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REVIEW

Recent Advances in Transdermal Drug Delivery

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Transdermal delivery of pharmacologically active agents has been extensively studied for the past 40 years. Despite the strong efforts, currently, only about 40 products are in market on about 20 drug molecules, due to the requirements that the patch area should be small enough for the patients to feel comfortable, and to the barrier properties of the stratum corneum. Various approaches to overcome the barrier function of skin through physical and chemical means have been broadly studied. The development of an effective transdermal delivery system is dictated by the unique physicochemical property each drug molecule possesses. In this review, we have summarized various physical and chemical approaches for transdermal flux enhancement, including the application of electricity, ultrasound, microneedle and chemical enhancers. Pressure sensitive adhesive such as acrylics, rubbers and silicones are described together with recent developments. Factors affecting dosage form design, particularly for drug in adhesive system, like adhesion and crystallization are also discussed.

Key words: Transdermal drug delivery, Permeation enhancers, Pressure sensitive adhesive, Matrix system, Adhesion, Crystallization

INTRODUCTION

Skin represents the largest and most easily accessible organ of the body. Topical therapy has been practiced for a long time to treat local ailments. Since the approval of the first scopolamine patch in 1979, transdermal drug delivery began to foster as a systemic mode of drug administration. A plethora of research has been dedicated to this arena. Although transdermal drug delivery system (TDDS) is not a mean to achieve rapid bolus-type or chronopharmacological drug input, it has been proved beneficial in reducing the frequency of dose, achieving target delivery and avoiding hepatic first pass metabolism (Mitragotri, 2004). The administration is easier and there is possibility of immediate withdrawal of the treatment if necessary. Furthermore, steady absorption of drug over hours or days is usually preferable to the blood level spikes and troughs produced by oral dosage forms.

Although transdermal route is an attractive alternative to oral and hypodermic administration, limited number of drugs is available as transdermal products. This is due to the stringent requirements pertaining to the barrier function primarily by the stratum corneum (SC) layer of the skin (Naik et al., 2000). Regardless of the dosage forms like semisolid, gel, cream, suspension, microemulsion and patch, a drug molecule released from the dosage form has to pass through the skin layers by a multistep sequential process before it reaches systemic circulation. The process includes partitioning and diffusion through the lipophilic SC, partitioning into the aqueous epidermis and finally into the capillary network of the dermis. Diffusion through the SC is considered the rate-limiting step for the transdermal transport of drug molecules. Hence, a transdermal drug candidate must possess both lipophilic and hydrophilic characteristics. Too hydrophilic molecules will not partition into the SC, and too lipophilic molecules will not move down to the subsequent aqueous layer in the epidermis. Octanol-water partition coefficient has been used as one of the parameters to predict the partition

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behavior within the skin (Potts and Guy, 1992). Generally accepted range of log P for maximum permeation is between 1 and 3. Although the range can vary depending on physicochemical properties and three dimensional structure of a compound, the molecular weight of the drug should be less than 500 daltons, melting point below 200°C and dose less than 10 mg per day (Prausnitz et al., 2008), to be considered as a candidate for transdermal delivery. Some drugs are not appropriate for transdermal administration because of their physicochemical properties. They may be too large, charged, or have insufficient lipid solubility. Without any intervention skin would not allow the passage of those drugs for an effective transdermal delivery. Besides, drug may also have unfavorable pharmacokinetic or pharmacodynamic behavior such as too rapid clearance relative to achievable rate of skin delivery, first-pass cutaneous biotransformation (Choi et al., 1990; Gwak and Chun, 2001), a requirement for intermittent high peak and low trough blood profiles or simply insufficient potency (Villarino and Landoni, 2006).

In spite of the extensive research for the past 40 years or so, currently, only about 40 products on about 20 drug molecules are in the market (Table I), due to the limitations and difficulties discussed above. Only a small number of drug molecules could be the good candidate for the transdermal delivery. Hence, the major challenge facing in this transdermal area is how to expand the number of drug molecules that could be delivered through the skin. We think that the development of novel flux enhancement methods is essential for the continued success of this field, so that many drug molecules, which could be highly beneficial as a transdermal delivery dosage form, may be included. This review describes some physical and chemical methods to enhance percutaneous penetration. Physical methods such as iontophoresis, electroporation, sonophoresis and microneedles, and chemical methods such as prodrug, salt formation, ion pairs and solvents are reviewed and discussed. Pressure sensitive adhesive such as acrylics, rubbers and silicones are described together with recent developments with a focus on solvent-free technologies. Factors affecting drug in adhesive (DIA) system are also discussed.

