International Journal of Pharmaceutics 394 (2010) 68–74

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Inhibition of crystallization in drug-in-adhesive-type transdermal patches

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ARTICLE INFO

Article history:
Received 20 February 2010
Received in revised form 25 April 2010
Accepted 26 April 2010
Available online 9 May 2010

Keywords:
Captopril
Levonorgestrel
Enhancer
Transdermal
Crystallization
Irritation testing

ABSTRACT

In this study the ability of various additives to inhibit crystallization of two model drugs, captopril and levonorgestrel, in acrylate and silicone adhesives was investigated. Among the various additives tested, PVP was found to be the most effective in inhibiting the crystallization of both drugs. Incorporation of PVP in patches (PVP stabilized patches) allowed incorporation of both drugs in amounts higher than their respective saturation solubility in pure adhesives (saturated patches). Skin permeation profiles of the drugs from the patches across hairless rat skin were obtained using Franz diffusion cells. For the hydrophilic drug captopril the skin flux over the first 24 h was the same for the saturated and PVP stabilized patches, but after 24 h the PVP stabilized patches produced higher skin flux values. However this may be because the saturated patch was depleted of the drug after 24 h. It is not clear if PVP performs as a solubilizer or a crystallization inhibitor for hydrophilic drugs. For the lipophilic drug levonorgestrel, the skin flux profile from the saturated and PVP stabilized patches was the same, suggesting that PVP acts just as a drug solubilizer and does not produce supersaturation.

1. Introduction

Drug-in-adhesive-type patches have been gaining increasing popularity as effective transdermal delivery systems during the last two decades (Chien, 1991; Lipp and Muller-Fahrnow, 1999). The concentration gradient of the drug between the delivery system and the skin is one of the important factors controlling the rate of percutaneous drug absorption (Lipp, 1998). Keeping this in mind, transdermal matrix type patches containing high concentrations of drug are generally preferred and required (Hadgraft, 1999; Latsch et al., 2004). Crystallization of drug is, however, a serious problem faced in formulating such a patch design (Variankaval et al., 1999; Minghetti et al., 2007). It not only makes the patch lose its aesthetic appeal after crystallization, but also makes the patch unstable, reduces the amount of drug present in the patch and decreases the original flux shown by a particular patch formulation (Ma et al., 1996; Kim and Choi, 2002). The recent withdrawal of Neupro (Rotigotine patch) from the market is an example of the severe implications crystallization can have on a patch formulation (http://www.neupro.com/Home/Home.asp).

In this study, various additives were investigated for their ability to inhibit the crystallization of drugs in adhesives. We defined crystallization inhibition as the prevention of crystal formation in patches by additives, due to (a) prevention of crystal nucleation, (b) adsorption of the additives onto crystals and (c) formation of amorphous additive/drug co-precipitates. In the cases mentioned above, the patches will be supersaturated and the patches stabilized with the additives would produce higher skin flux values than the patches that do not contain any additives. We also propose another mechanism of crystallization inhibition by an additive which can be acting as a solubilizer of the drug. In this case, since the prevention of crystallization is due to the fact that the additive simply increased the solubility of the drug in the patch, the skin flux from the saturated patches and from the additive stabilized patches will be the same. To study how additives affect crystallization, levonorgestrel (LNG) and captopril (CPT) were chosen as model drugs. Levonorgestrel is a progestin used in conjunction with estradiol to treat postmenopausal symptoms such as hot flashes and development of osteoporosis (Loose and Stancel, 2006). It is marketed as a transdermal patch with estradiol under the name Climara Pro™. The patch is 22 cm^2 in area and delivers 0.015 mg of levonorgestrel per day. The patch uses copovidone to prevent drug crystallization but delivery rates of more than 0.04 mg/day require a patch size of more than 30 cm^2 (Harrison et al., 2007). Captopril, on the other hand, is a competitive inhibitor of angiotensin-converting enzyme and is widely used in the treatment of hypertensive disorders. It is administered orally in dosages of 25–50 mg, two to three times a day. Transdermal delivery of both drugs is limited, in part because both drugs are known to crystallize in adhesives (Park et al., 2001; Harrison et al., 2007), making it difficult to design patches which are stable over time.

