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Development of transdermal drug delivery system for zolmitriptan

Zolmitriptan 의 경피흡수에 관한 연구

朝鮮大學校 大學院

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指導敎授 崔 厚 均

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Robhash Kusam Subedi

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로버쓰 꾸섬 수베디

지도 교수 : 최후균

조선대학교 대학원 약학과

Chapter I

경피를 이용하여 약리학적으로 활성을 갖는 물질을 체내에 전달하기 위한 연구가 지난 40 여년 동안 광범위하게 연구되어져 왔다. 하지만 이런 노력에도 불구하고 패취 크기에 있어 환자가 거부감을 느끼지 않을 정도로 작게 제조되어야 하고, 약물 투과에 대한 각질층의 장벽 역할 때문에, 현재 약 20 여개 약물에 대해 40 여개 제품만이 상용화 되었다. 따라서 물리적, 화학적 수단을 통해 약물 투과에 대해 피부의 장벽으로서의 기능을 극복하기 위한 다양한 연구가 진행되어져 왔고, 효과적인 경피전달시스템의 개발은 각각의 약물 분자가 지니고 있는 독특한 물리화학적 특성에 의존한다는 것이 밝혀졌다. 따라서 이 장에서는 전기, 초음파, microneedle, 화학적 흡수촉진제를 포함하여 경피흡수율을 증진시키기 위한 다양한 물리적 또는 화학적 접근방법에 대해

고찰하였다. 또한 경피전달에 적용 가능한 점착제 예를들면, 아크릴계, 고무계, 실리콘계 점착제에 대해서도 고찰하였다. 덧붙여 경피전달시스템에 영향을 미치는 인자들 특히, 약물에 대해 영향을 미치는 인자 예를들면 점착력, 재결정화에 대해 살펴보았다.

Chapter II

이 장에서는 zolmitriptan 의 경피 흡수에 대한 점착제, 매트릭스의 두께, 용매, 재결정억제제의 사용여부, 약물 함량, 투과촉진제의 함량을 포함한 다양한 formulation 인자들의 영향을 연구하였다. 히드록시 관능기를 갖는 아크릴계 점착제는 우수한 점착력과 높은 약물 투과도를 보였다. Zolmitriptan 의 pseudopolymorphs 는 피부투과도에 영향을 미치는 서로 다른 고체 상태의 특성을 가지고 있는 것으로 밝혀졌다. Polyoxyethylene alkyl ethers 와 라우릴 알코올은 무모마우스의 피부를 통한 zolmitriptan 의 피부투과도를 크게 증진시킨 반면, zolmitriptan 의 재결정화를 유도하는 문제점을 보였다. 하지만 재결정 억제제로서 Kollidon® 30 과 프로필렌 글리콜 (PG)의 도입은 zolmitriptan 의 투과도 양상을 변화시키지 않고 재결정화를 억제시키는 효과를 얻었다. 또한 안정성 연구에 따르면 cineole 와 limonene 과 같은 terpenes 류는 재결정 억제제를 사용하지 않고도 패치 내에서 zolmitriptan 의 재결정화를 유발시키지 않고 안정화된 formulations 을 구성할 수 있음을 보여주었다.

Abstract

Development of transdermal drug delivery system for zolmitriptan

Chapter 1 : Transdermal drug delivery

Chapter 2 : Transdermal delivery of zolmitriptan

Robhash Kusam Subedi
Advisor: Prof. Hoo-Kyun Choi, PhD
Department of Pharmacy, Graduate School of Chosun University

Chapter 1

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. Chapter I provides

the summary of various physical or 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.

Chapter 2

The effects of different formulation variables including pressure sensitive adhesive (PSA), thickness of the matrix, solvent system, inclusion of crystallization inhibitor, loading amount of drug and enhancers on the transdermal absorption of zolmitriptan were investigated. Acrylic adhesive with hydroxyl functional group provided good adhesion force and high flux of zolmitriptan. Pseudopolymorphs of zolmitriptan were found to possess different solid-state properties that affected the permeation rate. Polyoxyethylene alkyl ethers and lauryl alcohol (LA) significantly increased the permeation of zolmitriptan through hairless mouse skin. However, these enhancers induced crystallization of zolmitriptan. Kollidon® 30 and propylene glycol (PG) delayed the crystallization without altering the permeation profile of zolmitriptan. Stability studies suggested that terpenes

did not induce crystallization of zolmitriptan in the patch and stable formulations could be produced by using cineole and limonene, or their combination.

Chapter 1: Transdermal drug delivery

1. 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 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^{o}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 as such 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 market (Table 1.1), 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.

2. Techniques to enhance transdermal permeation

2.1 Physical Methods

2.1.1 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,

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

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 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).

2.1.2 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).

2.1.3 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).

2.1.4 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.

2.2 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.

2.2.1 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).

2.2.2 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).

2.2.3 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.

2.2.4 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 (ß-cyclodextrin, hydroxypropyl ß-cyclodextrin), terpenes (p-menthane, d-limonene, dipentene, menthol) and pyrrolidones (N-methyl-pyrrolidone, 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).

3. 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 1.2 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 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).

4. Design of transdermal patch

4.1 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 1.1).

4.2 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.

4.3 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 physicochemical 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).

5. System design considerations

5.1 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 anti-nucleating 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).

5.2 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 anti-nucleating 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.

6. 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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Table 1.1. 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	Daytrana®

	disorder)	
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®

Table 1.2. 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
PIB	BASF	Oppanol®	B 10 SFN	Molecular weight of 40000
			B 15 SFN	Molecular weight of 85000
			B 80	Molecular weight of 800000
	Exxon	Vistanex™	L-80	Molecular weight of 750000-1050000
			L-100	Molecular weight of 1060000-1440000
			L-120	Molecular weight of 1450000-1870000
	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

Chapter 2: Transdermal delivery of zolmitriptan

1. Introduction

Zolmitriptan is a potent and selective serotonin (5-HT $_{1B/1D}$) receptor agonist. It is a second-generation triptan and used in the acute treatment of migraine attacks with or without aura and cluster headaches. Zolmitriptan has also shown efficacy in the treatment of persistent and/or recurrent migraine headache (Dowson and Charlesworth, 2002). It is generally well tolerated, with most adverse events being mild-to-moderate, transient and resolving without intervention or the need for treatment withdrawal. However, orally delivered triptan drugs may produce gastrointestinal disturbances (Cipolla et al., 2001). As an improved way of drug delivery, intranasal spray and mucoadhesive microemulsion formulations for zolmitriptan were studied (Yates et al., 2002; Vyas et al., 2005). However, due to low bioavailability after oral administration (Seaber et al., 1997) and inconveniences related to intranasal dosing, the development of new mode of zolmitriptan delivery is required. Recently, transdermal iontophoretic delivery of zolmitriptan was reported (Patel et al., 2009). It was claimed in the report that therapeutic amounts of zolmitriptan were obtained at a faster rate than the existing dosage forms. Despite the potential of this electrically assisted system for zolmitriptan, simpler and more patient friendly matrix

system based transdermal drug delivery system (TDDS) for zolmitriptan would be valuable in providing clinical benefit of prolonged pain-free response to patients. Based on the daily dose of 5 mg and approximate bioavailability of 40% (Seaber et al., 1997), only about 2 mg need to be delivered transdermally. Although skin offers an important mode of systemic drug delivery, the barrier properties of stratum corneum limit the permeation of drug molecules. Significant effort has been devoted to develop strategies for overcoming the impermeability of intact human skin. Among them, penetration enhancers are widely used to reversibly decrease the resistance (Williams and Barry, 2004).