TECHNIQUES TO ENHANCE TRANSDERMAL PERMEATION

Physical methods

Iontophoresis

Iontophoresis involves the application of a small electrical potential across the skin to deliver hydrophilic and charged molecules through skin. Flux by iontophoresis can be described by Nernst-Plank equation,

$$J_t = -D\left(\frac{dC}{dx} + \frac{CZF}{RT}\frac{dV}{dx}\right) + vC$$

where J_t is the total flux, F is Faraday constant, D is diffusion coefficient for the ion, dC/dx is the concentration gradient of ion through skin, Z is charge of ion, T is absolute temperature, dV/dx is applied voltage gradient across the skin, R is gas constant and v is the electroosmotic volume flow. Hence the total flux (J_t) is the sum of each contribution from passive diffusion (J_p), electro-repulsion (J_{er}) and electroosmosis (J_{eo}).

$$J_t = J_p + J_{er} + J_{eo}$$

Electroosmosis during iontophoresis originates due to the net negative charge of the current passing channels (pores) in skin at physiological pH (Burnette and Ongpipattanakul, 1987). Thus, the channels are permselective to cations. This causes a net flow of solvent in the direction of anode-to-cathode. This solvent flow facilitates the flux of cations (from anode), inhibits that of anions (from cathode), and enables the enhanced transport of neutral/polar solutes, especially for high molecular weight peptide/protein drugs. Electrical current is applied through two electrodes placed on the patient's skin (Scheindlin, 2004). The donor electrode delivers the charged therapeutic agent and receptor electrode closes the circuit. Flux could be enhanced by increasing amount of drug in the formulation. However, the observed flux may not be linear to the amount of drug; in many cases it reaches a plateau (Marro et al., 2001). At constant ion concentrations, increasing the current is followed by higher iontophoretic flux. Similar with the case of drug concentration, saturation phenomenon is often observed and the flux response can start to plateau at higher current levels (Kalia et al., 2004). pH of the formulation could affect the degree of ionization of the drug molecule and consequently the iontophoretic flux. pH also could affect the charge of the current conducting pathway (permselectivity) and change the electroosmotic flow. It has also been reported that the magnitude and direction of electroosmotic flow through skin can be modulated by chemicals such as ionic surfactants, lipophilic cationic peptides (Nafarelin), lipophilic-blockers (propranolol, timolol and metoprolol) and polypeptides (poly-L-lysine) (Guy et al., 2000; Hirvonen et al., 1996; Hirvonen and Guy, 1997). Hence, the balance between electroosmosis and electrorepulsion plays a very important role in the transport through

Table I. Summary of marketed transdermal products

Drug	Disease/treatment	Product
Scopolamine	Motion sickness	Transderm-Scop®
Nitroglycerin	Angina pectoris	Transderm-Nitro®, Nitrodisc®, Deponit®, Minitran®, Nitro-dur®, Nicotinell®
Nicotine	Smoking cessation	Nicoderm®, Nicostop®, Habitrol®, Nicotrol®, Prostep®
Estradiol	Postmenstrual syndrome	Estraderm®, Estran®, Climaderm®, Climara®, Alora®, Fematrix®, Fempatch®, Vivelle®
Testosterone	Hypogonadism	TestoDermTTS®, AndroDerm®
Clonidine	Hypertension	Catapress-TTS®
Fentanyl	Analgesia	Duragesic®, Matrifen®
Buprenorphine	Analgesia	BuTrans®
Progestin/estrogen	Cotraceptives	OrthoEvra®
Estradiol/Norethindrone	Hormone replacement therapy (HRT)	CombiPatch®
Estrogen/Progesterone	HRT	Nuvelle TS®
Selegiline	Depression	EmSam®
Rotigotine	Parkinson's	Neupro®
Methylphenidate	ADHD (Attention deficit hyperactivity disorder)	Daytrana®
Lidocaine	Post-herpetic neuralgia	Lidoderm®, Synera® (lidocaine+Tetracaine)
Ketoprofen, Piroxicam, Diclofenac	Inflamation/pain	Ketotop®, Trast®, Rheumastop®, Nupatch®
Rivastigmine	Alzheimer's disease	Exelon®
Oxybutynin	Hyper active bladder	Oxytrol® (USA), Kentera® (Europe)
Granisetron	Nausea, vomitting	Sansuco®
Capsaicin	Postherpetic neuralgia	Qutenza®

skin. For a basic drug like lysine (pKa 10.8), increased delivery was observed at pH 7.4 than at pH 4 due to the combination effect of electrorepulsion and electroosmosis. In contrast, higher transport of histidine (pKa 1.82, 6.04, 9.17) was observed at pH 4 than at pH 7.4 because histidine is predominantly uncharged at higher pH and the transport is solely dependent on electroosmosis (Green et al., 1991). One important point of iontophoresis is the water content in stratum corneum, because the ions are mainly flowing through the aqueous domain. Various techniques like electric conductance, transepidermal water loss or fourier transform near infrared spectroscopy have been used to measure the stratum corneum water content (Suh et al., 2005).

Electroporation

Electroporation is the transitory structural pertubation of the lipid bilayer membranes by the application of short electric pulse (milliseconds or microseconds). It is generally known that 0.5 to 1.0 volt of transmembrane potential difference should be applied for the electroporation to occur for a single lipid bilayer. It has been shown that electroporation can also induce the alteration of stratum corneum lipid domain (Prausnitz, 1996). This will increase the permeation of small compounds like fentanyl to moderately sized molecules like calcein and macromolecules like calcitonin (Denet et al., 2004). Increase in transport has also been reported with lipophilic (e.g. timolol), hydrophilic (e.g. metoprolol), charged (e.g. heparin) and neutral molecules (e.g. mannitol) (Denet and Préat, 2003; Prausnitz et al., 1995; Vanbever and Préat, 1998). Flux magnitude was dependent upon the magnitude of applied voltage (Prausnitz et al., 1993). *In vivo* study using hairless rat showed that fentanyl rapidly responded to electric pulses. Rapid transdermal delivery of fentanyl (within 15 min) at therapeutic level was obtained by skin electroporation, inducing a deep analgesia lasting for about an hour (Vanbever et al., 1998).