This study is focused on finding the saturation solubility of each of the two drugs in an acrylate (Duro-Tak 2516) and a silicone (Blend of 70% Bio Psa-4301 and 30% Bio Psa-4101) adhesive. To increase the amount of drugs which can be incorporated

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doi:10.1016/j.ijpharm.2010.04.042

in the adhesive, additives were added to inhibit crystallization. The additives which were screened for crystallization inhibition were poloxamer (Lutrol F127), polyvinylpyrrolidone (PVP 360) and copovidone (Kollidon VA64). The additives were tested for their ability to inhibit crystallization by a novel method of mixing the drug and the additive in an organic solvent and looking for crystals under a microscope after the solvent is evaporated. PVP, which was found to be the most effective additive in inhibiting the crystallization on the slides, was then used in patch formulations to test for the minimum concentration needed to inhibit crystallization. After stabilization of the patches, the transdermal delivery of the drugs from these patches was then tested using a hairless rat skin (HRS) model mounted on a Franz type diffusion cell assembly. Hairless rat skin data has been shown to be correlated to human skin in the past and several transdermal studies have been done and reported using the HRS model (Van Ravenzwaay and Leibold, 2004; Paturi et al., 2010). HRS model was selected over other hairy rodent models (such as Sprague–Dawley rats) as it correlates to human skin better as compared to other models (Godin and Touitou, 2007).

2. Materials and methods

2.1. Materials

Levonorgestrel and captopril were obtained from Sigma–Aldrich (St. Louis, MO, USA). poloxamer (Lutrol F127) and copovidone (Kollidon VA64) were obtained as gift samples from BASF, The Chemical Company (NJ, USA). PVP (PVP 360) was obtained from Sigma–Aldrich (St. Louis, MO, USA). Duro-Tak 2516 was gifted by National Starch & Chemical (Kleve, Germany). BIO-PSA 7-4301 and BIO-PSA 7-4101 were gifted by Dow Corning Corporation (Midland, MI, USA). Backing membrane 9734 and Release liner 9744 were obtained as gift samples from 3 M Scotchpak (St. Paul, MN, USA). HPLC grade methanol, tetrahydrofuran, propylene glycol and phosphoric acid were supplied by Fisher Scientific (Pittsburgh, PA, USA). Hairless rats were obtained from Charles River (Wilmington, MA, USA).

2.2. Preparation of microscopic slides for different additives

The drugs and the additives were dissolved in a minimum amount of an organic solvent in different ratios and then placed on microscopic slides. The solvent was then allowed to evaporate by keeping the slides at room temperature for 72 h. The slides were monitored for appearance of drug crystals visually and microscopically (Leica MZ6). Images were taken using a DFC camera attached to the microscope.

2.3. Preparation of drug in adhesive transdermal patches

The drugs were dissolved in a minimum amount of organic solvent and added to the adhesives under constant stirring with a magnetic bar. The solution was stirred for 15 min to ensure complete mixing. The drug containing adhesive mix was then cast on a release liner using a Gardner film casting knife (BYK-AG-4300 series, Columbia, MD) followed by drying in an oven at 70 °C for 30 min. The additive, PVP, was mixed in a minimum amount of organic solvent and added to the drug-adhesive mix while stirring. Oleic acid was also added to the adhesive mix in specified concentrations while stirring. After drying in the oven, the backing membrane was placed on the cast layer with the help of a roller. The patches were then observed under a microscope over the entire area for the presence of crystals.

2.4. Quantification of drug in patches

The amount of captopril present per cm^2 of patch area was determined for both saturated and PVP stabilized patches. For this, 1 cm^2 of the respective patches was cut ($n = 3$), the release liner was removed and the contents of the patch were extracted using 10 ml of methanol. The resulting mixture was centrifuged and the supernatant was analyzed for captopril by HPLC.

2.5. Skin permeation experiments

Skin permeation experiments were carried out for both drugs from solutions and patch formulations using hairless rat skin. Hairless rats weighing 350–400 g were euthanized using CO_2 asphyxiation. Abdominal skin was removed and underlying fat was cleared. The skin was cut in appropriate sizes and mounted on the Franz diffusion assembly (Logan, Somerset, NJ, USA) with the dermis side facing the receptor compartment. For permeation studies from solutions, the donor compartment consisted of 300 μl of the respective donor solutions for each of the drugs. For the patch permeation studies, the release liner was removed and the patch was applied on the stratum corneum side of the skin. The effective diffusion area was 0.64 cm^2. The receptor compartment was filled with 5 ml of propylene glycol and water in ratio of 1:1 and maintained at 37 °C. The receptor medium was stirred at 600 rpm and gentamycin sulfate in concentration of 80 mg/l was added to it to avoid microbial growth (Chisty et al., 2002; Valiveti et al., 2004). Receptor solution (0.5 ml) was taken out for each sample time point and replaced with fresh receptor medium. The samples were analyzed using the respective HPLC methods. Sink conditions were ensured by the high saturation solubility of levonorgestrel (250 μg/ml) and captopril (>80 mg/ml) in the receptor medium.

2.6. In vitro drug release studies

The release studies were performed using a modified Franz diffusion cell assembly (Jain et al., 2003; Gupta et al., 2009). The backing membrane side of the patches was stuck on a parafilm membrane which was bigger than the actual size of the patch with the help of a water impermeable adhesive. The release liner was removed and the patch was mounted on the diffusion cell with the patch facing the receptor compartment. The receptor compartment was filled with propylene glycol and phosphate buffer (pH 7.4) in ratio of 1:1 and maintained at 37 °C. The receptor medium was continuously stirred at 600 rpm and 0.5 ml of receptor solution was taken for each sample time point which was immediately replaced with fresh receptor solution. The samples were analyzed using the respective HPLC methods.