The present study was conducted to investigate the feasibility of developing TDDS for zolmitriptan. *In vitro* permeation studies were done to characterize permeation of zolmitriptan across hairless mouse skin from various PSA based formulations, containing different chemical enhancers and crystallization inhibitors.

2. Materials and methods

2.1 Materials

Zolmitriptan was obtained from Gaobo Pharm-Chemicals (Beijing, China). Polyglyceryl-3 oleate (Plurol olieque ® CC497), propylene glycol mono laurate (Lauroglycol®) and polyoxy glycerate (Labrafil® 1944) were obtained from Masung Co. (Seoul, South Korea). PEG sorbitan monooleate (Tween 80®), sorbitan monooleate (Span 80®), propylene glycol (PG) and oleyl alcohol were purchased from Junsei Chemicals (Japan). Isopropyl palmitate (IPP®), isopropyl myristate (IPM®), PEG-12 palm kernel glycerides (Crovol® PK 40), and PEG-20 almond glycerides (Crovol® A 40) were obtained from Croda (Parsippany, NJ, USA). Lauryl alcohol (LA), (R)-(+) limonene, polyoxyethylene lauryl ether (Brij 30®) and polyoxyethylene cetyl ether (Brij 52®) were purchased from Sigma Chemical (St. Louis, MO, USA). Acrylic and polyisobutylene (PIB) PSA solutions in organic solvents were obtained from National Starch and Chemical Company (Bridgewater, NJ, USA). Silicone PSA was obtained from Dow Corning (Midland, MI, USA). Chitosan (low molecular weight) and ß-cyclodextrin were purchased from Sigma Aldrich (GmbH, Germany). Kollicoat® SR 30D and Kollidon® 30 were obtained from BASF (Ludwigshafen, Germany). All other chemicals were reagent grade or above and were used without further purification.

2.2. Methods

2.2.1. Preparation of patch containing zolmitriptan

Drug solution was prepared by dissolving zolmitriptan in suitable solvent. After adding enhancer and PSA to the drug solution, the mixture was stirred using teflon-coated magnetic bar. The resulting drug-PSA solution was coated onto release liner. Silicone adhesive solution was cast on the release liner (ScotchPak® 1022, 3M, USA) that is coated with fluropolymer. After the solvent was removed, dried film was laminated with a polyester backing film (ScotchPak® 9732, 3M, USA).

2.2.2 Diffusion study

System comprising of a multi channel peristaltic pump (IPC-24, ismatec, Switzerland), a fraction collector (Retriecer IV, ISCO, NE, USA), a circulating water bath (Jeio-Tech, South Korea) and flow-through diffusion cells were used. Each flow-through cell had two arms, which allowed the receiver cell medium pumped to a fraction collector. The diffusion cell temperature was maintained at 37^{o}C by circulating water through the outer part of jacketed receiver cell. Each of the flow-through diffusion cell components was connected via silicone rubber tubing with an internal

diameter of 0.015 inches. The surface area of receiver cell opening was $2cm^2$, and its volume was 5.5ml. Skin was excised from hairless mouse that was sacrificed with diethyl ether. Subcutaneous fat was removed with scissors and scalpel. The receiver cell was filled with pH 6 buffer solution and the media stirred by teflon-coated magnetic bar. The transdermal device was placed on the stratum corneum and the excised skin was mounted onto each receiver cell. And O-ring and cell top were placed on the top of each skin. These components were then clamped. The samples were collected every 4 h for 24 h and analyzed by high performance liquid chromatography (HPLC).

2.2.3 Analytical method

Zolmitriptan was analyzed by an HPLC system (Shimadzu Scientific Instruments, MD), consisting of a UV detector (SPD-10A), reversed-phase C8 column (4.6x 150mm, 5µm, Luna), a pump (LC-10AD), and an automatic injector (SIL-10A). The method previously described (Vyas et al., 2005) was slightly modified. Briefly, the wavelength of the UV detector was 229 nm, the column temperature was maintained at 30^oC, the flow rate was 1mL/min and injection volume was 10µl. The mobile phase consisted of acetonitrile/ 50 mM phosphate buffer pH 7.5 (17.5/82.5).

2.2.4 Differential scanning calorimetry (DSC)

Thermal analysis was carried out using a DSC unit (Pyris 6 DSC, Perkin-Elmer, Netherlands). Indium was used to calibrate the temperature scale and enthalpic response. Samples were placed in aluminum pans and heated at a scanning rate of 10 °C/min from 25 to 170 °C.

2.2.5 X-ray diffraction study (XRD)

XRD patterns were obtained using an X-ray diffractometer (GMAX-1200, Rigaku Co., Japan). The X-ray copper target tube was operated at 40 kV and 30 mA. The instrument geometry was reflection. The X-ray generator power was 2 kW. The scan time was 1°/min and the step size was 0.03. The X-ray passed through 2° divergence slit. The diffracted radiation from the sample passed through 0.48° divergence slit and 0.30 mm receiving slit. The matrix sample was attached onto a glass holder.

2.2.6 Release study

Patch of 15 cm^2 was held in position by attaching it to a sinker at the bottom of dissolution flask. 500 ml of phosphate buffer (pH 6.8) was used as dissolution medium, temperature was set to 32^oC and paddle rpm of 50 provided the agitation. 2 ml sample was withdrawn at the intervals of 0.5h, 1 h, 4 h, 8 h, 12 h, 24 h and 48 h; equal volume of buffer was replaced. Samples were centrifuged at 13000 rpm for 30 mins and analyzed by HPLC.

The study was done in triplicate.

