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RESEARCH PAPER

Induction and Inhibition of Crystallization in Drug-in-Adhesive-Type Transdermal Patches

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ABSTRACT

Purpose To screen crystallization inhibitors, perform accelerated stability testing and predict saturation solubility of levonorgestrel in drug-in-adhesive patches.

Methods Differential scanning calorimetry (DSC) studies were compared against slide crystallization studies for screening additives. Release studies were performed from crystallized and supersaturated patches. Die cutting was used for accelerated stability testing of patches. Time lag experiments were performed to predict saturation solubility of levonorgestrel in acrylate adhesive, DuroTak-2516.

Results DSC studies indicated poloxamer to be the best additive whereas slide crystallization studies showed polyvinylpyrrolidone to be better. Supersaturated patches showed higher release profiles relative to crystallized patches. Crystals were observed in crystallized patches even after 96 h of release studies. Die-cutting of patches helped in development of crystals in less time as compared to uncut sheets indicating its usefulness in accelerated stability testing. Saturation solubility of levonorgestrel in DuroTak-2516 was predicted to be 0.09% *w/w* which was in close agreement with value of 0.1% *w/w* from solubility calculator on vendor's website.

Conclusions Crystallization was shown to have negative impact on drug release and patch performance. Slide crystallization studies, die cutting and time lag experiments can be used as tools to help stabilize the otherwise unstable patches.

KEY WORDS adhesive · crystallization · die-cutting · levonorgestrel · transdermal

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INTRODUCTION

Transdermal drug delivery systems have been gaining increasing popularity among delivery systems on market. The rate at which a transdermal product is coming to the market has tripled since 2002 with a new transdermal product now being launched every 7.5 months (1). Among the different designs of transdermal patches available on market, drug-in-adhesive (DIA) systems are the most popular ones. The recent change of patch design from reservoir to drug-in-adhesive for Duragesic (fentanyl) patch can exemplify the benefits such as no leakage or dose dumping, which a DIA design offers. The drug-in-adhesive patches, however, suffer from their own limitations. Crystallization of drug in these kinds of patches is one of such serious problems the industry is facing at present (2–4). Neupro (Rotigotine) patch marketed by Schwarz Pharma was withdrawn from the market in 2008 due to development of snow flake crystals (5).

Several additives have demonstrated effectiveness in inhibiting crystallization of drugs in DIA patches (3,4,6). They are believed to act by prevention of crystal nucleation, adsorption onto crystals, or forming additive/drug co-precipitates (7,8). All these mechanisms would however lead to generation of supersaturated patches and increase the permeation and release profile of drugs. Based on recent studies, solubilization of drug without creation of supersaturated state seems to be a more important phenomenon for achieving crystallization inhibition using additives. In this study, slide crystallization studies were compared to differential scanning calorimetry (DSC) studies to screen additives for their crystallization inhibition/ drug solubilization potential. Levonorgestrel was selected as the model drug, due to high probability of crystallization in patches, while Poloxamer (Lutrol F127), Polyvinylpyrrolidone (PVP 360), and Copovidone (Kollidon VA64) were screened for their crystallization inhibition effects. Levonorgestrel is a progestin and is marketed as a transdermal patch with estradiol under the name Climara Pro™. It has a very low water solubility of 1.4 mg/l and a logP of 3.37 (9,10). Moreover, transdermal delivery of levonorgestrel is limited to some extent from patch delivery systems, because it is known to crystallize in adhesive, making it difficult to design patches which are stable over time (11). In Climara Pro™ patches, there are no reported stability issues till date; the formulation contains copovidone as an excipient which might be stabilizing the patches against crystallization.

DSC studies have been used in the past to predict interactions between drugs and additives as well as to screen crystallization inhibitors (8,12). In this study, we present another method of screening known as slide crystallization study which when used in conjunction with DSC can predict results more accurately. Actual patches were made with levonorgestrel and additives to confirm the results from both studies.

To understand how crystallization can affect performance of transdermal patches after marketing, release studies were performed. Patches were made fresh before each experiment and compared to patches which were stored at room temperature for one month to allow crystallization to occur. Patches of levonorgestrel were prepared in an acrylate (Duro-Tak 2516) adhesive in concentrations above saturation solubility using solvent cast method and release studies were carried out via a Franz type diffusion cell assembly. Crystallization in patches is generally a very slow process and may not be apparent immediately after manufacturing the product. On the other hand, long term stability studies in which patches are made with different concentrations of drug and monitored for long periods of time are very cumbersome and time consuming. Accelerated stability testing of patches can therefore be of great advantage and need to study the process of crystallization in patches. Cutting the patches with a die has been shown to induce stress and accelerate the process of crystallization (13,14). Patches with different concentrations of levonorgestrel were consequently prepared followed by comparing die-cut patches to uncut sheets for time taken to observe formation of initial crystals. Patches were also made with different concentrations of levonorgestrel and stored at room temperature and at −20°C to examine the effect of temperature on process of crystallization.

