



Influence of formulation variables in transdermal drug delivery system containing zolmitriptan

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ABSTRACT

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 significantly increased the permeation of zolmitriptan through hairless mouse skin. However, these enhancers induced crystallization of zolmitriptan. Kollidon® 30 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.

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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 (Vyas et al., 2005; Yates et al., 2002). 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 deliv-

ery 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 is needed 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 palmi-

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tate (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). Low substituted hydroxypropyl cellulose (HPC LH 11). Chitosan (low molecular weight) and β -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 organic solvent. After adding enhancer and PSA to the drug solution, the mixture was stirred using teflon-coated magnetic bar to obtain homogeneous solution. 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 fluoropolymer. After the solvent was removed, dried film was laminated with a polyester backing film (ScotchPak® 9732, 3M, USA). The values of drug loading, excipients and enhancers are expressed as % with respect to the dry polymer weight.

2.2.2. Diffusion study

System comprising of a multi channel peristaltic pump (IPC-24, Ismatec, Switzerland), a fraction collector (Retriever 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 °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 in. The surface area of receiver cell opening was 2 cm², and its volume was 5.5 mL. 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 6.0 buffer solution and the media stirred by teflon-coated magnetic bar. The transdermal patch 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 (4.6 mm × 150 mm, 5 μ m, 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 °C, the flow rate was 1 mL/min, and injection volume was 10 μ L. 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 tem-

perature pans and heated at a scanning rate of 10 °C/min from 25 to 170 °C.

2.2.5. X-ray diffraction study

X-ray diffraction (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⁻¹ 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 cm² 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 at 32 °C and paddle speed of 50 rpm provided the agitation. 2 mL sample was withdrawn at 0.5 h, 1 h, 4 h, 8 h, 12 h, 24 h and 48 h post study. An equal volume of buffer was replaced after taking the sample. Samples were centrifuged at 13,000 rpm for 30 min and analyzed by HPLC. The study was performed in triplicate.

3. Results and discussion

3.1. Effect of adhesive matrix

PSA is one of the most important components 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 matrices at 5% (w/w) drug loading. As the first step to select appropriate PSA, solubility of the drug was evaluated in various PSA solutions. 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 1. It has been reported that 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 could be due to the interaction between amine group of zolmitriptan and carboxyl group of the adhesive. In previous study, low permeation rate of tacrine was observed due to the interaction between the amine group of tacrine and carboxyl group of acrylic adhesive (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 1). Therefore, both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 were

Table 1

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

Adhesive matrix	Trade name	Flux (μ 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

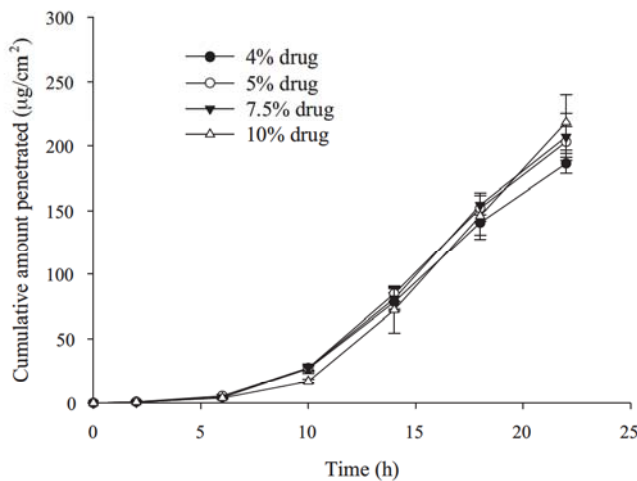


Fig. 1. Effect of drug concentration on the permeation of zolmitriptan from different formulations in Duro-Tak® 87-2510 matrix. Values are expressed as mean \pm standard deviation ($n = 3$).

considered for further study. Initial studies were performed in Duro-Tak® 87-2510 matrix, as slightly 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 Duro-Tak® 87-2510 matrix increased from 4% to 10% (w/w) of the dry polymer weight, indicating that saturation of zolmitriptan within the PSA may be obtained at ca. 4% (w/w) (Fig. 1). The patch was clear at 4% (w/w) drug load; however, milky appearance was observed in the patches containing 5% (w/w) or more drug load. Therefore, 4% (w/w) drug load was used for further study. In the case of Duro-Tak® 87-2516, 5% (w/w) drug load was used for further study as the patches were clear at this level of drug content.