3. Results and discussion

3.1 Effect of adhesive matrix

PSA is one of the most important factors in fabricating a transdermal drug delivery system. The effect of PSA matrix on the permeation of zolmitriptan was investigated using silicone, PIB and acrylic adhesive matrixes at 5% w/w drug loading. The hydrochloride salt form of zolmitriptan possessed extremely low permeability (data not shown), so zolmitriptan was used as a base form. As the first step to select appropriate PSA, solubility of the drug was evaluated in various PSA in organic solvents. The solubility of zolmitriptan was found to be inadequate in silicone, SBS, and PIB adhesive solutions as the solutions were milky and drug particles were formed in the adhesive matrix after drying. Based on higher solubility of zolmitriptan in acrylic adhesives, permeation of zolmitriptan from acrylic adhesives across the hairless mouse skin was investigated and the results are shown in Table 2.1. Different functional groups in acrylic PSAs impart different physicochemical properties to the matrix (Venkatraman and Gale, 1998), which results in different permeation rates of the drugs (Hai et al., 2008). The permeation rate was lowest in the adhesive containing carboxyl functional group. This is known to be due to the interaction between amine group of zolmitriptan and carboxyl group of the adhesive. In previous study,

low permeation rate of tacrine due to the interaction between the amine group of tacrine and carboxyl group of acrylic adhesive was also reported (Kim et al., 2000). Permeation rate of zolmitriptan in the acrylic adhesive matrix was highest with acrylic adhesive containing hydroxyl functional group. Further study on different kinds of acrylic adhesives containing hydroxyl functional group revealed that more than 2 fold flux could be obtained with both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 matrixes as compared to Duro-Tak® 87-2287 matrix (Table 2.1). Therefore, both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 were considered for further study. Initial studies were performed in Duro-Tak® 87-2510 matrix, as higher flux of zolmitriptan was obtained from this matrix.

3.2. Effect of drug concentration and thickness

The flux of zolmitriptan did not change significantly as the drug loading in the matrix increased from 4% to 10% of the dry polymer weight in Duro-Tak® 87-2510 matrix, indicating that saturation of zolmitriptan within the PSA was reached at ca. 4% (Fig. 2.1). The patch was clear at 4% drug load; however, milky appearance was observed from the patch containing 5% or more drug load. Therefore, 4% drug load was used for further study.

It has been reported that the thickness of the matrix may change the permeation rate of a drug across the skin (Kim and Choi, 2003). The effect of

thickness at 4% drug load in Duro-Tak® 87-2510 matrix was investigated to optimize the thickness (Fig. 2.2). The penetration rate of zolmitriptan increased when matrix thickness increased up to 95μm and remained similar up to 130μm. Further increase in the thickness resulted in lower permeation rate. Therefore the matrix thickness of 100μm was selected for further study.

3.3. Effect of solvent system

Zolmitriptan exhibits polymorphism and seven different crystalline forms were reported (Van Der Schaaf, et al., 2007). Different polymorphs, pseudopolymorphs or the amorphous form differ in their physical properties such as melting point and solubility. These parameters can appreciably influence pharmaceutical properties of the drug. It was reported that when zolmitriptan was crystallized using various solvents, different solvates having distinct XRD pattern were formed (Van Der Schaaf, et al., 2007). During the preparation of transdermal patch, drug substance may encapsulate solvent molecules in the process of drying. To investigate this phenomenon, drug solution was prepared using various solvents including ethyl acetate, butanol, 2-propanol, ethylmethyl ketone (EMK) and tetrahydrofuran (THF); followed by drying in vacuum oven for 24 h. The dried crystalline forms of zolmitriptan were subjected to DSC analysis for the characterization of solid-state property. As seen in Fig. 2.3, the melting peak of zolmitriptan at around

140^{o}C was reduced and broadened in the case of each solvate. The DSC thermograms were also accompanied by additional peak near 80^{o}C that corresponded to the boiling points of each solvent used except butanol. With THF solvate, no clear peak was observed. XRD studies were also conducted to have a better insight into the crystallinity of the solvates. X-ray diffractograms of different solvates are given in Fig. 2.4. Each solvate possessed distinct crystalline pattern except the case of THF where no crystalline peak was observed. The absence of characteristic peaks for THF solvate in DSC thermogram and X-ray diffractogram implied that it might exist as amorphous form. Patches made using these solvates also markedly differed in the physical properties. Notably, large rod shaped crystals were observed in formulation containing THF solvate after few hours of drying. X-ray diffractogram of the patch showed increase in crystallinity at 21.6 and 23.7 positions of 2Θ. The crystal formation could be a result of unstable amorphous state of THF solvate. Furthermore, permeation study was conducted to evaluate whether the differences observed among the solvates affect penetration characteristics. As clearly seen in Fig. 2.5, highest permeation profile was obtained with EMK solvate and the least with THF solvate. The lowest flux obtained in case of THF solvate could be due to the rapid crystallization in the transdermal patch. The drug crystals should first dissolve and then be released from the system in order to be permeated

across the skin and the dissolution process is usually rate limiting and tends to affect delivery rate. Ethyl acetate, 2-propanol and butanol solvates possessed similar permeation characteristics. In order to explore whether the solubility of zolmitriptan solvates or release rate from PSA matrix had any correlation with the permeation rate, solubility and release rate of the solvates was measured in pH 6.8 phosphate buffer. However, solubility of the solvates in pH 6.8 buffer did not correlate with the flux obtained (R^2= 0.005). Similarly, release of the solvates from the patches did not show significant correlation with the flux obtained (R^2 = 0.214). Table 2.2 provides summary on solubility and dissolution of the solvates.

The difference in crystalline property may not be the sole factor responsible for the difference in penetration properties observed, however, it certainly has been shown to be an important factor. These observations suggest that choice of appropriate solvent has some importance in designing the transdermal drug delivery system for drugs showing polymorphic behavior.

3.4. Effect of penetration enhancers

To reversibly overcome the barrier properties of stratum corneum, which limits the permeation of drug molecules, penetration enhancers are commonly employed in the transdermal systems (Williams and Barry, 2004).

Firstly, screening of enhancers was carried out at 4% drug load in Duro-Tak® 87-2510 matrix. Polyoxyethylene alkyl ethers including Brij 30® and Brij 52® significantly enhanced the flux of zolmitriptan at the level of 5% (Fig. 2.6). However, crystals were formed shortly after the preparation. Additives used in the transdermal formulations are known to be an influential factor for crystallization of drug in acrylic PSA (Ma et al., 1996). Among the other enhancers screened, only terpenes (cineole and limonene) provided higher flux of zolmitriptan (Table 2.3). Limonene was reported to increase the diffusivity of sumatriptan across the skin (Femenia-Font et al., 2005). It was worthwhile to explore the relationship between the enhancement effect observed and solubility of zolmitriptan in the various enhancers (Table 2.4). Nevertheless, no correlation was found between the solubility of zolmitriptan in enhancers and the permeation observed (R^2= 0.082). Similar findings were reported in previous studies. Solubility of ketoprofen and tacrine in the enhancers studied did not correlate with the permeation enhancement observed (Cho and Choi, 1998; Kim et al., 2000).