Sonophoresis

Ultrasound, especially in the frequencies between 20 to 100 KHz, has shown to greatly enhance the permeability of skin for facilitating transdermal drug delivery (Mitragotri and Kost, 2000). Ultrasound induced cavitation leads to the formation of localized regions of high permeability (Mitragotri, 2005). Skin could either be permeabilized with short application of ultrasound before the application of drug or drug and ultrasound could be applied simultaneously to the

skin (Ogura et al., 2008). Several parameters including frequency, intensity, duty cycle and application time, could be adjusted to achieve a safe reversible breach in the skin (Merino et al., 2003).

Microneedles

Microneedles could painlessly disrupt the barrier of the skin and create pores resulting in an increased penetration. First reported application of microneedles demonstrated improved permeation of calcein (Henry et al., 1998). In the recent years, microneedles have been extensively investigated for the delivery of compounds like diclofenac, desmopressin and even vectors for gene therapy (Badran et al., 2008).

Despite the potential for delivery of high molecular weight drugs and the advancements in fabrication technologies, these methods often pose problems in the delivery of accurate dose administration and patient compliance (Panchagnula et al., 2000). Instrumentation in a cost effective way and concerns regarding the possible damage to skin are challenging factors to prove the clinical benefits of these systems. Hence, these techniques come into the picture when relatively simpler chemical strategies fail.

Chemical methods

Since not all the molecules for transdermal administration possess ideal physicochemical properties, manipulation of the drugs or addition of vehicles may become necessary to achieve therapeutic benefits. Various approaches commonly applied are presented below.

Prodrug

The use of prodrug could improve transdermal delivery of drugs with unfavorable partition coefficient or solubility. A promoiety is added to increase the transport of drug across the SC. Then in the viable epidermis, parent drug is released by hydrolysis. A balance between lipid and aqueous solubility is important to optimize permeation across the skin since drug has to go through a multistep process before it reaches systemic circulation. Therefore, prodrugs to increase transdermal permeation incorporate functional groups in the promoiety that will increase not only lipid but also aqueous solubility. The permeability of 5-fluorouracil significantly increased by forming a prodrug (Sloan and Wasdo, 2003). The high delivery rate of 5-fluorouracil was achieved owing to the optimum solubility of prodrug in both isopropyl myristate and water. Combinations of adequate aqueous solubility and lipophilicity of naproxen aminoacyloxyalkyl prodrugs, having faster rate of enzymatic hydrolysis, resulted in improved dermal delivery of naproxen (Rautio, 1999). Transdermal delivery of ketorolac was improved with a shorter lag time as 1-propyl ester form than that of ketorolac (Doh et al., 2003).

Salt formation

For the optimization of physicochemical properties, molecule could be changed to suitable salt form(s). Monoethanolamine, diethanolamine and triethanolamine salts of piroxicam were prepared and their permeability across hairless mouse skin was compared with the parent compound. Mono and di-ethanolamine salts had higher solubility in various vehicles tested and also demonstrated enhanced permeation across the hairless mouse skin (Cheong and Choi, 2002). Salt formation lowered the melting point and crystalline lattice energy. Although salt formation increased aqueous solubility, it did not bring significant change in octanol/water partition coefficient. When acrylic adhesive based matrix system was used, highest flux was obtained with piroxicam-monoethanolamine salt (Cheong and Choi, 2003).

Ion pairs

Charged molecules do not readily partition into or permeate across the skin. Formation of ion pairs with oppositely charged species to the charged drug neutralizes the charge, giving complex with higher permeability. The ion pair then dissociates in the aqueous layer of epidermis releasing the parent drug molecule, which subsequently diffuses within the deeper layer. Hatanaka et al. reported enhanced transport of cephalexin through the ion pair formation with 1-alkylsulfonates at pH 3.0 and tetraalkylammoniums at pH 7.0 (Hatanaka et al., 2000). They concluded that the maximum enhancement via ion pair skin transport of zwitterionic drugs would be attained by choosing a counter ion having high lipophilicity and small volume, and a solvent with suitable pH and low dielectric constant. Organic acids were reported to form ion pairs that greatly enhanced the skin permeation (Ren et al., 2008). All the organic acids examined had a potent enhancing effect on the permeation of indapamide, and the most prominent result was obtained with lactic acid.