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% (w/w) drug load in Duro-Tak® 87-2510 matrix was investigated to optimize the thickness (Fig. 2). The penetration rate of zolmitriptan increased when matrix thickness increased up to 95 μm and remained similar up to 130 μm . Fur-

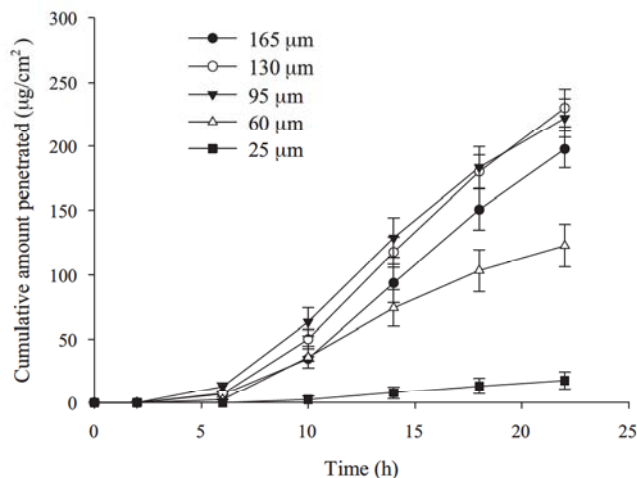


Fig. 2. Effect of thickness on the permeation of zolmitriptan from formulation containing 4% (w/w) drug in Duro-Tak® 87-2510 matrix. Values are expressed as

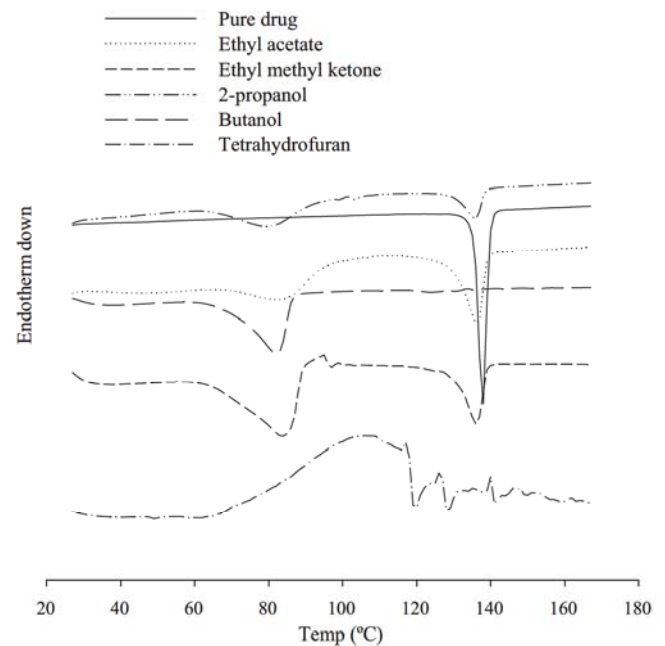


Fig. 3. DSC thermograms of different solvates of zolmitriptan prepared using ethyl acetate, butanol, 2-propanol, EMK and THF.

ther increase in the thickness resulted in lower permeation rate. Therefore, the matrix thickness of 100 μm was selected for further studies with both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 matrices.

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 solvents 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. 3, the melting peak of zolmitriptan at around 140°C was reduced and broadened in the case of each solvate. The DSC thermograms were also accompanied by additional peak near 80°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. 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