Several enhancers were also screened at the level of 5% with Duro-Tak® 87-2516 as PSA matrix and 100μm dried thickness (Table 2.3). Brij 52®, Brij 30®, Plurol olieque® CC97, IPP, IPM, lauroglycol, limonene and LA were associated with enhanced permeation profile. At increased drug concentration, LA at the level of 10% provided highest flux of zolmitriptan

(Fig. 2.7). In the absence of enhancer, increasing the drug content did not provide higher flux (data not shown). Other selected enhancers, at the level of 10%, could not provide flux comparable with LA at 7% drug load (Table 2.5). Nevertheless, stability of the patches, containing 10% LA and 7% drug, was unsatisfactory because crystals appeared after 1 week of casting. Crystallized patch showed reduced permeation profile (data not shown).

3.5. Effect of crystallization inhibitors

3.5.1. Duro-Tak® 87-2510 matrix

In order to prevent crystallization of zolmitriptan in the patch containing Brij 52®, various crystallization inhibitors were screened at the level of 5%, with 4% drug load in Duro-Tak® 87-2510 matrix. Among the excipients explored, Cremophor ELP®, Low substituted Hydroxypropyl cellulose (HPC LH 11), chitosan, Carbomer® NF 971, 2 hydroxypropyl ß-cyclodextrin, Kollicoat® SR 30D and hydroxypropyl methylcellulose (HPMC) could not inhibit crystallization. Patches containing Lutrol® 127, Cremophor RH®40, Eudragit E®100, EC and PG were clear immediately after casting but crystals appeared within 24 h. Combination of Eudragit RL®100 and Eudragit RS®100 was found to be better than each used alone. But none of the Eudragit based formulations could delay the formation of visible crystals

over 24 h. With 2-hydroxypropyl ß-cyclodextrin, precipitation was observed after adding adhesive to the drug solution. Only in the formulation containing Kollidon® 30, crystals were not observed for a period of one month. Furthermore, Kollidon® 30 did not interfere with the enhancement properties of Brij 52®. DSC thermograms of the patches were measured to confirm the absence of crystals in the patches containing Kollidon® 30 (Fig. 2.8). Since DSC alone cannot guarantee the absence of crystallinity, XRD study was done with patches containing drug and Brij 52®, with or without Kollidon® 30. Fig. 2.9 shows increase in crystallinity at various 2Ɵ positions with patches containing 5% Brij 52® and 4% drug. No such crystalline peak was seen in patches containing 5% Kollidon® 30, 5% Brij 52® and 4% drug. Kollidon® 30 has been frequently used as a drug crystallization inhibitor in pharmaceutical formulations (Ma et al., 1996; Ziller and Rupprecht, 1988). Inhibitory effect of Kollidon® 30 on drug crystallization could be primarily attributed to the protective steric hindrance for crystallization of drug molecules. Kollidon® 30 may also interact and adsorb onto the zolmitriptan nuclei or initial crystals, preventing crystal growth. However, appearance of the patches containing Kollidon® 30 were not satisfactory. This was due to the precipitation of Kollidon® 30 in the PSA solution, the phenomenon was confirmed by casting a blank patch containing only PSA and Kollidon® 30. Hence, transdermal system based on Kollidon® 30 alone could not be used.

To develop a combined system for crystallization inhibition, various polymers were screened in combination with Kollidon® 30. Among the additives screened in the combination system, only EC was found to form homogenous film without crystals. Patches prepared by including other excipients were milky and not homogeneous. The morphology of patches containing combination of EC and Kollidon® 30 was better than that containing Kollidon® 30 alone. The optimum ratio of EC: Kollidon® 30 in the matrix was found to be 1:2. Employing the combined system enabled to obtain crystal free patches even when higher levels of enhancer were used. However, the crystallization could not be delayed for more than a month.

3.5.2. Duro-Tak® 87-2516 matrix

Since, satisfactory results was not obtained with Duro-Tak® 87-2510 based formulations, further studies were performed with Duro-Tak® 87-2516 matrix. Although permeation of zolmitriptan was lower in Duro-Tak® 87-2516 than in Duro-Tak® 87-2510, former could accommodate more drug and the effect of the enhancers were more prominent (Table 2.3). The combined crystallization inhibitory system with EC and Kollidon® 30 was employed using Duro-Tak® 87-2516 matrix. Fig. 2.10 shows the effect of various amounts of Brij 52®, in the Duro-Tak® 87-2516 matrix along with EC and Kollidon® 30. Permeation of zolmitriptan increased with higher levels of

enhancer. But similar with the case of Duro-Tak® 87-2510 matrix, Brij 52® induced crystallization of zolmitriptan could not be delayed for more than a month.

To prevent LA induced crystallization of zolmitriptan in Duro-Tak® 87-2516 matrix, effect of including EC, Eudragit E®100 and PG were studied. Since Kollidon® 30 impaired the aesthetic value of patch, it was not selected for the study; all other crystallization inhibitors did not interfere with the morphology of the patch. However, crystals appeared in patches containing Eudragit E®100 and EC within a week of casting. Only patches containing PG were free of visible crystals. Other studies have also demonstrated efficacy of PG in TDDS. Crystallization of ibuprofen in transdermal patches was inhibited till 50 days, by incorporating PG in the formulation (Cilurzo et al., 2005). Furthermore, increase in flux was observed by including PG in the formulation (Fig. 2.11). Several investigations have found that PG also acts as permeation enhancer. In a recent study, PG increased the flux of gestodene by 3.00 fold and that of ethinylestradiol by 4.06 fold, through mice skin (Gao et al., 2009). Antinucleant agents have been known to reduce the thermodynamic activity of drug thereby reducing the permeation across the skin (Kotiyan and Vavia, 2001). Whereas in some cases, crystallization inhibitor used may not affect the permeability of drug. For example, in the transdermal system for estradiol, eudragit polymers did not reduce the drug

release from the adhesive system (Kotiyan and Vavia, 2001). The crystallization inhibition and permeation enhancement observed in permeation containing PG could be in part explained by the high solubility of zolmitriptan in PG (Table 1.4). However, the crystallization inhibition could not be delayed for more than a month.