Chemical enhancers

Molecules that decrease the barrier function of SC are termed chemical enhancers. The enhancer may either disrupt lipid organization and increase drug diffusion coefficient or interact with keratin in corneocytes, opening up the dense protein structure. Alteration of the chemical environment could also favor the

partitioning of drug in the SC (Barry, 2001). Enhancers fall into different chemical classes such as hydrocarbons (n-alkanes having chain lengths between 9 and 18 carbon atoms), alkanols and alkenols (alcohols, polyethylene glycol, propylene glycol), acids (lauric acid, myristic acid, stearic acid, oleic acid), esters (isopropyl myristate, glyceryl monolaurate, glyceryl mono oleate, glyceryl monocaprylate, ethyloleate, ethyldecanoate), alkyl amino esters (N,N-dimethylamino acetate, 1-(N,N-dimethylamino)-2-propanol decanoate), amides (Azone®, dimethyl formamide, dimethylacetamide), amines (polyethyleneglycol oleamine, phenethylamine, stearylamine, triethylamine, dodecylamine), aromatic compounds (carvacrol, thymol, anethole), sulfoxides (dimethyl sulfoxide, N-decylmethyl sulfoxide), cyclic carbohydrates (β-cyclodextrin, hydroxypropyl β-cyclodextrin), terpenes (p-menthane, d-limonene, dipentene, menthol) and pyrrolidones (N-methylpyrrolidone, 1-ethylpyrrolidone, 1-butyl pyrrolidone). Regardless of the formulation type, enhancer should first be released from the transdermal delivery system before it can act on the skin. The dependence of release rate on the intrinsic properties of enhancer and the nature of adhesive was studied in DIA type TDDS (Qvist et al., 2002). It was found that the type of enhancer had larger influence on the release rate than the type of adhesive. However, this study measured release of the enhancers directly into aqueous medium and did not use skin as a model membrane. It is obvious that the release into aqueous medium will mainly depend on the solubility of the enhancer in the receptor medium and the results will be different from the trend of partitioning into the skin. In another study characterizing the release of enhancer, transdermal permeation through hairless mouse skin was found to be dependent on the enhancer content in polyacrylate based matrix type TDDS (Funke et al., 2002). More extensive studies are required to elucidate relationship between physicochemical properties of enhancer and partitioning into the skin. Once the enhancers reach SC, the rate and extent of change in skin permeability is governed by the characteristics of the enhancer. Several studies were conducted to investigate correlation between characteristics of enhancers and enhancing effect. Park et al. investigated the influence of polyoxyethoxylated non-ionic surfactants on the transport of ibuprofen across rat skin. They reported 7-9 hydrophile-lipophile balance (HLB) values of polyoxyethoxylated non-ionic surfactants were effective promoters of ibuprofen flux (Park et al., 2000). In a study with the effect of various vehicles on the skin permeability of isosorbide dinitrate, based on the second order polynomial equation, enhancers with moderate lipophilicity (HLB value of about 7) were found to be more effective than those with extreme lipophilicity (Myoung and Choi, 2002). In a recent investigation, flux of pentazocine solution in isopropyl myristate was found to be dependent on the HLB values of glycerol ester of fatty acid (Furuishi et al., 2007). The optimum HLB value of the enhancers was reported to be around 8. Interestingly, when esters of sorbitol and fatty acid, polyethylene glycol alkyl esters, and caprylic/capric triglycerides were tested for enhancement effect with physostigmine, the higher permeation was observed with lipophilic enhancers within the same group of surfactants (Kim et al., 2002). The permeation enhancement by the enhancer seemed to be dictated by the nature of drug along with the other variables like PSA and additives.

Ideally, the increase in permeation enhancement should not cause skin irritation or any other kind of damage to the skin. To achieve this goal, the localization of the enhancer's effect only to the SC is necessary, though it is very difficult. The safety issue further decreases the number of enhancers that could actually be included in the formulation. Karande et al. reported morphological changes in the skin microenvironment in the presence of enhancers using Fourier Transform Infrared Spectroscopy (FTIR) (Karande et al., 2005). They related the irritation potential of enhancers with the competitive hydrogen bonding, which could change the native hydrogen bonding in proteins leading to unfolding. The amount applied and irritation were found to be well related in the chemical classes of azone-like compounds, zwitterionic surfactants and non-ionic surfactants. However, amount applied was not well correlated with the irritation response in some classes of enhancers like anionic and cationic surfactants, fatty esters and fatty amines.

Diffusional resistance in the SC is constituted by a complex interaction of lipid and proteinaceous components, which creates fairly distinct hydrophilic and lipophilic penetration pathways (Barry, 1987). Chemicals such as dimethyl sulfoxide, N-decylmethyl sulfoxide, urea and surfactants also interact with keratin in the corneocytes (Walters et al., 1988). It has been suggested that penetration of a surfactant into the intracellular matrix of the SC, followed by interaction and binding with keratin filaments, may result in a disruption of order within the corneocyte. This causes an increase in diffusion coefficient, thereby increasing permeability. The better understanding of the make-up and function of the stratum corneum in recent years has resulted in a diverse range of compounds being tested for their ability to facilitate permeation of the co-administered moieties (Roderick et al., 1996).

In a recent study, Guillard et al. studied the molecular mechanism of enhancers using FTIR. They reported that lipophilic enhancers have dominant fluidizing action on the ceramide alkyl chain organization that increases the space between lipid bilayer packing. Whereas, hydrophilic enhancers do not interact with lipid bilayer, rather decrease the strength of H-bonds within the polar head group of the ceramides (Guillard et al., 2009). Both types of mechanisms reduce the resistance of skin to drug diffusion.