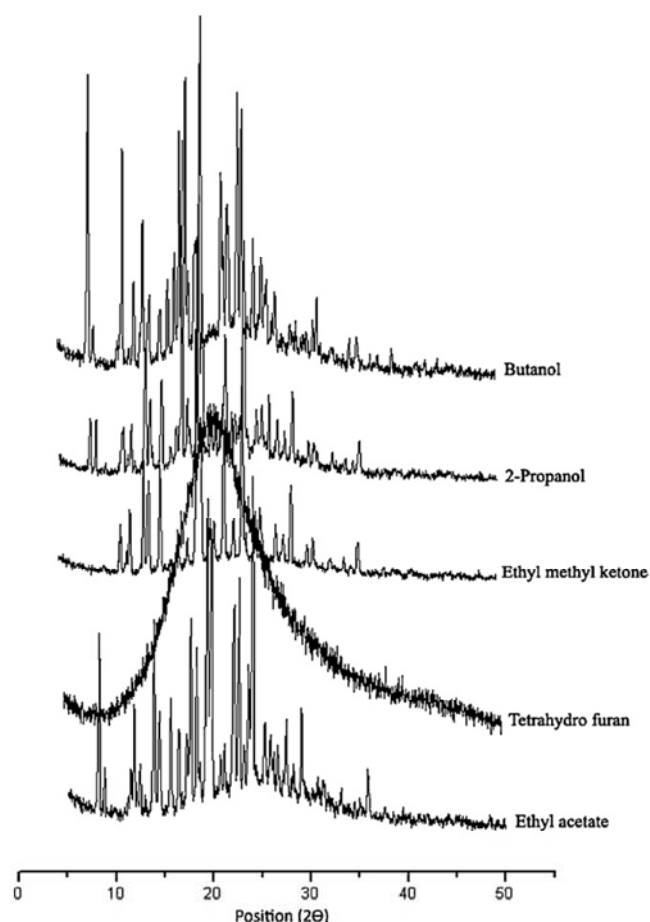


Fig. 4. X-ray diffractogram of zolmitriptan solvates prepared using EMK, ethyl acetate, 2-propanol, butanol and THF.

unstable amorphous state of THF solvate. Furthermore, permeation study was conducted to evaluate whether there were any differences among the solvates in terms of penetration characteristics. As clearly seen in Fig. 5, the highest permeation profile was obtained with EMK solvate and the least with THF solvate. The lowest flux obtained in case of THF solvate may be due to the rapid crystal-

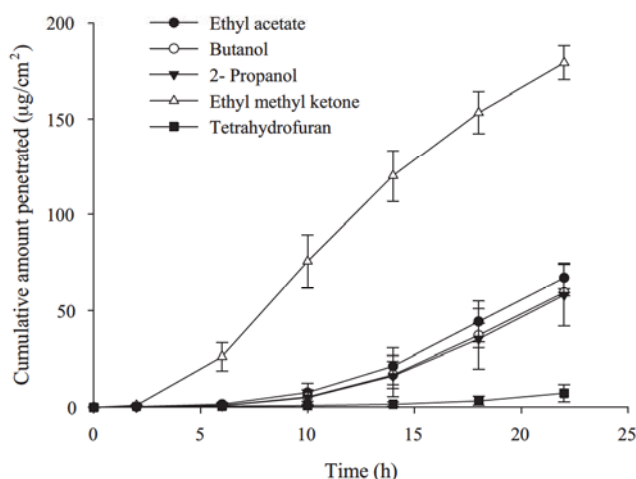


Fig. 5. Effect of solvent systems on the permeation of zolmitriptan at 4% (w/w) drug load in Duro-Tak® 87-2510 matrix. Different solvents were used to either dissolve or disperse drug in the PSA matrix, prior to casting. Values are expressed as

Table 2
Solubility and dissolution of various zolmitriptan solvates ($n = 3$).

Solvate	Solubility (mg/mL)	Cumulative release (%)
1 No solvate	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

lization in the PSA matrix. 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 (Subedi et al., 2010). 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 were measured in pH 6.8 phosphate buffer (Table 2). 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 ($R^2 = 0.214$).

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

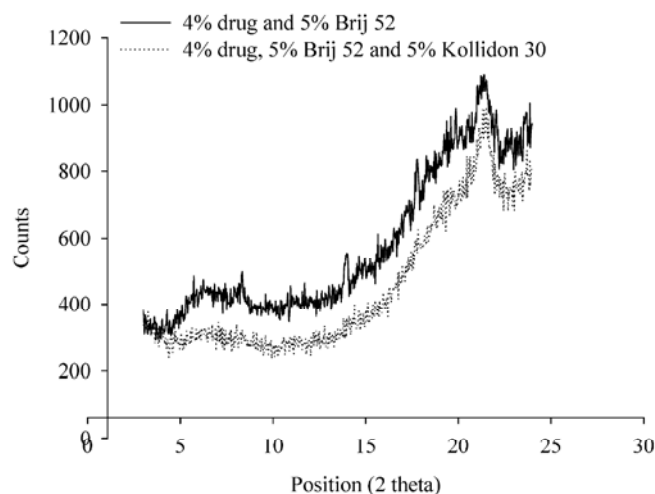
To reversibly overcome the barrier properties of stratum corneum, penetration enhancers are commonly employed in the transdermal systems (Williams and Barry, 2004). Table 3 gives the summary of enhancer screening with both Duro-Tak® 87-2510 and Duro-Tak® 87-2516 matrices. Polyoxyethylene alkyl ethers

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

Enhancers	Enhancement ratio ^a	
	Duro-Tak® 87-2510	Duro-Tak® 87-2516
Control	1.00	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® PC		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	

Table 4Chemical stability of zolmitriptan patch, formulated in Duro-Tak® 87-2516 matrix, at elevated temperatures. Values are expressed as mean \pm standard deviation ($n=3$).