3.6. Stability studies

To explore the commercial viability of product, stability studies were also conducted. Various test formulations were packed in aluminum foils and subjected to accelerated stability testing. Patches were also kept at room temperature. Appearance of crystals was visually monitored. The samples were also evaluated for drug content and skin permeation kinetics. Although combination of EC and Kollidon® 30 inhibited Brij 52® induced crystallization of zolmitriptan in both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 matrices, stability study revealed that patches developed crystals after a period of one month. Similarly, PG also could not delay the crystallization of zolmitriptan, in presence of LA, for more than a month. Crystallized patches showed reduced permeation profile and decreased adhesion force (data not shown). Among the formulations studied, the ones containing terpenes, as enhancer, remained clear with time. Permeation studies with aged samples did not show reduced profile indicating that the

matrix was not changed (Fig. 2.12). Patches containing terpenes were also observed for any change in morphology or crystallization at various temperatures. Crystallization was found to be dependent on the storage temperature. At elevated temperatures crystals appeared in the patch at faster rate (Table 2.6). Patches were stable at the storage condition of 40^{o}C for 2 months. However, spots appeared at 3rd month that developed into crystals. At 50^{o}C, spots appeared at 2nd month and the morphology of patch changed to yellowish at the 3rd month. Other investigations have also reported that temperature is a critical factor governing the induction time of crystallization (Kim and Choi, 2002). Chemical assay was performed as a part of stability studies which showed that drug content in patches stored at 40^{o}C did not change for 3 months (Table 2.7). At 50^{o}C, drug content declined after 2 months indicating that temperature induced change in matrix at higher temperature. Patches stored at room temperature were stable for the study period of 6 months.

4. Conclusions

Zolmitriptan was formulated into a transdermal patch in an attempt to present a better mode of drug delivery. Permeation of zolmitriptan from the matrix was influenced by different formulation variables like the nature of adhesive, enhancer, thickness of matrix, drug load and the solvent system used. Solvent systems, associated with different polymorphs, were found to influence the permeation rate. Crystallization was primarily dependent on the temperature and enhancers used. Stable formulations were identified through stability testing. The present study suggests that, matrix based transdermal dosage form of zolmitriptan could be explored for the management of migraine.

5. References

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Table 2.1. Penetration rate for zolmitriptan from different acrylic adhesive matrixes at 5% drug load. (n=3)

Adhesive matrix	Trade name	Flux ($\mu g/cm^2/h$)
without functional group	Duro-Tak® 87-4098	6.16
with carboxyl- functional group	Duro-Tak® 87-2677	0.22
With hydroxyl- functional group	Duro-Tak® 87-2510	15.6
	Duro-Tak® 87-2287	6.5
	Duro-Tak® 87-2516	14.4

Table 2.2. Summary on solubility and dissolution of various solvates. Values are expressed as mean ± standard deviation. (n=3)

	Solvate	Solubility (mg/ml)	Cumulative release (%)
1	Pure drug	12.9±0.1	-
2	Ethyl acetate	13.9 ±0.2	73.1±2.3
3	Ethyl methyl ketone	19.9±0.6	101.6±1.1
4	2-propanol	15.6±0.1	97.6±2.5
5	1-butanol	15.7±0.3	85.3±7.5
6	Tetrahydrofuran	24.7±0.3	68.4±5.0

Table 2.3. Summary of enhancer screening for zolmitriptan from Duro-Tak® 87-2510 and Duro-Tak® 87-2516 matrices. (n=3)

	Enhancement Ratio	
Enhancers	Duro-Tak® 87-2510	Duro-Tak® 87-2516
Control	1.00	
Plurol olieque ® CC497	0.68	1.28
Span 80®	0.63	1.09
Tween 80®	0.66	0.84
Transcutol®	0.98	0.94
Oleyl alcohol	0.35	0.96
Brij 52®	1.37	1.44
Brij 30®	1.15	1.33
Brij 58®	0.77	0.79
Cineole	1.39	1.11
Labrafil®1944	0.54	0.93
Crovol® A40	1.02	0.99
Crovol® PK40	0.70	1.08
IPP	0.58	1.33
IPM	0.56	1.33
Lauryl alcohol	0.40	1.45
Lauroglycol	0.43	1.30
Limonene	1.13	1.29
Labrafac PG®		0.98
Oleic acid		0.60
Labrafil®2609	0.39	
Brij 72®	0.72	
Brij 97®	0.90	
Brij 700®	0.30	
Incrocas®	0.51	

* Enhancement ratio = Flux with enhancer/Flux without enhancer

Table 2.4. Solubility of zolmitriptan in various vehicles at 24 h, room temperature. Values are expressed as mean ± standard deviation. (n=3)

	Enhancers	Solubility (μg/ml)
1	Limonene	29.3±2.7
2	Labrafil®2609	5606.0±334.5
3	Plurol olieque ® CC497	6397.1±324.2
4	Brij 30®	4847.2±677.6
5	IPM®	80.5±24.5
6	Oleyl Alcohol	893.6±80.3
7	Span 80®	8171.9±144.9
8	Crovol PK 40®	6640.5±1689.4
9	Transcutol®	11885.9±1044.2
10	Tween 80®	10512.1±842.4
11	LA	871.2±38.5
12	Cineole	1456.7±131.4
13	IPP®	127.0±61.8
14	Propylene glycol	75679.6±2315.2

Table 2.5. Permeation of zolmitriptan from Duro-Tak® 87-2516 matrix containing various enhancers at the level of 10 % v/w, with 7% w/w drug load and 100µm dried thickness. (n=3)

	Enhancers	Flux (µg/cm^2/h)
1	Control	13.1
2	LA	27.1
3	IPP	22.8
4	IPM	22.5
5	Cineole	14.9
6	Limonene	14.1

Table 2.6. Physical stability of zolmitriptan patch, formulated in Duro-Tak® 87-2516 matrix, at elevated temperatures.

Formulation	1 month		2 months		3 months	
	40°C	50°C	40°C	50°C	40°C	50°C
5.5% Zolmitriptan, 5% Cineole	Clear	Clear	Clear	Spots	Spots	Yellowish
5.5% Zolmitriptan, 2.5% Limonene, 2.5% Cineole	Clear	Clear	Clear	Spots	Spots	Yellowish

Table 2.7. Chemical stability of zolmitriptan patch, formulated in Duro-Tak® 87-2516 matrix, at elevated temperatures. Values are expressed as mean ± standard deviation. (n=3)

Formulation	1 month		2 months		3 months	
	40°C	50°C	40°C	50°C	40°C	50°C
5.5% Zolmitriptan, 5% Cineole	96.3±4.1	93.9±1.9	93.0±2.7	84.3±5.7	92.8±4.8	84.1±7.4
5.5% Zolmitriptan, 2.5% Limonene, 2.5% Cineole	95.0±1.8	97.4±1.1	92.6±3.3	85.9±1.9	96.8±2.9	88.5±3.6