2.7. Quantitative analysis by high performance liquid chromatography

2.7.1. Analysis of levonorgestrel

HPLC analysis of levonorgestrel was performed according to Matejicek and Kuban (2007) with modifications. The assay was done on Waters Alliance 2695 separations module (Milford, MA, USA). The amount of levonorgestrel permeated in the receptor compartment was determined by spiking 10 μl of the sample onto a C_{18} column (Zorbax Eclipse XDB, 3.0 mm × 150 mm, 5 μm particle size). Elution was performed with methanol/water (7:3 v/v). The flow rate was 1.0 ml/min and the detection wavelength employed was 243 nm.

2.7.2. Analysis of captopril

HPLC analysis of captopril was performed according to Huang et al. (2002) with modifications. The assay was done on Waters

Alliance 2695 separations module (Milford, MA, USA). The amount of captopril permeated in the receptor compartment was determined by spiking 10 μl of the sample onto a C_{18} column (Altech, 4.6 mm × 150 mm, 5 μm particle size) maintained at 35 °C. Elution was performed with methanol/water (4.5:5.5, v/v) containing 0.016% phosphoric acid. The flow rate was 1.2 ml/min and the detection wavelength employed was 220 nm.

2.8. Assessment of irritation potential (IP) of oleic acid

IP of oleic acid was tested using Epiderm (EPI-200-SIT), a model of cell culture derived from human epidermal keratinocytes. Epiderm tissues were obtained and stored as per the protocol (EPI-200-SIT) supplied by MatTek. The irritation testing was done by exposing the tissues to 30 μl of the test substance (10% oleic acid in Propylene Glycol) for 1 h in triplicates and studying their effect on cell viability by the standard MTT assay provided in the protocol. The cell viability of the test solution was then compared to that of the negative controls to assess the IP. The test chemical was classified as irritant if the relative % cell viability of the test chemical was equal to or less than 50% of the negative control as per the protocol.

3. Results

3.1. Solubility of drugs in adhesives

The solubility of drugs was tested in acrylate (Duro-Tak 2516) and silicone (BIO-PSA) adhesives. Drugs were added to the adhesives in increasing concentrations (% w/w of final patch formulation). The maximum concentration at which the patches did not show any crystallization after 120 days was taken as the saturation solubility of the drug in the respective adhesive. Table 1 shows the maximum amount of drug which could be incorporated in the adhesives. Captopril could be added up to concentrations of 10.7% (w/w) and 0.75% (w/w) in acrylate and silicone adhesives respectively. Levonorgestrel could be added up to a concentration of 1% (w/w) in the acrylate adhesive whereas it showed crystallization even at the very low concentration of 0.037% (w/w) in the silicone adhesive.

Table 1
Saturation solubility of captopril and levonorgestrel in the two adhesives. Values indicate % (w/w) of the final patch formulation.

Adhesive	Drug	
	Captopril	Levonorgestrel
Duro-Tak 2516	10.7%	1%
Bio-Psa	0.75%	Crystallization seen even at 0.037%

3.2. Ability of additives to inhibit crystallization on slides

Various additives were tested for their ability to prevent crystal formation of levonorgestrel and captopril using the microscopic slide preparation method discussed earlier. The amount of crystals formed decreased with increase in the ratio of additive to drug (Figs. 1 and 2). For captopril, the ratios of additive to drug which could inhibit crystallization were 3:7, 1:1 and 6:4 for PVP, copovidone and poloxamer respectively. For levonorgestrel, the ratios of additives to drug which could inhibit crystallization were 6:4 and 7:3 for PVP and poloxamer respectively whereas for copovidone even at concentrations of 12 times that of drug some dendritic growth was seen occasionally (Table 2). Hence, PVP was found to be most effective in preventing crystal formation for both drugs and was used in further studies for inhibiting drug crystallization in patches.

