the delivery of anti-infectives, analgesics etc. across skin [81].

Tapper (2001) patented an apparatus to mitigate tissue damage. Iontophoretic treatment involving reversal of electrical current at very low frequencies (0.0027 Hz to 10 Hz) was used. This method enabled long term dosimetry with single and multiple drugs of any polarity. In addition, at higher drug concentration, the need for buffering agents was eliminated. The system delivered substances with large and/or small molecular size and weight at the delivery site [82, 83]. Higo *et al.* (2001) designed an iontophoresis device having excellent contouring ability at its site of attachment. The device was provided with a cup shaped support including a concave part where electrification hole was formed. In addition, the device had a provision for attaching

an electrode on the flat part of the rim of the concave part. An electrolyte layer or drug holding layer could be fitted into the concave part [84]. The iontophoretic device patented by Haak *et al.* (2001) consisted of an electronic circuit connected to electrode assemblies using an electrically conductive adhesive. In one of the technique the electrically conductive adhesive acted as an electrode and electronically connected the circuit to a drug-containing reservoir. In another technique, the electrically conductive adhesive functioned as a drug reservoir. The data revealed that electrically conductive adhesive increased the time required to substantially hydrate an electrode assembly. In addition, electrically conductive adhesive film provided good electrical conduction between the power source and underlying electrode structure [85]. Garde *et al.* (2002) patented a device consisting of a controller normally being in low power consumption state, a removable patch including electrodes, a reservoir for holding an ionizable drug for transdermal delivery and a return reservoir. The drug was delivered from the patch when the patch was on the skin and when controller was in the operational state. In one of the cases, connector further comprised a switch having make/break contacts and this switch was connected between power source and controller. In another case, patch comprised of two reservoirs including an anode and a cathode. One of the reservoirs could be used for holding an ionizable drug. When the patch was attached to skin, controller was said to be in an operational state [86]. A method for loading a material into an iontophoretic reservoir electrode including a backing with interior surface was patented. This had a bibulous reservoir having contact with reservoir electrode. A closure to engage backing for forming a releasable seal to isolate reservoir from ambient environment was provided [87]. Iga *et al.* (2003) patented a method for administering parathyroid hormone by iontophoresis. The method required application of electric current at least twice a day. Female rats were ovariectomized and intradermally injected with an aqueous solution of parathyroid hormone three times at 1 hr intervals at different doses of 1  $\mu\text{g}/\text{Kg}$  or 5  $\mu\text{g}/\text{Kg}$ , and also repeatedly using different administration routes and dosing schedules. The osteogenic effect was observed to increase in proportion to the administration frequency [88].

Sage Jr *et al.* (2003) designed an iontophoretic apparatus with novel electrode systems, which avoided skin burns (due to pH change or excessive current application) at the delivery site. The anode was formed from a low cost metal like copper, nickel, iron, aluminium, zinc or mixture, which was further coated with a layer of precious or chemically inert metal e.g. silver. The designed anode exhibited good shelf stability, good voltage characteristics and stability over a prolonged period of usage. *In vitro* studies were performed by employing copper anode, current density of 0.2  $\text{mA}/\text{cm}^2$  with 150 mM sodium chloride saline and 3% w/w agarose as cathode electrolyte. The anode potential increased to maximum of 100-150 mV within 1 hr and then gradually decreased to a steady state value of 40 mV in 5-6 hr, thereafter, it remained constant for 15-16 hr. The copper ion concentration in anode porcine skin was < 5 ppm, demonstrating effective regulation of transport of copper ions. No detrimental pH effects were observed. Use of carbon coated silver cathode and zinc chloride electrolyte

during *in vitro* testing using porcine skin with a 2 mA/cm<sup>2</sup> current density revealed stable cathode potential with flat -1.1 V over 24 hr period. Similar results were found when carbon coated silver cathode was used employing ZnSO<sub>4</sub>, Cu Cl<sub>2</sub>, or CuSO<sub>4</sub> electrolyte in the devices. The *in vivo* electrode performance was similar to *in vitro* data and suggested good electrode performance over 24 hr period [89]. Inoue *et al.* (2003) designed an iontophoresis device having two electrodes one of which contained chloride ions and a hydrophilic conductive layer containing the active ingredient. The device had an electrode member and a power supply with provision for polarity inversion in order to switch current direction between the two electrode structures. The data revealed that the electrode material affected the absorption rate of lidocaine. No voltage variation was recorded when Ag/AgCl<sub>2</sub> was used in both electrodes. However, in inactive electrode, voltage rapidly increased and then became insulated so that energisation could be continued. Total chloride ion content in the electrode also affected the absorption rate of drugs. It was demonstrated that increase in chloride content in one of the electrodes led to enhanced absorption of a basic drug fentanyl up to 13.2 mg. On the other hand, the increase in absorption of a basic drug, diclofenac was negligible (from 5.6 to 6.3 mg) [90].