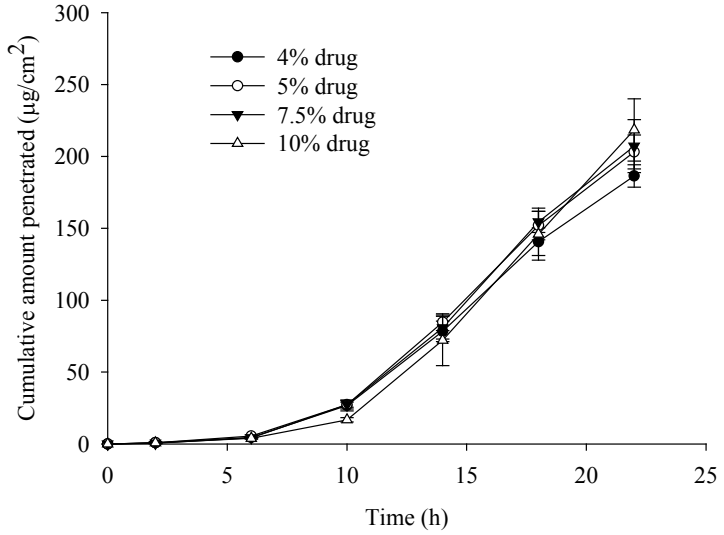

Fig. 2.1. Effect of drug concentration on the permeation of zolmitriptan from different formulations in Duro-Tak® 87-2510 matrix. Values are expressed as mean ± standard deviation. (n=3)

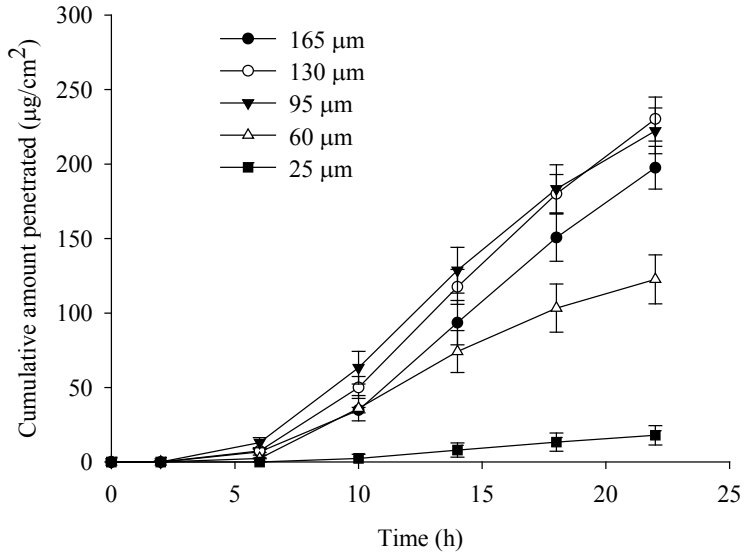

Fig. 2.2. Effect of thickness on the permeation of zolmitriptan from formulation containing 4% drug in Duro-Tak® 87-2510 matrix. Values are expressed as mean ± standard deviation. (n=3)

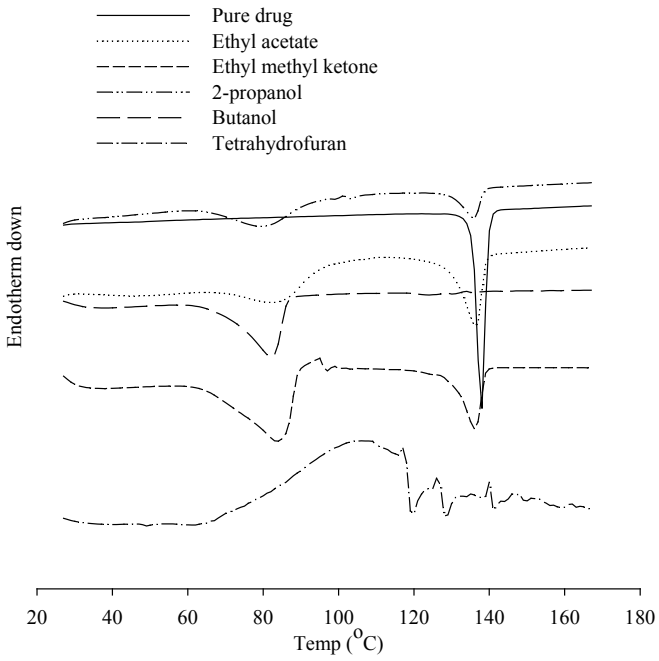

Fig. 2.3. DSC thermograms of different solvates of zolmitriptan prepared using ethyl acetate, butanol, 2-propanol, EMK and THF.

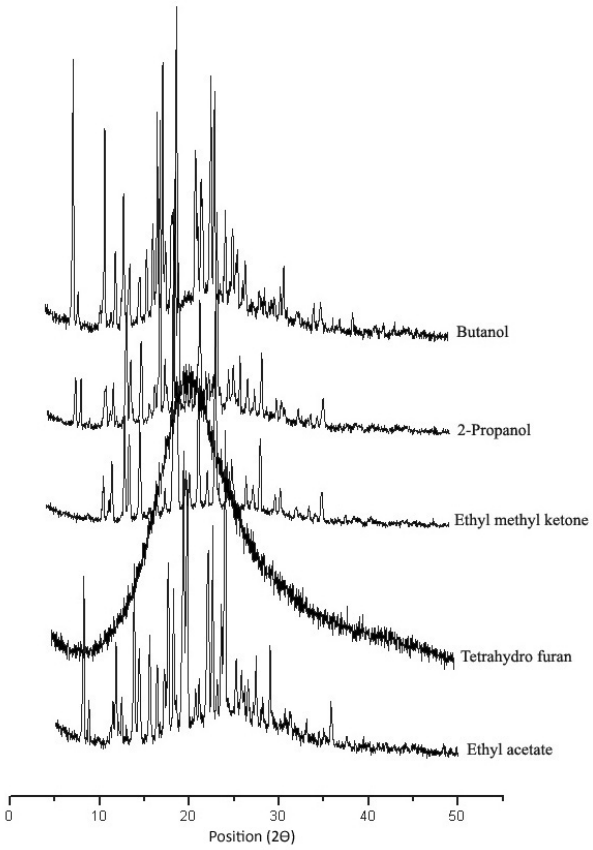

Fig. 2.4. X-ray diffractogram of zolmitriptan solvates prepared using EMK, ethyl acetate, 2-propanol, butanol and THF.