Drug solubility in transdermal adhesives is a critical factor which determines the amount of drug which can be added and act as a driving force in a transdermal patch. Attempts have been made in the past to predict saturation solubility of drugs in adhesives. Solubility calculator available on www.transdermaladhesives.com (15) gives as estimation of drug solubility in a range of DuroTak adhesives. Similarly, Myatt *et al.* (16) tried to predict the solubility of fluoroscene in a polymer using Higuchi kinetics of release of fluoroscene from patches of different concentration. We used a new approach of diffusion across a thin layer of polymer to predict saturation solubility of levonorgestrel in DuroTak 2516. DuroTak is a series of acrylate adhesives in which the individual adhesives differ from each other in the properties of their polymers. DuroTak 2516 is a vinyl acetate/acrylate copolymer that contains a relatively high level of hydroxy functional acrylate (2-hydroxyethyl acrylate), and therefore is one of the most hydrophilic adhesives (7). When a drug is allowed to diffuse across a polymer membrane, from its infinite source, on one side to sink conditions to the other side, a classical time lag situation is created where after some time the drug diffuses across the membrane at a constant rate (17,18). This rate can be illustrated by the following correlation:

$$(dQ/dt)ss = DCs/l \tag{1}$$

Where (dQ/dt)ss is the rate of diffusion at steady state, D is the diffusion coefficient of drug in the polymer, Cs is the saturation solubility of drug in polymer, and l is the thickness of membrane. Also the lag time, T, can be given by equation:

$$T = l^2/6D \tag{2}$$

Combining both equations will yield:

$$(dQ/dt)ss = lCs/6T \tag{3}$$

Thus, the measurement of steady state slope of a plot of Q *vs* t {(dQ/dt)ss} and lag time (T) by extrapolation of the curve to x axis can give us the value of both D and Cs.

MATERIAL AND METHODS

Materials

Levonorgestrel was obtained from Sigma Aldrich (St. Louis, MO, USA). Poloxamer (Lutrol F127) and Copovidone (Kollidon VA64) were obtained as gift samples from BASF (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). Backing membrane 9734 and Release liner 9744 were obtained as gift samples from 3M Scotchpak (St. Paul, MN, USA). HPLC grade Acetonitrile and Propylene glycol was supplied by Fisher Scientific (Pittsburgh, PA, USA).

Preparation of Microscopic Slides for Different Additives

The drug and 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 under polarized light (Leica DM750). Images were taken using a DFC camera attached to the microscope.

Differential Scanning Calorimetry

Thermal measurements were performed with a TA instrument (Newcastle, DE) DSC-2910 equipped with a TA instrument computer. In DSC, standard open pans of aluminum were used as sample holder and reference. A total of 5 mg of sample was loaded in pans for measurements. Samples were analyzed under a constant flow of nitrogen with scanning rate of 10 Kmin^{-1}. At least three replicates of each measurement were performed. Scans were first run for pure levonorgestrel and then for mixtures of levonorgestrel and copovidone, PVP or poloxamer in different ratios but keeping the weight constant as 5 mg.

Preparation of Drug in Adhesive Transdermal Patches

Levonorgestrel was added to the adhesive under constant stirring with a magnetic bar. The solution was stirred overnight 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 or poloxamer, was also added with levonorgestrel to the adhesive mix while stirring wherever needed. 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 microscopically under polarized light (Leica DM750) over entire area for presence of crystals.

In Vitro Drug Release Studies

The release studies were performed using a modified Franz diffusion cell assembly (PermeGear, Hellertown, PA, USA) (19,20). 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 water 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

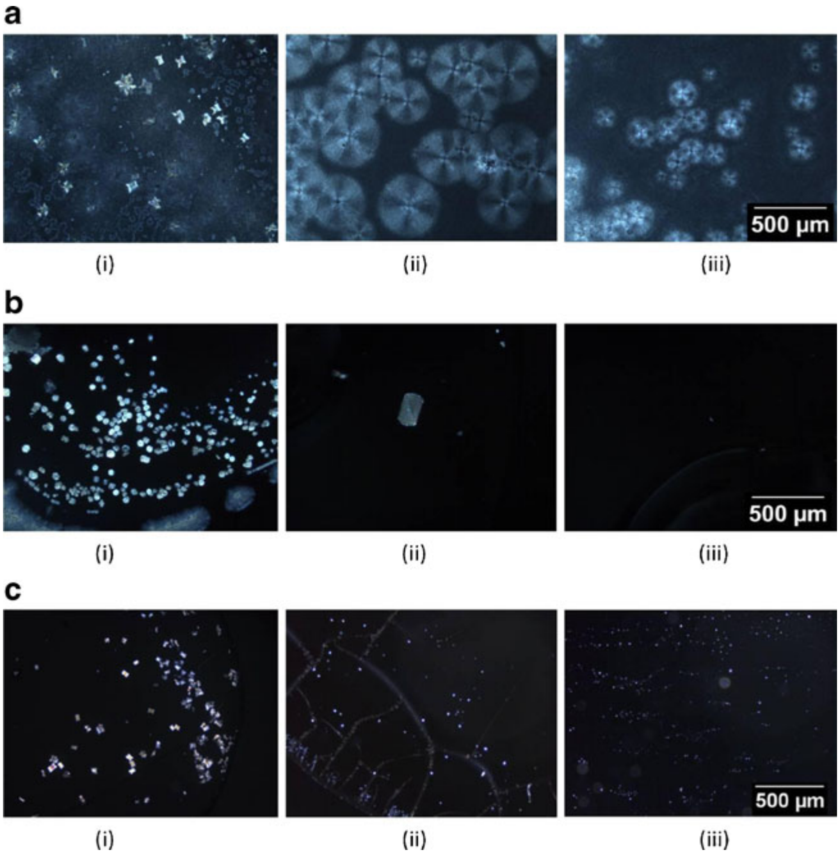

Fig. 1 (**a**) Effect of addition of poloxamer on crystallization of levonorgestrel in different poloxamer to levonorgestrel ratios, (*i*) 8:2, (*ii*) 9:1, (*iii*) 10:1. (**b**) Effect of addition of PVP on crystallization of levonorgestrel in different PVP to levonorgestrel ratios, (*i*) 6:4, (*ii*) 7:3, (*iii*) 8:2. (**c**) Effect of addition of copovidone on crystallization of levonorgestrel in different copovidone to levonorgestrel ratios, (*i*) 8:2, (*ii*) 9:1, (*iii*) 10:1.