Enhancer could also form a complex with the drug thus modifying its physicochemical properties. Drakulic et al. applied molecular modeling to investigate the role of molecular interactions between terpenes and drugs. They reported that hydrocarbon and oxygen containing terpenes could form complexes with drugs leading to penetration enhancement (Drakulic et al., 2008).

In a search for enhancers with lower toxicity, biocompatibility and biodegradability, sucrose based surfactants were explored in a recent study (El-laithy, 2009). Among sugar esters used, almost 5-fold greater flux of timolol maleate was obtained with lauryl sugar ester. Since lauryl sugar ester has 12-carbon chain length, corresponding to the chain length of the steroid nucleus of cholesterol, the study suggested that it might be involved in disrupting ceramide-cholesterol or cholesterol-cholesterol interaction. Lee and Moon reported that glycerin induced skin hydration enhanced the permeation of nicotinic acid (Lee and Moon, 2007). Hydrating vehicles decrease the lipid phase transition temperature of SC. Better understanding of the mechanism for permeation enhancement is invaluable in achieving safe and effective reduction of skin barrier. A great deal of research continues to identify generally regarded as safe (GRAS) substances with permeation-enhancing effect (Akimoto et al., 2001; Barry, 2001; Benson, 2005).

PRESSURE SENSITIVE ADHESIVES

The invention of rubber PSA by Henry Day in eighteenth century was a milestone in the development of PSA products. It was not until 1920s that limited application of PSAs in hospital and first aid uses expanded to industrial applications (Satas, 1989). Since then, both the technology and market for PSAs have dramatically risen. Materials that adhere to a substrate with the application of light pressure and do not leave any residue upon removal are termed PSAs. Primarily, acrylic, rubber and silicone based adhesives are widely used in TDDS. Acrylic adhesives comprise polymers of various esters of acrylic or methacrylic acid, acrylamide, methacrylamide, N-alkoxyalkyl or N-alkyl-acrylamides. Rubber based adhesives include materials such as styrene-butadiene, polyisobutylene (PIB), polybutadiene, polyisoprene, block copolymers like polystyrene-polyisoprene-polystyrene (SIS), polystyrene-polybutadiene-polystyrene (SBS), polystylene-poly(ethylene/butylenes)-polystylene (SEBS) and polystylene-poly(ethylene/propylene)-polystylene (SEPS). Tan and Pfister have given a good review on PSAs for TDDS (Tan and Pfister, 1999). Acrylic PSAs are produced by copolymerization of acrylic esters, acrylic acid and other functional monomers. The types of monomers, cross linking of functional groups and molecular weight could be varied to tailor the polymer properties. PIB is a vinyl polymer that is made from the monomer isobutylene by cationic polymerization. A combination of low and high molecular weight PIBs is used to achieve a balance of tack and cohesive strength. Other elastomers, tackifiers, or fillers could also be added to achieve the desired application properties. Silicone PSAs have a long history of medical application. A condensation reaction is used to prepare silicone PSA from polysiloxane polymer and a silicate resin, by dissolving both the compounds in a nonpolar hydrocarbon solvent. Increasing the polymer content provides a softer and tackier adhesive, whereas higher resin levels result in lower tack but higher adhesion and resistance to cold flow. Silicone PSAs that are compatible with drugs having amine-functional have been manufactured by end-capping the reactive silanol end groups through an additional manufacturing process. Table II lists some of commonly used preformulated adhesives for TDDS along with their intrinsic properties.

Recently, the interest in solvent-free technologies to manufacture PSAs has increased (Wolff, 2000). Alternatives to solvent borne systems have the potential to eliminate the limitations and concerns connected with the use of organic solvents. Emulsion based PSAs have been presented as an alternative to the solvent based PSAs. The dispersions are incombustible and do not contain any expensive solvents that might cause pollution (Satas, 1989). However, for the same degree of cross-linking or gel content, emulsion PSA film has much lower shear holding power compared to that of solvent-based PSA (Tobing et al., 2003). In addition, emulsion film, due to the presence of surfactant, becomes opaque after exposure to water vapor giving rise to the problem known as “water whitening”. To overcome these problems, emulsion systems exhibiting water resistance have been explored by many researchers (Lee et al., 1993; Mayer et al., 1995; Yang et al., 2000). Hot-melt adhesives, which do not contain

Table II. Commonly used transdermal pressure sensitive adhesives

Type of PSA	Supplier	Brand name	Grade	Remarks
Acrylics	National Starch	Duro-Tak®	87-9088, 87-900A, 87-9301	non-functional group
			87-2516, 87-2510, 87-2525	OH functional group
			87-2196, 87-2825, 87-2052	COOH functional group
			87-2979, 87-2074	COOH/OH functional group
			87-502A, 87-503A, 87-502A	Rubber hybrid
	Dow Chemical Co.	Morstik™	607	Acrylic, self cross-linking PSA with viscosity of 2500-5000 cps
			717	Acrylic, self cross-linking PSA with viscosity of 3000-6000 cps
Polyisobutylene	BASF	Oppanol®	B 10 SFN	Molecular weight of 40,000
			B 15 SFN	Molecular weight of 85,000
			B 80	Molecular weight of 800,000
	Exxon	Vistanex™	L-80	Molecular weight of 750,000-1,050,000
			L-100	Molecular weight of 1,060,000-1,440,000
			L-120	Molecular weight of 1,450,000-1,870,000
	National Starch	Duro-Tak®	87-608 A	-
Polysiloxane	Dow Chemical Co.	Bio-PSA®	7-4501	Viscosity of 700 cps
			7-4601	Viscosity of 1000 cps
			7-4202	Viscosity of 800 cps