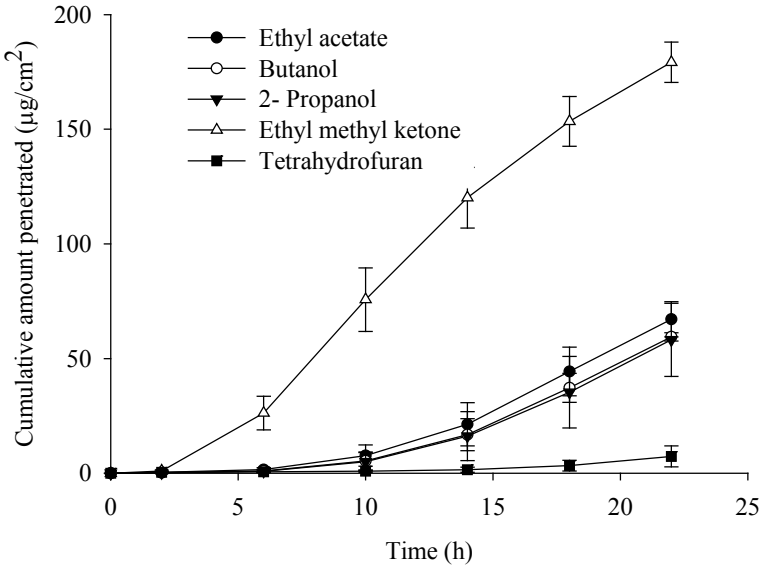

Fig. 2.5. Effect of solvent systems on the permeation of zolmitriptan at 4% drug load in Duro-Tak® 87-2510 matrix. Different solvents were used to either dissolve or disperse drug in the PSA matrix, prior to casting. Values are expressed as mean ± standard deviation. (n=3)

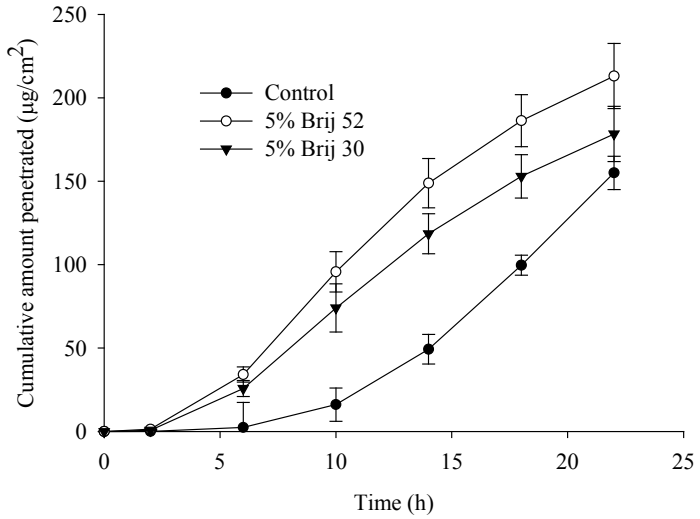

Fig. 2.6. Effect of including Brij 30® and Brij 52® at the level of 5%, in formulations containing 4% drug load in Duro-Tak® 87-2510 matrix. Values are expressed as mean ± standard deviation. (n=3)

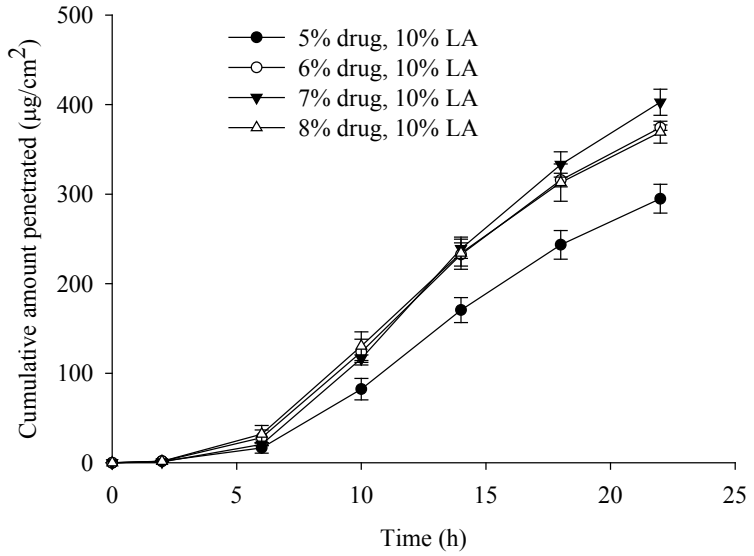

Fig. 2.7. Effect of increased drug loading on the permeation of zolmitriptan from patches containing 10% v/w LA in Duro-Tak® 87-2516 matrix. Values are expressed as mean ± standard deviation. (n=3)

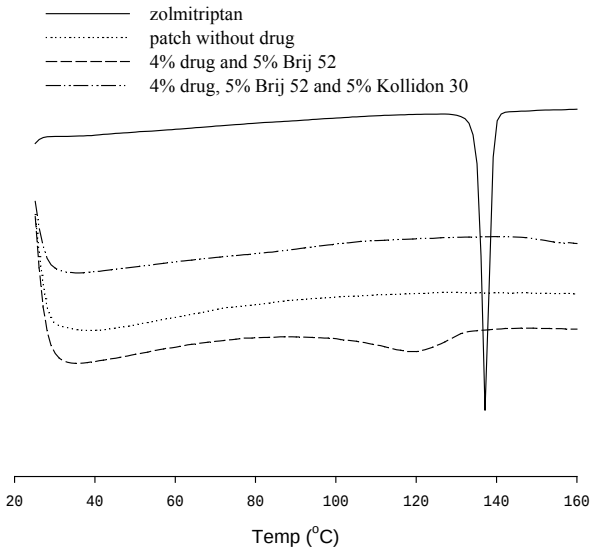

Fig. 2.8. DSC thermograms of drug, blank patch; patch containing 4% drug and 5% Brij 52®, with or without 5% Kollidon® 30, in Duro-Tak® 87-2510 matrix.

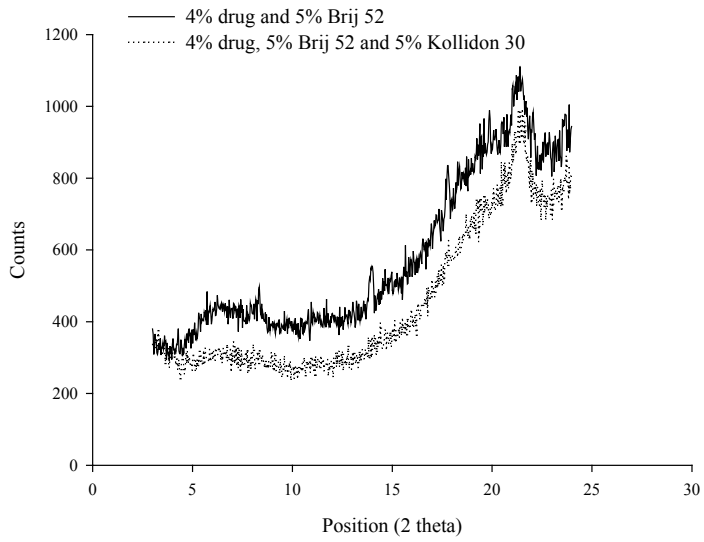

Fig. 2.9. X-ray diffractograms of patch containing 4% drug and 5% Brij 52®, with or without 5% Kollidon® 30, in Duro-Tak® 87-2510 matrix.