Table I The Ratio of Additive to Drug Needed to Inhibit the Crystallization of Levonorgestrel on Slides

Additive	Ratio of additive to levonorgestrel needed to inhibit crystallization
Poloxamer	Crystals seen even at 10 times the amount of drug
PVP	8:2
Copovidone	Crystals seen even at 10 times the amount of drug

Table II Calorimetric Data for Levonorgestrel and Different Additive Systems

Additive	Ratio of additive to levonorgestrel	Enthalpy (J/g)		% Difference
		Experimental	Expected	
Pure drug	–	130.2 ± 10.2	–	–
PVP	5:5	48.22 ± 3.3	65.1	25.92
	7:3	28.70 ± 0.2	39.06	26.53
Poloxamer	5:5	30.76 ± 1.8	65.1	52.74
	7:3	17.1 ± 0.3	39.06	56.2
Copovidone	5:5	53.6 ± 2.0	65.1	17.66
	7:3	31.23 ± 1.1	39.06	20.04

replaced with fresh receptor solution. The samples were analyzed using HPLC method. Patches were also taken off from the Franz cells at specific time points in between and observed under the microscope for the presence of crystals.

Quantitative Analysis by High Performance Liquid Chromatography

HPLC analysis of levonorgestrel was performed 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, 3.0×150 mm, 5 μm particle size). Elution was performed with acetonitrile/water using gradient system. The flow rate was 0.6 mL/min and the detection wavelength employed was 243 nm.

Accelerated Stability Testing with Die Cutting

Drug in adhesive patches were made with different concentrations of levonorgestrel. Individual patches of 5 cm^2 were cut out of one complete sheet using a circular die. The cut patches were stored at room temperature in ziplock bags and observed under polarized light microscope at regular intervals for the presence of crystals. Uncut sheet of patches with same concentration of levonorgestrel were also stored in same conditions as die-cut patches to serve as controls. Time required for crystals to appear for first time in both kinds of patches were noted and compared.

Effect of Storage Conditions

Drug in adhesive patches were made with different concentrations of levonorgestrel. Patches were packed in ziplock bags and one batch was stored at room temperature and other batch was stored at −20°C in the refrigerator. The

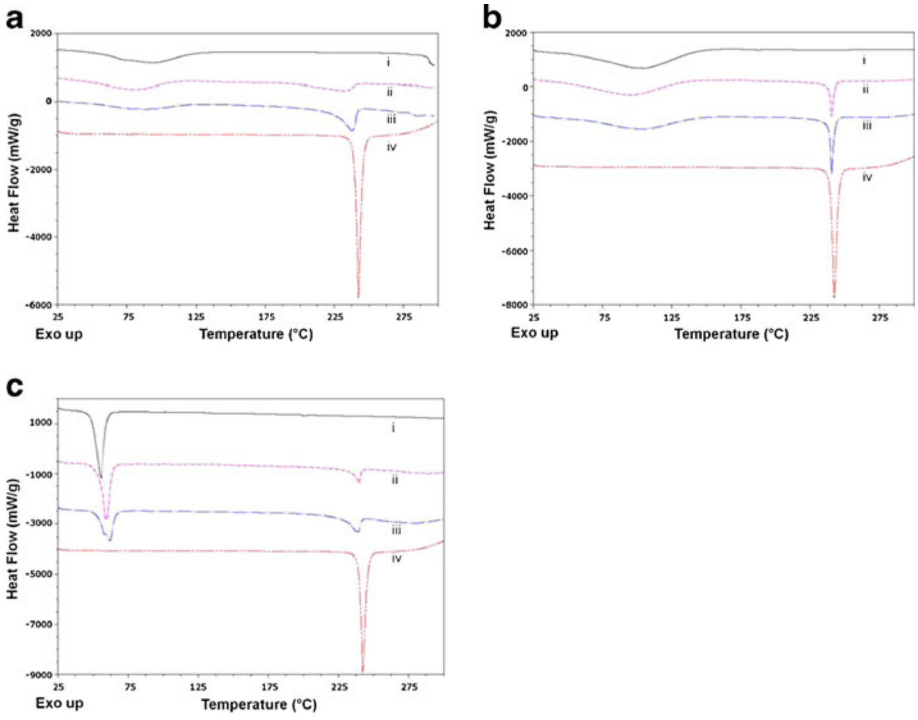

Fig. 2 DSC curves of levonorgestrel and different additive systems: (**a**) copovidone, (**b**) PVP, (**c**) poloxamer, *Curve I*: pure additive; *Curve II*: additive to levonorgestrel = 7:3; *Curve III*: additive to levonorgestrel = 5:5; *Curve IV*: pure levonorgestrel.

patches were taken out of the bags and observed under polarized light microscope for presence of crystals at regular intervals. Time required for crystals to appear for first time was noted for both storage conditions.

Time-Lag Experiment

Placebo patches were made with adhesive DuroTak 2516 similar to normal patch preparation process as described earlier in section "Preparation of Drug in Adhesive Transdermal Patches" except that the patches were first made on a dialysis membrane (molecular weight cut off 14 KD) instead of release liner and then covered with release liner after drying. This was done so that the drug could diffuse form one compartment to other after the release liner is taken off and the patch is loaded between two compartments of the side by side diffusion cell (PermeGear, Hellertown, PA, USA). The thickness of prepared patches was measured with the help of vernier calipers. The diffusion experiments were carried out using side-by-side diffusion cell assembly. The release liner was taken off and patch was placed between the two compartments of Franz cells with dialysis membrane facing the left hand side compartment of the side by side Franz cell. The right hand side compartment was filled with suspension of levonorgestrel in propylene glycol and water in ratio of 1:1 containing extra undissolved drug to maintain a constant source of drug during diffusion. The left hand side compartment was filled with propylene glycol and water in ratio of 1:1. The effective diffusion area was 0.64 cm^2 and the solutions were stirred at 600 rpm. Sampling was done from the left hand side compartment at predetermined time points where the entire compartment was emptied and refilled to ensure perfect sink conditions. Samples were analyzed using HPLC method as described before.