Formulation	Assay					
	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 \pm 4.06	93.9 \pm 1.93	93.0 \pm 2.74	84.3 \pm 5.67	92.8 \pm 4.87	84.1 \pm 7.41
5.5% zolmitriptan, 2.5% limonene, 2.5% cineole	95.0 \pm 1.80	97.4 \pm 1.11	92.6 \pm 3.26	85.9 \pm 1.99	96.8 \pm 2.86	88.5 \pm 3.65

**Fig. 6.** X-ray diffractograms of patch containing 4% (w/w) drug and 5% (v/w) Brij® 52, with or without 5% (w/w) Kollidon® 30, in Duro-Tak® 87-2510 matrix.

including Brij® 30 and Brij® 52 significantly enhanced the flux of zolmitriptan at the level of 5% (v/w). 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, Plurol olieque® CC97, IPP, IPM, lauroglycol, limonene and LA also significantly enhanced the flux of zolmitriptan from Duro-Tak® 87-2516 matrix; however, crystals were formed as a matter of time. Only terpenes (cineole and limonene) provided higher flux of zolmitriptan than the control without inducing crystallization in the PSA matrix. It was also reported in the literature that terpene (limonene) in solution formulation increased the diffusivity of triptan (sumatriptan) across the skin (Femenia-Font et al., 2005).

3.5. Effect of crystallization inhibitors

In order to prevent crystallization of zolmitriptan in the patch containing Brij® 52, various crystallization inhibitors were screened at the level of 5% (w/w), with 4% (w/w) drug load in Duro-Tak® 87-2510 matrix. Among the excipients explored, Cremophor ELP®, HPC LH 11, chitosan, Carbomer® NF 971, 2-hydroxypropyl β -cyclodextrin, Kollicoat® SR30D, hydroxypropyl methylcellulose (HPMC), Lutrol® 127, Cremophor® RH 40, Eudragit® E100, Eudragit® RL100, Eudragit® RS100 EC and PG could not inhibit the crystallization. Only in the formulation containing Kollidon® 30, crystals were not observed for a period of one month. Fig. 6 shows increase in crystallinity at various 2θ positions in patches without Kollidon® 30. No such crystalline peak was seen in patches containing 5% (w/w) Kollidon® 30, 5% (v/w) Brij® 52 and 4% (w/w) 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

the crystallization for more than a month and appearance of the patches containing Kollidon® 30 was not satisfactory due to the precipitation of Kollidon® 30 in the PSA solution. To further investigate inhibition of crystallization, various polymers were screened in combination with Kollidon® 30. Among the additives screened in the combination system, only EC was compatible with Kollidon® 30, to form a homogenous film. However, similar with the case of Kollidon® 30, even in the combined system, crystallization could not be delayed for more than a month.

Since, satisfactory results were not obtained with Duro-Tak® 87-2510 based formulations, further studies were performed with Duro-Tak® 87-2516 matrix. The combined crystallization inhibitory system with EC and Kollidon® 30 was employed using Duro-Tak® 87-2516 matrix. Nevertheless, Brij® 52 induced crystallization of zolmitriptan could not be prevented in the Duro-Tak® 87-2516 matrix for more than a month.

3.6. Physical and chemical stability

Since the use of crystallization inhibitors was not successful, enhancers that would not cause crystallization were examined. Appearance of crystals was visually monitored. Among the formulations studied, the ones containing terpenes as enhancer remained clear with time. Permeation studies with aged samples (2 months in RT) did not show any reduction in permeation rate, indicating that the matrix might be physically stable. Patches containing terpenes were also observed for any change in morphology or crystals at various temperatures. Crystallization was found to be dependent on the storage temperature. At elevated temperatures crystals appeared in the patch at faster rate. Patches were stable at the storage condition of 40 °C for 2 months. However, spots appeared at 3rd month that developed into crystals. At 50 °C, spots appeared at 2nd month and the color 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 stability was also evaluated at various temperatures. The drug content in patches stored at 40 °C did not change for 3 months (Table 4). At 50 °C, drug content started to decline after 2 months. Patches stored at room temperature were visually monitored for appearance of crystals, and were found to be 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

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