either solvent or aqueous carrier for the adhesive components, are also becoming popular (Russell, 1975). These adhesives are solid at room temperature, but they liquefy when heated to relatively lower temperature. Physicochemical properties of drug and polymer and their compatibility with process conditions, such as requirements related to melt viscosity, and the need to ensure thermal and chemical stability of the formulations are the technology-specific limitations (Wolff, 2000). Studies to achieve improved performance at low temperature could broaden the scope of hot-melt PSAs (Hatfield, 2008).

DESIGN OF TRANSDERMAL PATCH

Types of patch

Broadly, transdermal designs are classified as membrane controlled and matrix type. In both types, a peripheral adhesive system may be optionally present. A transdermal patch has three key elements: backing membrane, drug layer, and release liner that is peeled off before application. The reservoir patch contains a drug reservoir sandwiched between a backing and a rate controlling membrane. The membrane can be either microporous or a nonporous continuous film. The microporous membranes contain interconnected pores that are made of polyethylene or polypropylene. These pores are filled with liquid such as mineral oil or ethanol. The drug is transported through the interconnected pores by diffusion through the liquid phase (Peterson et al., 1990). The nonporous continuous membranes are made of polyurethanes, polydimethylsiloxane, or ethylene vinylacetate copolymers. The drug transport mechanism involves partitioning of the drug in the upper side of the membrane and then diffusion through the polymer film. The matrix patches are slimmer and smaller than the reservoir patch, and are preferred both in terms of production ease and patient compliance. DIA designs, where active ingredient can be directly included in the adhesive layer, present a simple approach in matrix systems. The adhesive layer can be a single layer or a multilayer, sometimes with a membrane between layers. These designs are thin, flexible and comfortable to patients. Due to the many advantages of DIA, various transdermal patches have been successfully developed and launched in the market (Table I).

Selection of enhancers

Innumerable studies have been performed to study the effect of different vehicles on the percutaneous absorption. Some researchers have used the knowledge acquired from the study of suspension formulations to develop a transdermal patch. For example, binary solvent system comprising propylene glycol monocaprylate-diethylene glycol monoethyl ether along with oleic acid, identified as most effective vehicle for solution, was used to formulate transdermal

patch of ondansetron hydrochloride (Gwak et al., 2003). N-dodecylazepan-2-one, l-menthol and isopropyl myristate were identified as effective enhancers of indapamide flux in isopropyl myristate and ethanol based solution formulations (Ren et al., 2008). To develop a transdermal patch, combination of these enhancers were studied (Ren et al., 2009). Hai et al. reported that among the solution formulations, Myvacet® had the highest enhancing effect on the permeation of benztropine, followed by isopropyl myristate. Combinations of these enhancers were investigated to formulate transdermal patch (Hai et al., 2008). However, parameters optimized using solution or suspension formulations may not be applicable to the systems based on PSA matrix (Cheong and Choi, 2003; Cho and Choi, 1998; Kim et al., 2000). The effect of various vehicles on the percutaneous absorption of ketoprofen from solution formulations and from a PSA matrix was investigated (Cho and Choi, 1998). No correlation on the percutaneous absorption of ketoprofen could be found between the solution formulations and PSA matrix. The chemical potential of drug in solution formulation system seemed to change in PSA matrix system due to the interaction with adhesive in the system. This resulted in the discrepancy on the percutaneous absorptions of drug between the solution formulation and PSA matrix. Choi et al. reported the effects of fatty acids in propylene glycol (PG) on the percutaneous absorption of alendronate (Choi et al., 2008). The observed enhancing effect in the solution formulations containing 3% fatty acid in PG was in the following order; capric acid > oleic acid > caprylic acid > lauric acid > linoleic acid. When PSA matrix was used, the enhancement order changed as follows; caprylic acid > capric acid > lauric acid > oleic acid > linoleic acid. Similarly, transdermal delivery of tolterodine in isopropyl myristate indicated that 2-isopropyl-5-methylcyclohexyl 2-hydroxypanolate (MLA) was the best enhancer (Zhao et al., 2009). However, when fabricated in Duro-Tak®87-4098 matrix, permeation rate of tolterodine was highest in the presence of (E)-2-isopropyl-5-methylcyclohexyl octadec-9-enoate (MOA). Furthermore, the enhancement ratio obtained with MLA was 0.21 as compared to 1.51 owing to the presence of MOA. *In vitro* studies conducted using patch systems could have better possibility of correlation with the *in vivo* study. *In vitro* permeated amount of tolterodine formulated in PSA correlated well (R^2=0.993) with the area under curve obtained by applying transdermal patches to rat skin (Zhao et al., 2009).