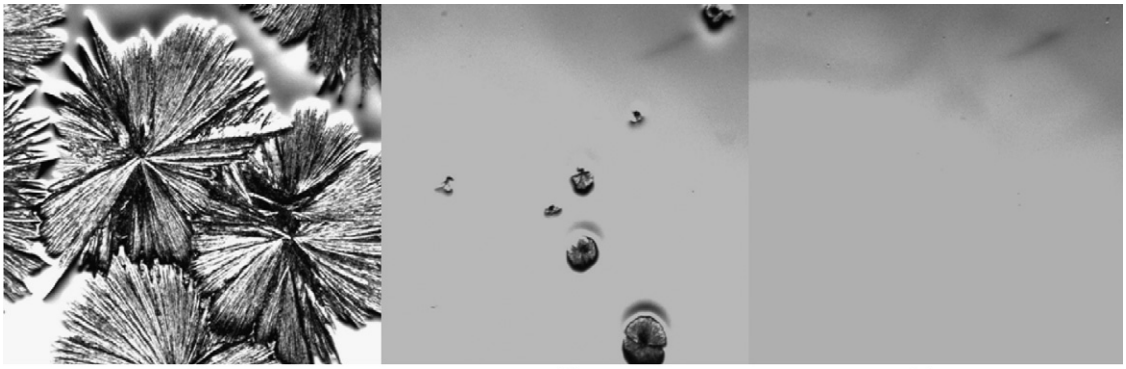

Fig. 1. Effect of addition of PVP on the crystallization of captopril on slides at different PVP to captopril ratios. (a) 1:9; (b) 2:8; (c) 3:7.

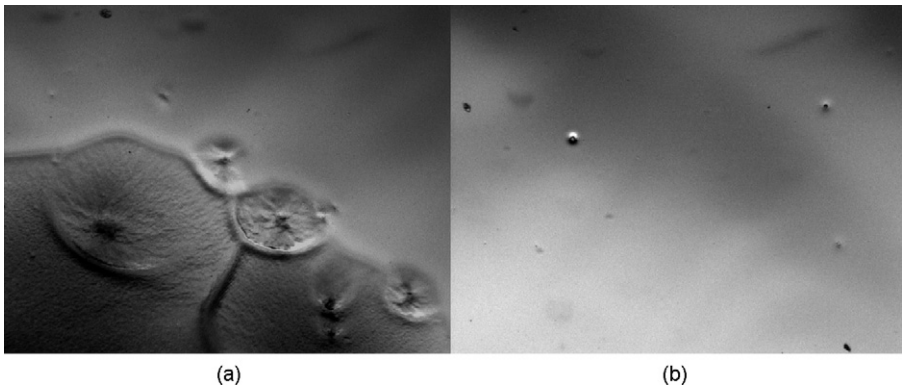

Fig. 2. Effect of addition of PVP on the crystallization of levonorgestrel on slides at different PVP to levonorgestrel ratios. (a) 1:1; (b) 6:4.

Table 2
Values reflecting the ratio of additive to drug needed to inhibit the crystallization of drugs on slides.

Additive	Drug	
	Captopril	Levonorgestrel
Poloxamer	6:4	7:3
PVP	3:7	6:4
Copovidone	1:1	Dendritic growth seen even at 12 times the amount of drug

Table 3
Ratio of PVP to drug needed to inhibit the crystallization of drugs in patches at specified concentrations (% w/w of the final patch formulation).

Adhesive	Captopril		Levonorgestrel	
	Concentration	Ratio of PVP to drug	Concentration	Ratio of PVP to drug
Duro-Tak 2516	21%	3:7	1.5%	17:1
Bio-Psa	3%	3:7	–	–

3.3. Crystallization inhibition by PVP in patches

The minimum amount of PVP needed to inhibit the crystallization of each of the drugs in patch formulations was tested using both adhesives. The drugs were added in concentrations twice of that showing crystallization in the patches without PVP. PVP was added in increasing concentrations till no crystallization was seen. The patches not showing any crystals after 120 days were considered stable. Table 3 shows the minimum amount of PVP needed for inhibiting the crystallization of the drugs. Figs. 3 and 4 show the microscopic images of crystals in pure adhesive patches and stabilized PVP patches. The stabilized patches were used in further experiments for assessment of skin permeation.

3.4. Quantification of drug in patches

The amount of captopril in saturated and PVP stabilized patches was found to be 1.27 ± 0.09 mg/cm^2 and 4.62 ± 0.1 mg/cm^2 respectively.

3.5. Skin permeation experiments

Skin permeation of levonorgestrel was studied from its 90% saturated solution in propylene glycol (PG) as donor solution. However, no detectable amount was found in the receptor compartment after 24 h. Hence, oleic acid was used as a permeation enhancer in a concentration of 10% (v/v). The 7-day permeation profile of levonorgestrel from its 90% saturation solution in PG using oleic acid as enhancer is shown in Fig. 5. Due to low drug solubility in PG (3.0 ± 0.2 mg/ml), only 810 ± 0.06 μg (300 μl of 90% saturation solubility) of drug was present in the donor compartment at the start of the study. The cumulative amounts of drug found in the receptor compartment after 2 and 3 days were 147 ± 25 μg and 230 ± 36 μg respectively which represent 18% and 28% of the total drug placed in the donor compartment. Hence, the decrease in flux after 3 days can be attributed, at least in part, to the depletion of the drug and reduction in the saturation level in the donor compartment. For the levonorgestrel permeation study from patches, two formulations were chosen. One patch had the saturation amount of the drug in Duro-Tak (1% w/w of adhesive) and the other had double the saturation amount in Duro-Tak (2% w/w of adhesive or 1.5% w/w of total