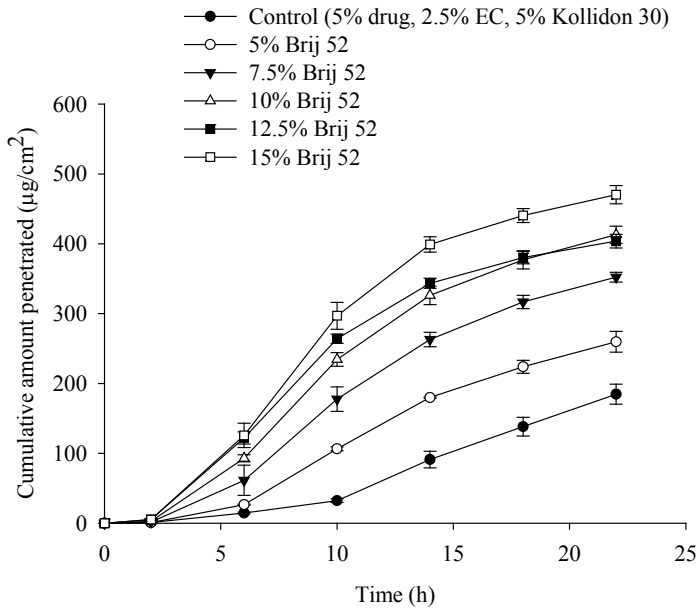

Fig. 2.10. Effect of combined system of crystallization inhibition on the permeation of zolmitriptan from patches containing 5% drug load, Brij 52® at various levels ranging from 5% to 15 % (w/w), EC and Kollidon® 30 at the levels of 2.5% and 5% (w/w) in Duro-Tak® 87-2516 matrix, on the permeation of zolmitriptan. Values are expressed as mean ± standard deviation. (n=3)

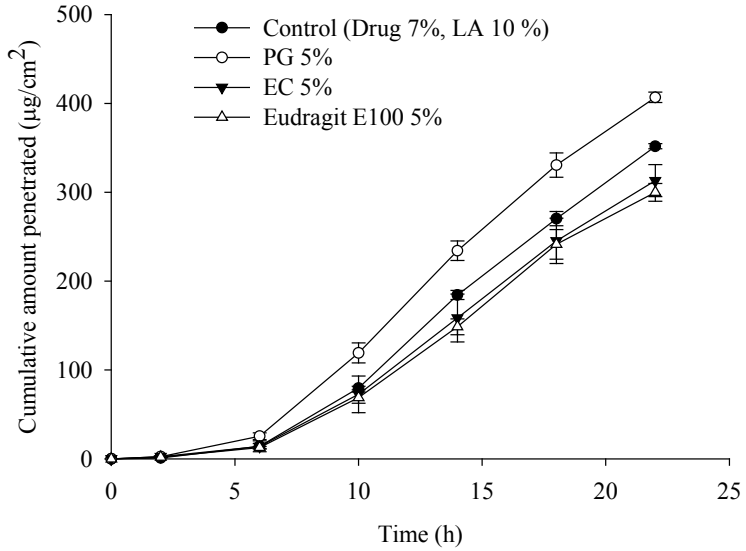

Fig. 2.11. Effect of including crystallization inhibitors at the level of 5% in formulations containing 7% drug load and 10% LA in Duro-Tak® 87-2516 matrix. Values are expressed as mean ± standard deviation. (n=3)

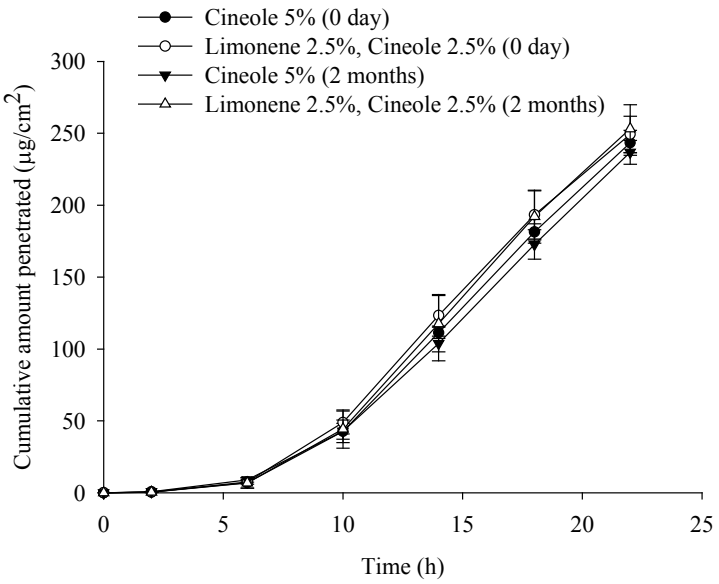

Fig. 2.12. Stability study with patches containing terpenes with 5.5% drug load in Duro-Tak® 87-2516 matrix. Values are expressed as mean ± standard deviation. (n=3)

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저작물 이용 허락서

학 과	약학과	학 번	20067753	과 정	박사
성 명	한글: 로버쓰 꾸썸 수베디 영문 : Robhash Kusam Subedi				
주 소	#303, HyongJin Villa, Chisan 2-dong, Gwangju				
연락처	E-MAIL: robhash@gmail.com				
논문제목	한글 : Zolmitriptan 의 경피흡수에 관한 연구 영어 : Development of transdermal drug delivery system for zolmitriptan				

본인이 저작한 위의 저작물에 대하여 다음과 같은 조건아래 조선대학교가 저작물을 이용할 수 있도록 허락하고 동의합니다.

- 다 음 -

1. 저작물의 DB 구축 및 인터넷을 포함한 정보통신망에의 공개를 위한 저작물의 복제, 기억장치에의 저장, 전송 등을 허락함
2. 위의 목적을 위하여 필요한 범위 내에서의 편집·형식상의 변경을 허락함. 다만, 저작물의 내용변경은 금지함
3. 배포·전송된 저작물의 영리적 목적을 위한 복제, 저장, 전송 등은 금지함.
4. 저작물에 대한 이용기간은 5 년으로 하고, 기간종료 3 개월 이내에 별도의 의사 표시가 없을 경우에는 저작물의 이용기간을 계속 연장함
5. 해당 저작물의 저작권을 타인에게 양도하거나 또는 출판을 허락을 하였을 경우에는 1 개월 이내에 대학에 이를 통보함
6. 조선대학교는 저작물의 이용허락 이후 해당 저작물로 인하여 발생하는 타인에 의한 권리 침해에 대하여 일체의 법적 책임을 지지 않음
7. 소속대학의 협정기관에 저작물의 제공 및 인터넷 등 정보통신망을 이용한 저작물의 전송·출력을 허락함

동의여부 : 동의 (○) 반대( )

2010 년 8 월 25 일

저작자: 로버쓰 꾸썸 수베디 (서명 또는 인)

조선대학교 총장 귀하