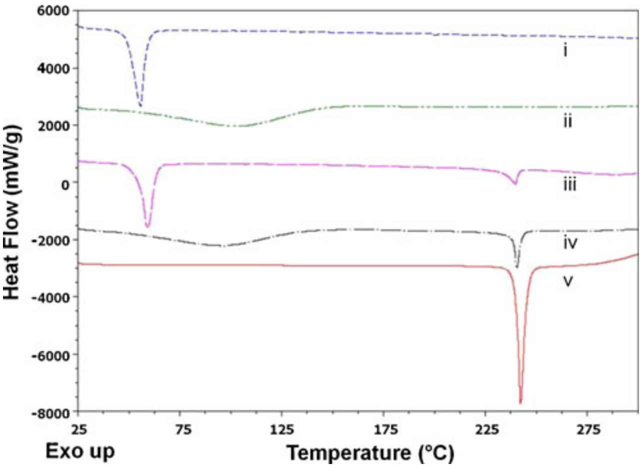

Fig. 3 Comparison of DSC curves of mixture of poloxamer and PVP with levonorgestrel in ratio of 7:3, *Curve I*: pure poloxamer, *Curve II*: pure PVP, *Curve III*: poloxamer with levonorgestrel, *Curve IV*: PVP with levonorgestrel, *Curve V*: pure levonorgestrel.

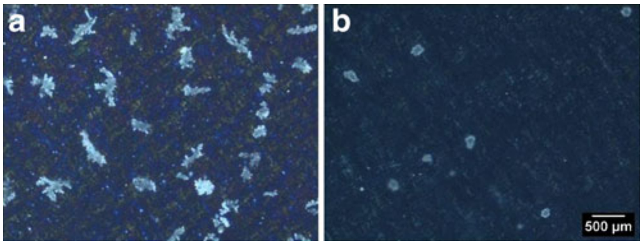

Fig. 4 Effect of addition of poloxamer (**a**) and PVP (**b**) on crystallization of levonorgestrel in patches of 1.18% *w/w* levonorgestrel and 11.76% *w/w* additives (image taken after 120 days).

RESULTS

Ability of Additives to Inhibit Crystallization on Slides

Various additives were tested for their ability to solubilize and prevent crystal formation of levonorgestrel using the microscopic slide preparation method discussed earlier. The

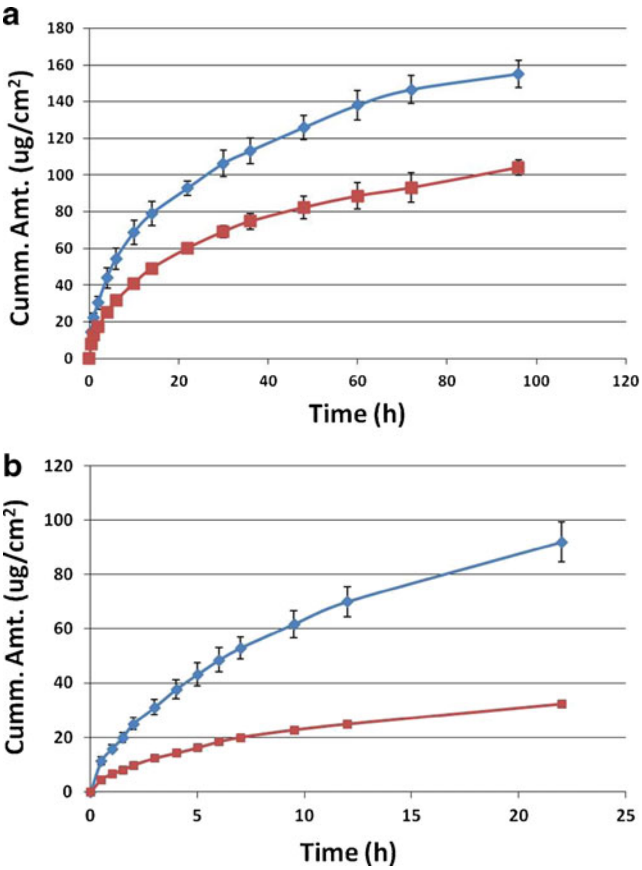

Fig. 5 Release profiles of levonorgestrel from its 1% (**a**) and 0.4% (**b**) *w/w* patches. *Solid squares*: Crystallized patches; *Solid diamonds*: Supersaturated patches (± SD, *n*=3).