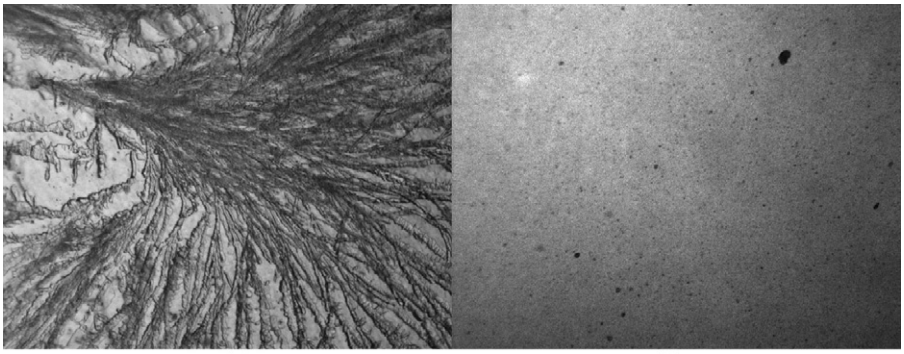

Fig. 3. Effect of addition of PVP on the crystallization of captopril in patches. (a) 13% (w/w) captopril patch without any addition of PVP after 5 days; (b) 21% captopril patch stabilized by addition of PVP in ratio of 3:7 after 120 days.

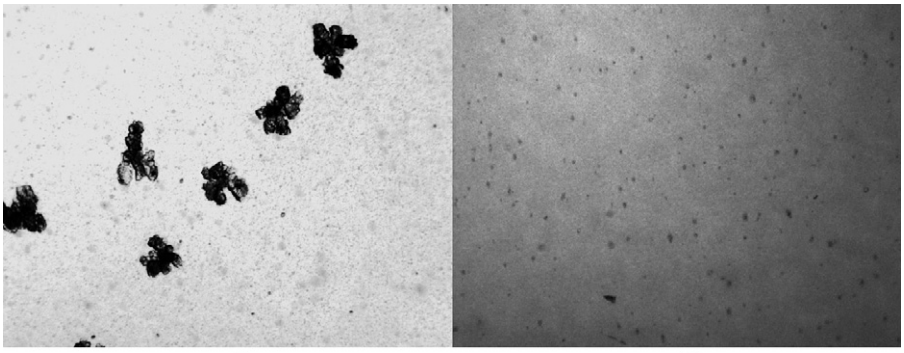

Fig. 4. Effect of addition of PVP on the crystallization of levonorgestrel in patches. (a) 1.2% levonorgestrel patch without any addition of PVP after 5 days; (b) 1.5% levonorgestrel patch stabilized by addition of PVP in ratio of 17:1 after 120 days.

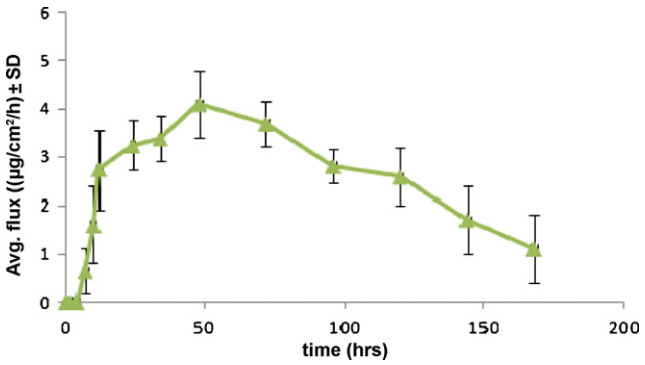

Fig. 5. Permeation profile of levonorgestrel from its 90% saturated solution in propylene glycol and 10% oleic acid.

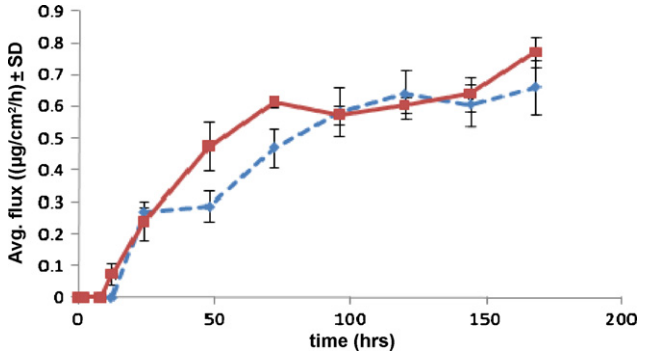

Fig. 6. Permeation profiles of levonorgestrel from patch formulations. Solid squares: patch of 1.5% levonorgestrel stabilized by addition of PVP. Solid diamonds: patch of 1% levonorgestrel with no PVP.

patch formulation), stabilized by PVP. Both patches also contained 10% oleic acid as the permeation enhancer. The permeation profiles from these patches are shown in Fig. 6. The steady state flux from both patches was reached after about 3 days and remained constant thereafter till 7 days. Increasing the amount of drug in patches by addition of PVP did not have any effect on the permeation profile of levonorgestrel. Both patches showed the same flux and cumulative amount values throughout the period of study.