Keusch *et al.* (2005) invented a reservoir electrode assembly for iontophoretic drug delivery included an electrode and a hydrophilic reservoir situated in electrically conductive relation to the electrode. The hydrophilic reservoir was formed from hydrophilic cross-linked polymeric material and one of its surfaces was adhered to the electrode and other to patient's skin. Additionally, the adhesive bond strength of surface of polymeric material to applied area of patient was less than the cohesive strength of polymeric material so that upon removal of reservoir assembly from applied area no polymeric material remained on skin and the hydrophilic reservoir remained intact and adherent to electrode. The use of glycerin (10% w/w), cross-linked polyvinyl pyrrolidone (16.67% w/w), sodium metabisulphite (0.05% w/w), EDTA sodium (0.015 w/w), citric acid (0.025 w/w) and water (63.155 w/w) yielded an adhesive strength greater than 40 g/inch. But when 25% w/w polyvinyl pyrrolidone was used, adhesive strength was greater than 60 g/inch. Polyethylene oxide (1-10% w/w), polyvinyl alcohol (10-30% w/w) or polyethylene glycol (20-60% w/w) could also be used to modify the reservoir characteristics [91].

A device for providing treatment by electrokinetic self-administration of a medicament into a treatment site was described. It contained a power source, two electrodes and a substrate in electrical contact with first electrode. Electric current was made to flow through the first electrode to deliver the medicament or conductive carrier. The iontophoretic electrode included an open mesh having cells in medicament (liquid/gel/ointment form). The device could be retained on individual's finger with the first electrode incorporated between the finger and the substrate. The device was demonstrated to yield greater than 90% efficiency in clinical trials for the treatment of genital herpes [92].

A planar disposable transdermal iontophoresis delivery system was fabricated that comprised of an oxidizable

species (Mg or Zn) and a reducible (AgCl<sub>2</sub>) species connected by a common conductor. This galvanic battery served as the sole source of power and control for the system. The galvanic battery was provided with a tested columbic capacity rating to predict dosage [93]. Another device having a layered structure that included a base layer of conductive material, which could react with water, was fabricated. Sections of the base layer were coated with two upper layers, which covered different portions of the base layer with a narrow strip of uncoated base layer remaining there. Where Zn and AgCl<sub>2</sub> were used as anode and cathode materials, respectively, Zn got consumed during passage of current. An exposed portion of the base conductive layer got oxidized and this increased the electrical connection to the electrode. This device was designed to deliver 0.5% fentanyl citrate into 4 human volunteers. The minimum effective concentration (0.63 ng/ml) was achieved in 2 patients within 15 min and in 30 min in the other two patients. In all subjects, peak plasma concentration was achieved in 30 min and was found to be coincident with the suspension of iontophoretic current [94].

## CURRENT & FUTURE DEVELOPMENTS

Extending the patent term of older drugs by formulating them in new dosage forms has generated enthusiasm among the pharmaceutical scientists to develop new dosage forms. In addition, new dosage forms are essential for other drugs in order to enhance their performance by reducing their dose, increasing absorption, delivering to the target site etc. The patented innovations in transdermal drug delivery arena aim at these goals. However, the ultimate test that an innovative technique should pass relates to its successful performance *in vivo*. Hence, the formulator faces a challenging task of translating the patented claims to actual practice. It is important to note that none of the generic fentanyl patches awaiting approval by US FDA could be launched in 2005. Similarly, the Evra patch landed into trouble as women using it were found to be at greater risk of blood clots. The article by Batheja and Michniak (2006) gives an analysis of US patents on transdermals filed in 2005 and shall aid the formulator in his quest for making percutaneous drug delivery more effective and patient compliant [95].

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