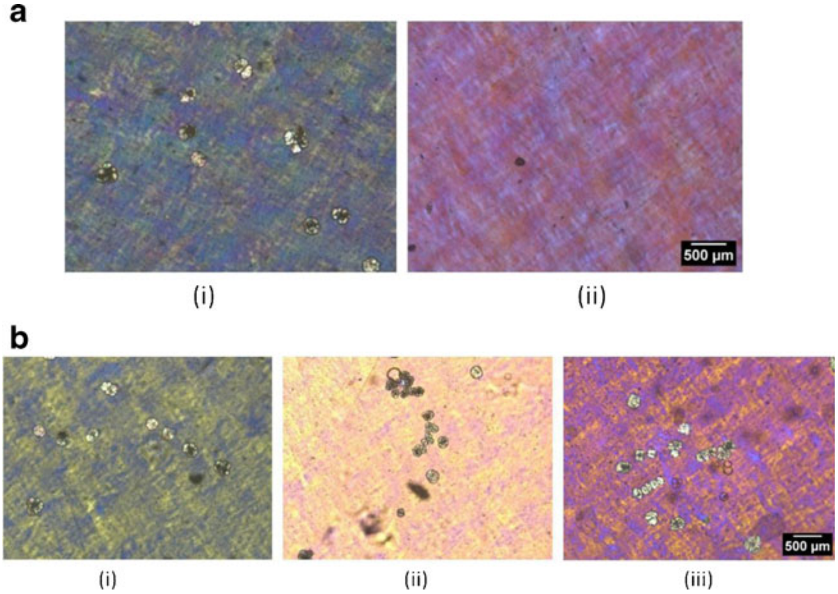

Fig. 6 (**a**) Images taken before release of levonorgestrel from a 1% *w/w* patch (*i*) crystallized patch; (*ii*) supersaturated patch. (**b**) Images taken after release of levonorgestrel from a 1% *w/w* crystallized patch (*i*) after 48 h; (*ii*) after 72 h and (*iii*) after 96 h.

amount of crystals formed decreased with increased ratio of additive to drug (Fig. 1a, b and c). The ratios of additives to drug which could inhibit crystallization were 8:2 for PVP whereas for poloxamer and copovidone, crystallization was seen even at 10 times the concentration of drug (Table I). Hence, PVP was found to be most effective in preventing crystal formation for levonorgestrel.

DSC Results

The DSC curves for levonorgestrel and its combination with copovidone, PVP and poloxamer in different ratios are shown in Fig. 2a, b and c, respectively. DSC curve of pure levonorgestrel shows a sharp endothermic peak due to melting (peak max 240°C; enthalpy change 130.2±10.2 J/g). Pure copovidone, PVP and poloxamer show single endothermic peaks at their respective melting points of 92.83, 105.62, and 55.76°C. Combination runs of additives with levonorgestrel show indication of interaction. Melting peaks of levonorgestrel become broader and there is a decrease in mean enthalpy values by around 17%, 25% and 52% with respect to the value calculated on basis of melting enthalpy of pure levonorgestrel for copovidone, PVP and poloxamer, respectively (Table II). Comparison of PVP and poloxamer, as shown in Fig. 3, indicates more interaction of levonorgestrel with poloxamer as compared to PVP, suggesting poloxamer to be a better crystallization inhibitor.

Solubilization of Levonorgestrel by PVP and Poloxamer in Patches

Patches of levonorgestrel were made in DuroTak-2516 in concentration above saturation (1.18% *w/w*) and PVP and poloxamer were added in same amounts (11.76% *w/w*) to

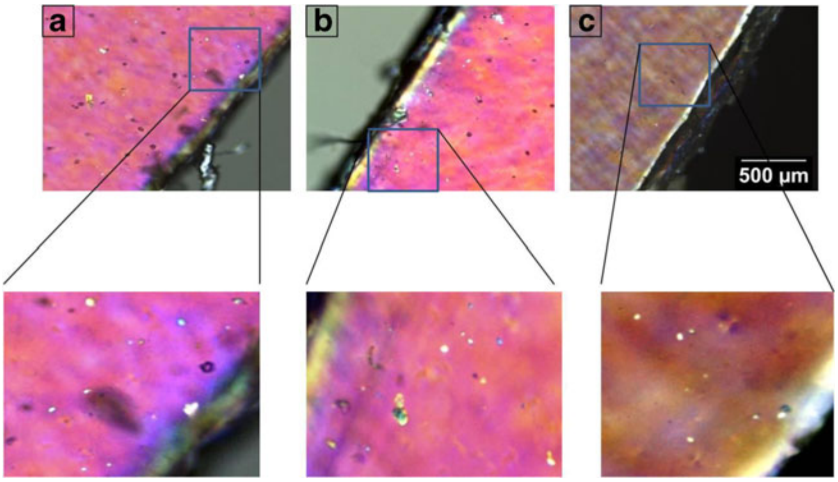

Fig. 7 Images of die-cut patches of levonorgestrel (**a**) 1% *w/w* after 1 day; (**b**) 0.6% *w/w* after 4 days and (**c**) 0.4% *w/w* after 6 days.

solubilize levonorgestrel. Figure 4 shows the microscopic image of both these patches after 120 days. Crystals bigger in size and more in number could be seen in patches made with poloxamer as compared to patches made with PVP.

Release of Levonorgestrel from Patches

The release profile of levonorgestrel from its 1% *w*/*w* supersaturated and crystallized patches is shown in Fig. 5a. The supersaturated patches showed higher release profile as compared to crystallized patches. Similar trend was also observed with 0.4% *w*/*w* patches as shown in Fig. 5b. Patches were also taken off and observed under the microscope during the release study. Figure 6a shows images of 1% crystallized and supersaturated patches before starting the release study whereas Fig. 6b shows images of patches taken out off at 2, 3 and 4 day time points for a 1% *w*/*w* crystallized patch. The images show presence of crystals even after 4 day time point.

Effect of Die Cutting

Die cutting induced crystallization in patches. Development of crystals was seen more at the edges of cut patches as compared to center. Figure 7 shows microscopic images of die-cut patches of levonorgestrel at different concentrations. Time taken for first crystals to appear increased with decrease in amount of drug added in patches. Comparison of time taken for first crystals to appear for die-cut and non die-cut patches is shown in Table III. Die-cut patches showed crystals faster as compared to non die-cut patches.

Effect of Storage Temperature

Images taken for patches stored at room temperature and at −20°C are shown in Fig. 8a and b. Time taken for first crystals to appear increased with decrease in concentration of levonrorgestrel for patches stored at room temperature. No crystals were seen in even the highest concentration patches for 90 days when stored at −20°C.