The permeation profile of captopril from its 90% saturated solution in PG is shown in Fig. 7. This was followed by permeation studies from patches. The initial studies were performed using the saturated patch of captopril in Duro-Tak. The study showed very minimal amounts of captopril permeating in the receptor compartment after 24 h. Hence, oleic acid was added as a permeation

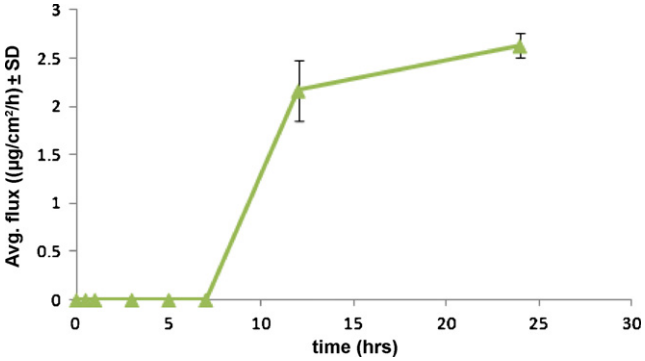

Fig. 7. Permeation profile of captopril from its 90% saturated solution in propylene glycol.

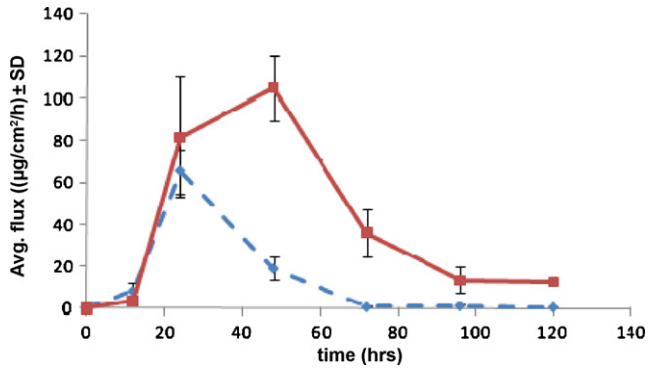

Fig. 8. Permeation profiles of captopril from patch formulations. Solid squares: patch of 21% captopril stabilized by addition of PVP. Solid diamonds: patch of 10.7% captopril with no PVP.

enhancer. Permeation studies were performed using two patch formulations. One patch had the saturated concentration of captopril (10.7%, w/w) in Duro-Tak and the other patch had about double the saturated concentration of captopril in Duro-Tak (21%, w/w), stabilized by PVP. Both patches also contained 10% oleic acid as the permeation enhancer. Fig. 8 shows the permeation profile of captopril from these patches. The flux from saturated patches reached the peak in 24 h and decreased thereafter. The PVP stabilized patches showed the same flux as the saturated patches for the initial 24 h but could maintain higher flux values after this for the entire period of the study, with the peak flux in 48 h, since the saturated patches were totally depleted of captopril before the 48 h time interval.

3.6. *In vitro drug release studies*

The cumulative release profiles from the saturated and PVP stabilized patches of levonorgestrel and captopril are shown in Figs. 9 and 10 respectively. The patches showed a steady and continuous release of drugs indicating that the drugs were dissolved in their respective patches uniformly. The release kinetics also followed a square root of time relationship in all the patches.

3.7. *IP assessment*

The relative % viability of 10% oleic acid solution in propylene glycol was found to be 96 ± 12% as shown in Fig. 11. Hence the solution was classified as non-irritant.

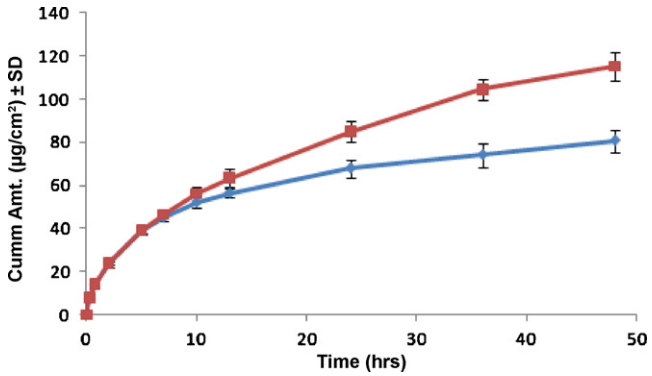

Fig. 9. Cumulative release profiles of levonorgestrel from patch formulations. Solid squares: patch of 1.5% levonorgestrel stabilized by addition of PVP. Solid diamonds: patch of 1% levonorgestrel with no PVP.