Pretreating the skin with enhancer could be another approach to improve the transdermal flux. When the skin was pretreated with a combination of PG:lauric acid (9:1), the permeation of a highly lipophilic drug, antiestrogen (log P=5.82), from a matrix based TDDS through the skin increased more than 10 fold (Funke et al., 2002). However, pretreatment can cause some inconvenience for the patients and may reduce patient compliance.

Selection of PSA

The functions of PSA in DIA are imparting a close contact with the skin, controlling thermodynamic activity of the drug and the release rate from the system, storage of the drug, and interaction with the drug. Therefore, selection of appropriate PSA matrix is one of the most important factors in fabricating DIA TDDS. The glass transition temperature of PSA, interaction between drug and functional group of PSA, adhesive force and many other properties can influence flux of drug from PSA across the skin. Owing to the high thermodynamic activity of drug in PIB adhesive matrix, higher permeability of ketoprofen was observed in PIB matrix as compared to acrylic matrix (Cho and Choi, 1998). But, the flux of tacrine saturated in acrylic PSA was almost doubled as compared to that from PIB matrix (Kim et al., 2000). However, when acrylic PSA with carboxylic functional group was used, almost no permeation was observed at concentration below 8% w/w of drug load due to interaction between amine group of tacrine and carboxylic group of acrylic adhesive. Similarly, transdermal patch of benztropine (5% w/w) formulated in acrylic PSA with carboxylic functional group did not show any skin permeation (Hai et al., 2008). Also, amine compatible silicone adhesives are available to prevent H-bond interactions between the silanol (Si-OH) groups of the adhesive and the amine groups of the drugs. As observed with isosorbide dinitrate, highly cross-linked acrylic adhesive without a functional group gave the highest permeation rate, followed by the acrylic adhesive containing carboxyl functional group (Myoung and Choi, 2002). On the contrary, highly cross-linked enhancer compatible acrylic adhesive greatly reduced the permeation of tulobuterol, estradiol and norethindrone acetate (Kim and Choi, 2003; Chun and Choi, 2005). In the study with physostigmine, highest flux was obtained with grafted acrylic adhesive followed by acrylic adhesive with hydroxyl functional group, without functional group and enhancer compatible acrylic adhesive (Kim et al., 2002). The results indicated that the potential interaction of drug and functional group of adhesive is an important factor in determining the release rate of the drug form TDDS. Therefore, optimum PSA can be different depending on physico-

chemical properties of the drug.

Drug solubility in adhesive matrix determines thermodynamic activity of the drug and proportionally affects the permeation rate. Based on the drug-polymer interaction parameter and solubility in acetonitrile, Li et al. have predicted the solubility of drug in the polymer (Li et al., 2002). But they studied the drug solubility only in isooctyl acrylate/acrylamide/vinyl acetate (75:5:20) adhesive, so the concept needs to be expanded to the other adhesive systems. Careful selection of matrix and permeation enhancer could enable formulation of more effective TDDS. Combination patch of estradiol and norethindrone acetate, developed with much lower drug contents per unit area than the Combitran®, was able to provide similar permeation rates (Chun and Choi, 2005).

SYSTEM DESIGN CONSIDERATIONS

Adhesion

Adhesion is an important functional attribute for a TDDS since transdermal device is expected to adhere to the skin for at least 24 h. The removal should be painless without leaving any residue on the skin. Moreover, the device should be non-irritating and non-sensitizing to the skin and be comfortable to wear (Venkatraman and Gale, 1998). Patch lift reduces the surface area of contact thereby changing the drug absorption in an unpredictable manner and in an extreme case, patch falling diminishes the delivery of drug (Wokovich et al., 2006). Raynaud et al., have studied the adhesiveness of Testopatch® after extreme conditions of sweating and water immersion (Raynaud et al., 2009). Except for the patches applied to the lower back, patches applied to arms and thighs presented good adhesive properties allowing its use without restrictions at the extreme conditions. Not only the compatibility of drug and excipient with adhesive but also the water affinity of adhesive may affect the adhesion property. Taghizadeh et al. reported that povidone K-30 (Kollidon® 30), a commonly used antinucleating excipient, has significant effect on the adhesion properties of acrylic PSA. Different interactions such as intermolecular and intramolecular hydrogen bonding between one of the adhesive's co-monomer, hydrogen bonding between Kollidon® 30 and acrylic PSA, and dipole-dipole interaction between Kollidon® 30 units could be responsible for the change in adhesion properties of the system (Taghizadeh et al., 2009). Depending upon the miscibility between Kollidon 30® and acrylic PSA, tack values could increase for soluble system or decrease for the immiscible system.

Especially for the DIA designs, presence of active ingredient along with the additives can modify the mechanical characteristics of PSA, and might make the adhesive more susceptible to creep/cohesive failure. In the studies with physostigmine (Kim et al., 2002) and procyclidine (Park and Choi, 2001), despite the high fluxes obtained in silicone matrixes, tack of PSA decreased upon drug loading. For the selection of appropriate PSA to develop TDDS, the tack as well as the permeability should be considered. Therefore, in the aforementioned cases, silicone matrix was not considered for the development of TDDS of physostigmine. Ho and Dodou performed rheological studies on the adhesive performance of silicone based DIA layers (Ho and Dodou, 2007). Addition of drug resulted in concentration dependent increase in cohesive strength independent of physicochemical properties of the tested drug. High tack silicone PSA complied with the criteria for good PSA, whereas in the case of low tack silicone PSA, drug loading prominently decreased the necessary fluid like properties required for bonding onto the skin.