Time Lag Experiment

Two patches of different thickness were made with Duro-Tak 2516 adhesive. The thickness and weight of 5 cm^2 of these patches are shown in Table IV. The amount of levonorgestrel permeating through just the dialysis membrane and patch of thickness 0.011 cm is shown in Fig. 9a and b respectively. Comparison of slopes of these curves shows that rate of diffusion of levonorgestrel through just the dialysis membrane was very high (4–5 times) as compared to the patches and as such resistance offered by the dialysis membrane could be neglected. Saturation solubility of levonorgestrel in the adhesive was calculated from the slopes and intercepts of the curves using Eq. (3).

Table III Time Taken for First Crystals to Appear in Accelerated Stability Testing

Levonorgestrel conc. in DIA patch (% *w/w*)	Time to see first event of crystallization at room temperature	
	Non Die-cut patches	Die-cut patches
1	2 days	1 day
0.6	13 days	4 days
0.4	22 days	6 days

The solubility of levonorgestrel was found to be 1.084 mg/cm^3 and 0.91 mg/cm^3 for patches of 0.011 cm and 0.027 cm thickness respectively. Conversion to weight percentage using the weight and volume of patch gives the solubility to be 0.09% *w*/*w* for both patches.

DISCUSSION

The use of increasing the concentration or initial loading of a drug in a transdermal system to improve transdermal delivery is known to everyone (21,22). Increasing the concentration makes the system more saturated and thus increases the thermodynamic activity of a drug in the system which in turn produces a higher driving force for a drug to permeate in skin. This phenomenon, however, can only be exploited till the time the concentration reaches the

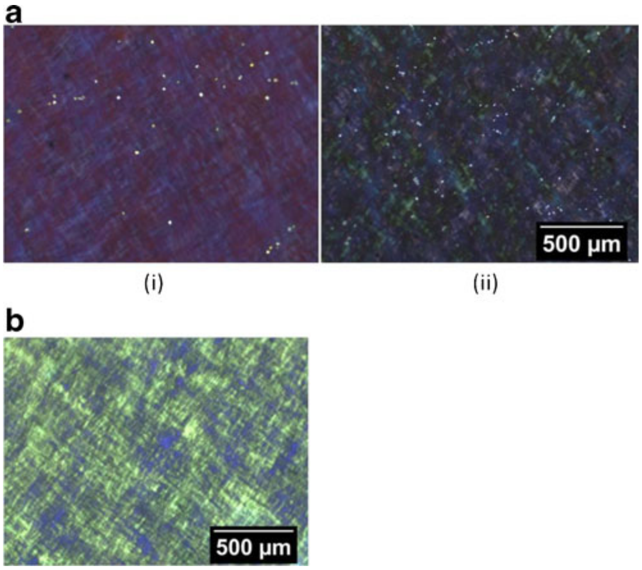

Fig. 8 (**a**) Microscopic images of (*i*) 1% *w/w* patch after 6 days; (*ii*) 0.6% *w/w* patch after 20 days. (**b**) Microscopic image of 1% *w/w* patch of levonorgestrel stored at −20°C after 90 days.

Table IV Properties of Patches Used for Time Lag Experiment, *A* Adhesive, *R* Release Liner, *D* Dialysis Membrane

Properties	Thickness of different components (mm)			Weight of different components (mg)		
	A + R + D	R + D	A	A + R + D	R + D	A
Patch 1	0.22 ± 0.01	0.11	0.11 ± 0.01	145 ± 2	80 ± 1	65 ± 2
Patch 2	0.38 ± 0.01	0.11	0.27 ± 0.01	226.4 ± 2	80 ± 1	146.4 ± 2

saturation solubility of drug in the system. In a drug-in-adhesive transdermal system, for an example, the drug can only be added in amounts up to its saturation solubility in the adhesive polymer. During the solvent cast method of preparing a drug-in-adhesive patch, if drug in added in amounts more than saturation the system becomes supersaturated and hence unstable. Drug might recrystallize from these systems over time but the process of recrystallization might be very slow (7,23,24). It may be because of the relatively low diffusion coefficients of drug in such highly viscous systems and the requirement of events of nucleation for the initiation of crystallization.

Incorporation of additives to inhibit crystallization and stabilize the systems is necessary when drug is added in amounts greater than saturation (25). Crystallization inhibitors are hypothesized to interact on molecular level with the dissolved drug and prevent the formation of crystal nuclei (8,26). DSC studies are therefore helpful in selecting the appropriate crystallization inhibitor for a particular drug. In this study, we compared DSC studies to slide crystallization studies to screen additives. DSC studies showed that poloxamer could reduce the enthalpy of levonorgestrel by 52% as compared to 25% with PVP and as such is a better crystallization inhibitor whereas slide crystallization studies showed PVP to be better than poloxamer. When actual patches were made with same amounts of PVP and poloxamer, crystal growth was found to be more pronounced and detectable in patches made with poloxamer. The discrepancy in the results from slide crystallization and DSC can be explained by the reasoning that DSC studies predicted the amount of solid state interaction induced by heating between levonorgestrel and additives. Reports have shown the importance of such interactions in the ability of an additive to act through prevention of formation of crystal nuclei or for getting adsorbed on crystal surface of drug. There are however other mechanisms reported such as solubilization of drug with polymer and resistance offered to diffusion of drug molecules due to increased viscosity which play an important role in the process. Slide crystallization studies, in addition to accounting for drug-polymer interactions, also account for these mechanisms and are more representative of what happens in real time patches.