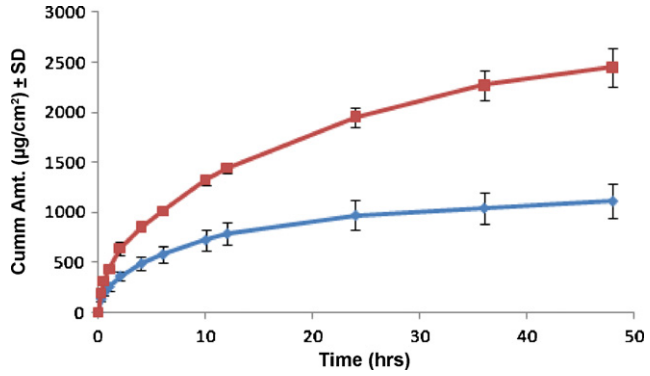

Fig. 10. Cumulative release profiles of captopril from patch formulations. Solid squares: patch of 21% captopril stabilized by addition of PVP. Solid diamonds: patch of 10.7% captopril with no PVP.

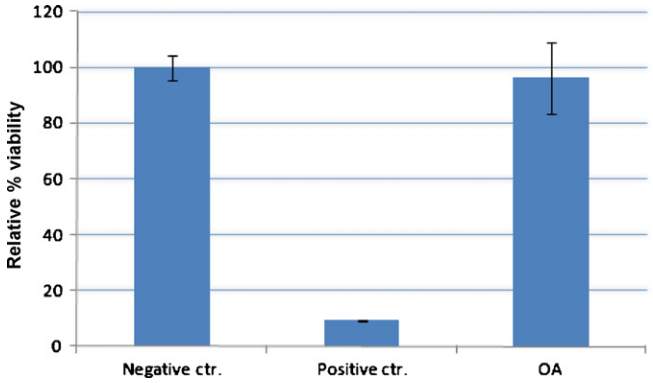

Fig. 11. IP testing of oleic acid. Negative control: solution of PBS, positive control: solution of 5% SDS, and OA: solution of 10% oleic acid in propylene glycol.

4. Discussion

There is a plethora of evidence in literature suggesting the improvement in transdermal delivery of a drug by use of penetration enhancers (Kanikkannan et al., 2000; Ibrahim and Li, 2009) or increasing the drug loading of the system (Li, 2007). The drug loading in a system can however be increased only up to the saturation solubility of the drug in that particular system. For example, while preparing a drug in adhesive transdermal system by solvent cast methods the saturation solubility of the drug in the adhesive is an important determinant of maximum drug loading. After dissolving the drug in a solution of the adhesive in organic solvent(s), the resulting wet matrix is coated onto a release liner and the organic solvent is evaporated. The process may lead to production of a supersaturated matrix if the drug loading is more than the saturation solubility of the drug in the resulting adhesive. Such a supersaturated matrix is unstable and the drug will recrystallize in such systems over time (Hadgraft, 1999; Latsch et al., 2004; Cilurzo et al., 2005). Recrystallization may however not be apparent immediately after manufacture because of the relatively low diffusion coefficients of drug in such highly viscous systems and the requirement of nucleation for the initiation of crystallization.

In the present study the effect of the nature of drug and adhesive on the saturation solubility of the drug was evaluated. A lipophilic drug, levonorgestrel ($\log P \sim 3.8$) and a relatively hydrophilic drug, captopril ($\log P \sim 1.9$) were chosen and solubility of these drugs were determined in an acrylate (Duro-Tak 2516) and a silicone (Blend of 70% Bio Psa-4301 and 30% Bio Psa-4101) adhesive. The drug solubility data for both drugs in the adhesives suggested that a hydrophilic drug (captopril) is more soluble in both adhesives as compared to a lipophilic drug (levonorgestrel). This is also in accordance with the fact that DURO-TAK 387-2516 is a vinyl acetate/acrylate copolymer that contains a relatively high level of hydroxy functional acrylate (2-hydroxyethyl acrylate) which makes it more hydrophilic than all acrylic copolymers (Y.T. Choi, Henkel Corporation, personal communication). Therefore, the saturation solubility of captopril in both adhesives was found to be higher than that of levonorgestrel.