It would sometimes be beneficial to mix adhesives with higher tack to the one that gives the highest flux for the improvement of adhesion properties. Miranda et al. described the combination of acrylic polymer with rubber-based polymers, for example PIB, to optimize drug solubility and skin adhesion (Miranda et al., 1995). The rate of drug delivery in such system could be adjusted by altering the composition of the polymers while maintaining acceptable shear, tack and peel adhesive properties. Transdermal patch of tulobuterol formulated in polyethylene grafted acrylic polymer was mixed with acrylic adhesive containing hydroxyl functional group to improve the peeling off effect in the presence of water (Kim and Choi, 2003).

Crystallization

Saturation of the drug in the matrix increases the thermodynamic activity and hence the permeation. However, high drug loading has a tendency to form crystals during storage. If the drug is present in a crystalline form, it is not available for immediate release from the system, and therefore not available for delivery. Although drug crystals can first be dissolved and then release from the system, such a process is usually rate limiting and tends to reduce delivery rate. Crystallization of drug in the matrix may not only decrease delivery rate but also deteriorate the quality of the TDDS by decreasing the adhesive force. Furthermore, surface crystals can come into direct contact with the skin, and could cause skin irritation. Hence, prevention of crystallization is an

important area for the development of TDDS.

In a previous study, effect of polymeric additives and solvents on the crystallization of ketoprofen within the adhesive matrix was studied (Kim and Choi, 2002). Among the tested solvent additives, Tween® 80 and Labrasol® significantly inhibited the crystallization of ketoprofen in the PIB matrix. However, the inhibitory effect of the solvents could not be correlated with the solubility of the drug in the solvent. Despite the inhibition of crystallization, adding Tween® 80, Labrasol® and Kollidon® 30 reduced the initial flux of ketoprofen obtained without additives. Among tested excipients, Kollidon® 30 was found to be the most effective crystallization inhibitor. Decrease in the flux of isosorbide dinitrate was also observed when Kollidon® 30 was used in acrylic adhesive matrix without functional group (Myoung and Choi, 2002). Kollidon® 30 has been used as a crystallization inhibitor and is known to act as an antinucleating agent that also inhibits crystal growth (Raghavan et al., 2001). The lower fluxes obtained in the presence of Kollidon® 30 could be either due to lower thermodynamic activity of drug due to the solubilizing effect of Kollidon® 30 or due to the decreased mobility of drug within the matrix due to the surrounding Kollidon® 30. In another investigation, when physostigmine was incorporated in the PIB matrix, crystallization was seen immediately after preparation of the patch (Kim et al., 2002). Adding 6% w/w of Kollidon® 30 prevented crystallization and permeation study showed that drug loading reached saturation at the level of 5% w/w as compared to 3% w/w without Kollidon® 30. Miranda et al. have reported the use of binary blends comprising PSA and Kollidon® 30 (Miranda et al., 1997). Incorporating Kollidon® 30 in the rubber based PSA increased the drug loading and inhibited crystallization for drugs like estradiol and norethindrone acetate. Kotiyan and Vavia (2001) showed that Eudragit® RL PO and Eudragit® E PO were effective crystallization inhibitors for estradiol in DIA patch. Formulations fabricated with Eudragit® E PO gave transparent systems with good film properties and a higher skin permeation profile as compared to that of the marketed system. Also, the feasibility of a monolayer patch based on polydimethylsiloxane PSA containing ibuprofen in supersaturated condition was studied (Cilurzo et al., 2005). The efficacy of three low molecular weight excipients (propylene glycol, Cremophor® EL and Cremophor® RH) and of two copolymers of methacrylic acid (Eudragit® E and Eudragit® RL) as crystallization inhibitors for ibuprofen were tested. Only propylene glycol, among the low molecular weight molecules tested, inhibited the crystallization of ibuprofen up to 50 days without affecting the skin permeation profile. The addition of Eudragit® E or Eudragit® RL in the matrices prevented drug crystallization for more than 12 months. It should be noted, however, that there is no universal crystallization inhibitor and the crystallization inhibitors may decrease or increase permeation rate of the drugs.

CONCLUSIONS

Various methods including chemicals, electric fields and ultrasound have been used to enhance transdermal drug transport. These techniques have rendered transdermal delivery a feasible way of systemically administering drugs. The scientific interest in this arena has increased significantly in the last two decades. Numerous investigations have been performed to safely breach the barrier function of skin enabling administration of therapeutic amount of drug. However, studies performed with solution or suspension formulations have limited application potential. Transdermal devices should be developed considering functional and applicable attributes of the system. Future research should be able to ensure improved delivery through better understanding of physicochemical properties of drug, physiology of skin, mechanism of action of enhancers, and the interaction between formulation components. In addition, through improvised design of devices, a greater range of molecules could be covered in transdermal delivery arena.

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