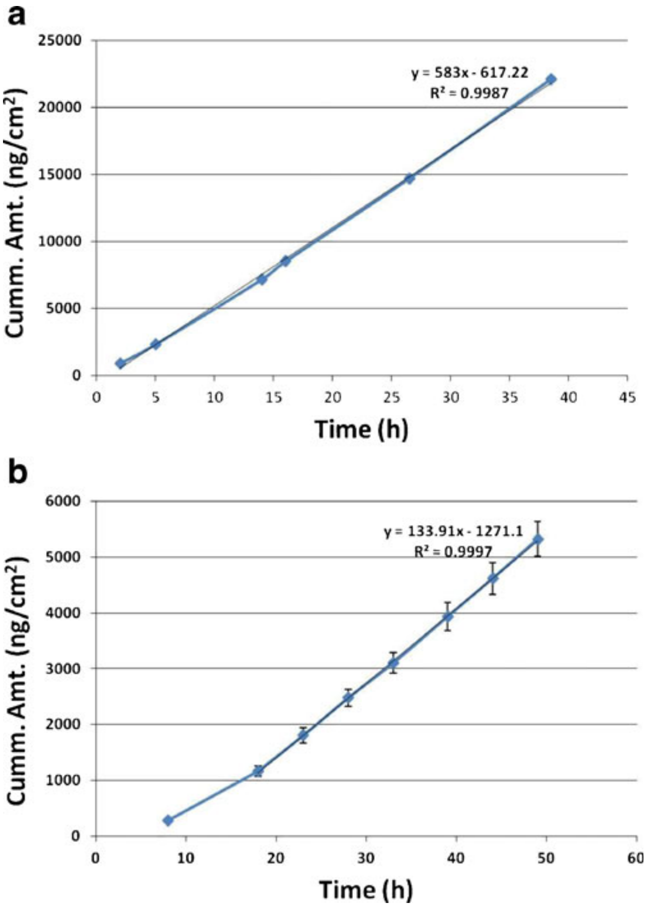

Fig. 9 Diffusion of levonorgestrel in time lag experiment through (**a**) dialysis membrane, (**b**) patch of thickness 0.11 mm (± SD, *n*=3).

Crystallization in patches can have negative impact on performance if it is not detected in early stages and happens after marketing. To see how crystallization affects patch performance, release profiles were compared from stored (crystallized) and fresh (supersaturated) patches. The release rate of levonorgestrel was significantly higher from supersaturated patches as compared to crystallized patches throughout the period of study. Therefore, crystallized patches might not release and deliver the expected amount of drug when used by patients. Furthermore, the presence of crystals in the patches even after 96 h of release shows that dissolution of crystals back to the molecular form of drug and its subsequent release from the patch is a slow process. It must, however, be also kept in mind that the extent of decrease in drug release from a crystallized patch cannot be generalized. It depends on the amount of crystals formed in the patch at that particular time which in turn is dictated by the amount of supersaturation at the time of manufacture and time elapsed since manufacture.

Different methods have been proposed to accelerate the process of crystallization in a drug-in-adhesive patch. Some of them include scrapping the surface of the patch, die cutting, freeze thaw cycles, shaking on shaker for extended periods of time or seed crystallization studies involving addition of small crystals on the surface of patch and monitoring the growth of added crystals over time (27). All these methods involve inducing some kind of stress in the patch thus accelerating the process of crystallization. There are however not many reports in literature for any of these studies, probably since most of this work is done by companies and is not published due to patent or other issues. In this study we have shown how die cutting can be helpful in reducing the time for crystallization and as such save a lot of time for pharmaceutical companies.

Storing the patches at low temperatures is one of the ways to increase the time of crystallization and keep the patch stable for longer periods. Schwarz pharma recommended storing patches of rotigotine in freezers to avoid the problem of crystallization (28). In this study, we have shown the effect of freezing on crystal development in levonorgestrel patches and compared it to normal room temperature storage conditions. Storing in freezer increased the crystal development time considerably. No crystals were seen even in 1% levonorgestrel patches after 90 days as compared to crystal development in 2 days at room temperature storage conditions. This can be due to the effect of low temperature on diffusion coefficient of drug in the adhesive polymer. Decreasing the temperature alleviates the diffusion coefficient of drug and as such does not allow drug to crystallize.

Prediction of saturation solubility of drug in adhesive polymer has always been a challenge. Several attempts have been made in the past for the same such as the solubility calculator on Henkel's website. It takes into consideration the water solubility of the drug and properties such as water uptake and solubility parameter of polymer to predict the solubility of drug in polymer (29). The calculator gave the value of saturation solubility of levonorgestrel to be 0.1% *w/w* in DuroTak-2516. Another attempt was made to measure saturation solubility using Higuchi kinetics (16). This method, however, can only be applied to situations where drug is dispersed in the polymer. In the process of making drug-in-adhesive patches by solvent cast method, supersaturated patches will be formed when drug is added in amounts more than saturation. As such, it does not represent a model applicable to Higuchi equation and is prone to give erroneous results. In this study, we represent another method adopted from experiments used to measure diffusional release of solute from polymeric matrix. The so called time lag experiment as mentioned in the introduction before gives the values of diffusion coefficient and saturation solubility of a drug in any polymer. For the purpose of conducting experiments which required a sheet of adhesive polymer, patches were made over a dialysis membrane. This allowed production of uniform sheet of polymer with no or minimal resistance to diffusion of levonorgestrel through the polymer. The value of saturation solubility of levonorgestrel in DuroTak-2516 predicted by this model was 0.09% *w/w* which agreed with the microscopic studies performed by accelerated stability testing and with the value predicted by the solubility calculator.