Incorporation of a drug in amounts higher than its saturation solubility in an adhesive requires the addition of additives which stabilize the systems against crystallization. This stabilization can be due to the additional solubility of the drug in the additive or due to some special property of the additive such as adsorption of drug crystals in the additive. Among the various additives tested, PVP was found to be the most effective additive in inhibiting the crystallization of both drugs. The ability of PVP to inhibit crystallization and form the amorphous co-precipitates with several drugs had previously been suggested (Ohm, 2000; Gong et al., 2005). Such high energy amorphous drug phases are also shown to have increased membrane transport through cellophane or rat gut membranes. However, no study is known to involve skin as the membrane but similar enhancements are also postulated with skin (Corrigon, 1995). Furthermore, PVP has also been shown to get adsorbed on growing crystal surfaces and inhibit crystallization of drugs in suspensions (Ma et al., 1996; Raghavan et al., 2001). The adhesives act as solvents for drugs, and PVP can interact with drugs by getting adsorbed on the crystal surfaces and inhibit crystallization. As mentioned in Tables 2 and 3, the higher amount of PVP needed in patch formulations as compared to those needed on slides can be due to the higher viscosity of the patch formulations and the difficulty that they may present in allowing the interactions between PVP and the growing drug crystals.

Addition of PVP enables higher amounts of drug loading in the adhesives, without drug crystallization occurring. However, for levonorgestrel, this increase in drug loading did not translate into increase in the permeation across the skin. Taking into consideration that permeation or flux across the skin is an inherent property of saturation level or thermodynamic activity of drug in the donor phase (Barry, 2001; Moser et al., 2001), PVP can be said to have acted just as a solubilizer for this drug. As such it did not change the saturation level or flux across skin for levonorgestrel. This is also supported by the release profile of levonorgestrel from its saturated and PVP stabilized patches which also remained same initially for both the patches. The effective steady state plasma concentration of levonorgestrel needed for treatment of hot flashes and osteoporosis require a delivery of 0.015–0.045 mg/day which correspond to delivery rate of 0.625 and 1.875 µg/h. The steady state flux obtained from the PVP stabilized patch of levonorgestrel (0.6 µg/cm^2/h) can enable the required delivery of 0.04 mg/day (1.66 µg/h) from a small patch. It can also lead to formulation of patch dosage form of levonorgestrel for the purpose of contraception which needs higher delivery rates of 0.08–0.125 mg/day. The concentration of oleic acid used in the patches was found to be non-irritant. However, the assay used is just a preliminary estimate and final prediction of irritation behavior should be done with in vivo studies with longer exposure times. In addition, PVP is known to have the inherent property of acting as a humectant. As such it can absorb water which is lost from the skin during the period of patch application and thus act as an anti-irritant (Chien, 2006; Chien, 2008).

For captopril, the PVP stabilized patches showed same flux for the initial 24 h but showed higher flux rates after 24 h as compared to saturated patches. The decrease in flux from the saturated patches after 24 h can be due to the decrease in saturation levels (to 32% of starting levels) of captopril in the patch after significant amounts of drug have permeated in the receptor compartment (884 ± 177 µg). However, for PVP stabilized patches permeation

of same amounts of drug in the receptor compartment after 24 h does not decrease the saturation levels to the same extent (to 78% of starting levels). This is due to higher amount of drug incorporated in the patch with PVP (4.62 ± 0.1) as mentioned earlier. The equivalence of skin flux from the two systems for the first 24 h of experimentation suggests again that PVP is acting as a solubilizer in the case of captopril as well. However as the saturated patch is almost entirely depleted of the drug during 24–48 h, it is not accurate to compare the flux from the saturated and PVP stabilized patches after this period. Therefore, PVP stabilized patches show higher flux rates after 24 h as compared to saturated patches. The highest amount of flux obtained from the PVP stabilized patches was $104.86 \pm 15.18\ \mu g/cm^2/h$. The lag time was between 8 and 12 h and the flux levels could be maintained above $40\ \mu g/cm^2/h$ for around 72 h. The lag time can possibly be further reduced by increasing the drug loading of the systems. In previous studies (Kobayashi et al., 1993; Park et al., 2001), the permeation rate of captopril through skin needed to maintain an effective plasma concentration is mentioned to be 1488 μg/h. Assuming a patch size of 30 cm^2, the flux rate of 49.6 $\mu g/cm^2/h$ is needed to achieve this concentration level. The patch prepared in this study could deliver the drug at this rate for at least 72 h and from a much smaller patch size area.

In conclusion, for the lipophilic drug levonorgestrel, the inclusion of additives such as PVP prevents crystallization by increasing the solubility of levonorgestrel in the adhesive plus PVP matrix. The flux obtained from the saturated and PVP stabilized patches were the same, indicating that no supersaturation was achieved from the PVP stabilized patches. For the hydrophilic drug captopril, the data suggests that the solubility of the drug in PVP is also important in the prevention of crystallization of this drug. Direct comparison between the saturated and PVP stabilized patches could be made only up to the 24 h testing period, because the saturated patch was totally depleted before the 48 h time period. However, other factors such as the effect of imbibed water and other parameters will need to be investigated before a final conclusion can be reached.

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