CONCLUSION

In conclusion, this work provides an insight to solutions for different problems of crystallization in drug-in-adhesive patches. Prediction of saturation solubility of a drug in adhesive via time lag experiment and accelerated stability testing with die cutting can help in saving a lot of time in the initial stages of patch development. Slide crystallization studies can be performed along with DSC studies to select the best crystallization inhibitor/solubilizer whereas freezing can provide a means to stabilize the otherwise unstable patches for longer periods.

REFERENCES

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–8.
2. Minghetti P, Cilurzo F, Pagani S, Casiraghi A, Assandri R, Montanari L. Formulation study of oxybutynin patches. Pharm Dev Technol. 2007;12(3):239–46.
3. Kim JH, Choi HK. Effect of additives on the crystallization and the permeation of ketoprofen from adhesive matrix. Int J Pharm. 2002;236(1–2):81–5.
4. Kotiyan PN, Vavia PR. Eudragits: role as crystallization inhibitors in drug-in-adhesive transdermal systems of estradiol. Eur J Pharm Biopharm. 2001;52(2):173–80.
5. http://www.neupro.com/Returning/Returning.asp (03/01/2012).
6. Cilurzo F, Minghetti P, Casiraghi A, Tosi L, Pagani S, Montanari L. Polymethacrylates as crystallization inhibitors in monolayer transdermal patches containing ibuprofen. Eur J Pharm Biopharm. 2005;60(1):61–6.
7. Jain P, Banga AK. Inhibition of crystallization in drug-in-adhesive-type transdermal patches. Int J Pharm. 2010;394(1–2):68–74.
8. Lipp R. Selection and use of crystallization inhibitors for matrix-type transdermal drug-delivery systems containing sex steroids. J Pharm Pharmacol. 1998;50(12):1343–9.
9. Chen G-S, Kim D-D, Chien YW. Dual-controlled transdermal delivery of levonorgestrel and estradiol: enhanced permeation and modulated delivery. J Control Release. 1995;34:129–43.
10. Chen S, Singh J. In vitro release of levonorgestrel from phase sensitive and thermosensitive smart polymer delivery systems. Pharm Dev Technol. 2005;10(2):319–25.
11. Harrison LI, Zurth C, Gunther C, Karara AH, Melikian A, Lipp R. Simultaneous estradiol and levonorgestrel transdermal delivery

from a 7-day patch: in vitro and in vivo drug deliveries of three formulations. Drug Dev Ind Pharm. 2007;33(4):373–80.

12. Bruni G, Berbenni V, Milanese C, Girella A, Marini A. Drug-excipient compatibility studies in binary and ternary mixtures by physico-chemical techniques. J Therm Anal Calorim. 2010;102:193–201.
13. Dohner JW, Bura SA. Improved method for preventing crystal formation in a dispersion of a liquid in a matrix. WO/1997/020550, 1997.
14. Isaac BF, Fabio SA, Evaristo SFJ. Inhibition of crystallization in transdermal devices US6465005, 2002.
15. http://transdermal.henkel.com/ (03/02/2012).
16. Myatt R, Oladiran G, Batchelor H. Solubility calculator. Drug Delivery Technol. 2008;8(3):56–9.
17. Van Laarhoven JA, Kruft MA, Vromans H. In vitro release properties of etonogestrel and ethinyl estradiol from a contraceptive vaginal ring. Int J Pharm. 2002;232(1–2):163–73.
18. Paul DR, McSpadden SK. Diffusional release of a solute from a polymeric matrix. J Membr Sci. 1976;1:33–48.
19. Jain SK, Chourasia MK, Sabitha M, Jain R, Jain AK, Ashawat M, *et al*. Development and characterization of transdermal drug delivery systems for diltiazem hydrochloride. Drug Deliv. 2003;10(3):169–77.
20. Gupta JRD, Irchhiaya R, Garud N, Tripathi P, Dubey P, Patel JR. Formulation and evaluation of matrix type transdermal patches of glibenclamide. Int J Pharm Sci Drug Res. 2009;1(1):46–50.
21. Leichtnam ML, Rolland H, Wuthrich P, Guy RH. Impact of antinucleants on transdermal delivery of testosterone from a spray. J Pharm Sci. 2007;96(1):84–92.
22. Reid ML, Brown MB, Jones SA. Manipulation of corticosteroid release from a transiently supersaturated topical metered dose aerosol using a residual miscible co-solvent. Pharm Res. 2008;25(11):2573–80.
23. Variankaval NE, Jacob KI, Dinh SM. Polymorphism of 17-beta estradiol in a transdermal drug delivery system. J Mater Sci Mater Med. 2002;13(3):271–80.
24. Pattnaik S, Swain K, Mallick S, Lin Z. Effect of casting solvent on crystallinity of ondansetron in transdermal films. Int J Pharm. 2011;406(1–2):106–10.
25. Raghavan SL, Trividic A, Davis AF, Hadgraft J. Crystallization of hydrocortisone acetate: influence of polymers. Int J Pharm. 2001;212(2):213–21.
26. Schulz M, Fussnegger B, Bodmeier R. Influence of adsorbents in transdermal matrix patches on the release and the physical state of ethinyl estradiol and levonorgestrel. Eur J Pharm Biopharm. 2011;77(2):240–8.
27. Van Buskirk GA, Arsulowicz D, Basu P, Block L, Cai B, Cleary GW, *et al.* Passive transdermal systems whitepaper incorporating current Chemistry, Manufacturing and Controls (CMC) Development Principles. AAPS PharmSciTech. 2012;13(1):218–30.
28. http://www.neupro.com/documents/Neupro_FDA_ENG.pdf (03/03/2012).
29. Foreman P, Luciano A, Yang H, Jacobson S. Transdermal adhesives: predicting drug solubility in transdermal adhesives. Drug Delivery Technol. 2005;5(7):46–51.