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# Evaluation of the Transdermal Permeation Behavior of Proterguride from Drug in Adhesive Matrix Patches Through Hairless Mouse Skin

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**ABSTRACT** The transdermal in vitro permeation behavior of the highly potent dopamine agonist Proterguride was investigated using hairless mouse skin as a model membrane. Drug in adhesive matrix formulations based on different types of pressure-sensitive adhesives (Eudragit® E 100 and Gelva®7883 as acrylates, Oppanol® B 15 SFN as polyisobutylene, and BioPSA® 7-4202 as silicone) with a drug load of 3% by weight were manufactured. All patches were examined for drug crystallization by polarized microscopy immediately after the manufacturing process and after storage for 30 days in sealed aluminium laminate bags at ambient temperature and at 40°C, respectively. Furthermore, the influence of the drug load in acrylate-based formulations onto the steady-state flux of Proterguride was examined. The Eudragit® E 100 system delivered a significantly higher steady-state flux than the systems based on Oppanol® B 15 SFN and also a somewhat higher steady-state flux than the Gelva®-based patch. An addition of 10% by weight of the crystallization inhibitor povidone 25 did not significantly influence the steady-state flux of Proterguride from acrylate matrices. The lipophilic silicone and polyisobutylene adhesives facilitated drug crystallization within the short storage periods at both conditions, probably due to the absence of povidone 25, which was incompatible with these polymers. Varying the drug load in acrylate-based formulations led to a linear increase of the steady-state flux until the steady-state flux of Proterguride leveled off and the patches tended to drug crystallization. It was found that Gelva®-based patches show good physical stability, good skin adhesion, and moderate flux values and, thus, can be evaluated as a basis for a suitable formulation for the transdermal administration of Proterguride.

**KEYWORDS** Transdermal drug delivery, Adhesives, Dopamine agonist, Proterguride, Matrix patches

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## INTRODUCTION

Transdermal drug delivery systems are of great interest due to their specific advantages, e.g., to avoid liver first-pass metabolism, to minimize application frequency, the possibility to interrupt drug input by taking off the transdermal therapeutic system (TTS), and to achieve constant plasma levels (Yum, 1989). Unfortunately, not every drug substance is suitable for this route of application. Candidate compounds should possess a balanced ratio of hydrophilicity and lipophilicity [logP (octanol/water) 1–2], they should produce pharmacodynamic effects at low plasma concentration levels (Barry, 2001; Prausnitz et al., 2004), and they should not cause skin irritation (Naik et al., 2000). The model drug Proterguride (Fig. 1) is a semisynthetic compound belonging to the ergoline group. The $pK_A$ value, determined in accordance with the method proposed by Zimmermann (1983), amounts to 7.8. Proterguride showed good solubility in polar organic solvents such as acetone or 2-propanol as well as a pH-dependent water solubility due to its basic character. The n-octanol/water pH 7 (phosphate-buffered) partition coefficient amounts to 24.5, corresponding to a log P value of 1.39.

Proterguride can be classified as a highly potent dopamine receptor agonist (Wachtel, 1983) that might be suitable for therapy for Parkinson's disease, restless leg syndrome, or the prophylaxis of migraine. Strong dopaminergic effects could be demonstrated by Hertzsch (1984) at a dose of 10 μg i.v., leading to maximum plasma levels of approximately 50 pg/mL. Especially in the case of dopamine agonists, the transdermal route of administration might become of great clinical importance due to the ability to achieve constant plasma levels and, thus, to imitate the physiological continuous release profile of dopamine. Pulsatile stimulation of dopaminergic receptors as it occurs with oral administration of dopaminergic drugs (Krause & Hümpel, 1988) is considered the cause of treatment-associated motor complications (Metman et al., 2001; Stocchi, 2003). Furthermore, long-term delivery of dopamine agonists in a more continuous way over at least 24 h is expected to greatly reduce the risk for early morning dyskinesia, which often goes along with panic attacks and pain (Stocchi, 2003). The transdermal in vitro permeation of Proterguride from drug in adhesive matrix patches was evaluated using static Franz diffusion cells and hairless mouse skin as a model membrane. The pressure-sensitive adhesives (PSAs) have an influence on the drug release (Kim et al., 2002), and thus, four different polymers were included in this study. From the polyacrylate group, Eudragit® E 100 (basic butylated methacrylate copolymer) and Gelva® 7883 multipolymer solution (vinylacetate–acrylate copolymer, dissolved in ethylacetate, solids 50%), from the silicone group BioPSA® 7-4202 (dissolved in ethylacetate, solids 60%), and Oppanol® B 15 SFN ($M_{rel}$ = 40.000–85.000) from the polyisobutylene group were chosen. Favorite PSAs were then selected to investigate the influence of the drug load on the steady-state flux.

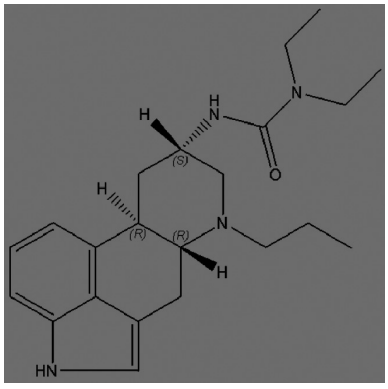


**FIGURE 1** Structure of Proterguride [1,1-Diethyl-3-(6-n-Propyl-8α-Ergolinyl)-Urea].

## MATERIALS AND METHODS

### Materials

Proterguride was synthesized by M. Flieger, Institute of Microbiology, Academy of Sciences of the Czech Republic, Prague. Eudragit® E 100 was obtained from Roehm Pharma Polymers (Darmstadt, Germany). BioPSA® 7-4202 was a gift from Dow Corning (Midland, MI, USA), Oppanol® B 15 SFN was a gift from BASF (Cologne, Germany) and Gelva® 7883 multipolymer solution was a gift from Solutia (St. Louis, MO, USA). Scotchpak®1022 Releaseliner and CoTran® 1022 backing material (polyethylene monolayer film) were gifts from 3M (St. Paul, MN, USA). Acetonitrile, gradient grade, was from Promochem (Wessel, Germany). 2-Hydroxypropyl-β-cyclodextrin was purchased from Fluka (Neu-Ulm, Germany). Povidone 25 (PVP) and all other solvents and chemicals were obtained from Merck (Darmstadt, Germany) and were of analytical grade; they were used as received.

## Methods

### *Manufacturing Process*

The TTS were manufactured as a continuous laminate with a width of 5 cm using a coating machine designed by Check Tec (Braunschweig, Germany; Fig. 2). First, the drug substance and, if necessary, PVP were dissolved in a mixture (1:1) of acetone and 2-propanol in case of acrylate-based formulations; in case of the silicone and the polyisobutylene adhesive, dichlormethane was used for dissolving the drug substance, because other polar organic solvents such as acetone or 2-propanol were incompatible with the lipophilic polymers. The adhesives were already dissolved, except Eudragit® E 100, which was dissolved in a mixture of acetone, ethanol, and 2-propanol (60/33.4/6.6) and Oppanol® B 15 SFN, which was dissolved in n-hexane. The Eudragit® E 100 solution received an addition of dibutylsebacate acting as a plasticizer and succinic acid for cross-linking the polymer (Eudragit® E 100 65%/dibutyl sebacate 29.2%/succinic acid 5.8%; w/w). A second step consisted of adding the drug solution to the adhesive solution and homogenizing it by stirring with a magnetic bar for 40 min. The vessels were covered with a laboratory film (Parafilm® M, Pechiney Plastic Packaging, Neenah, WI, USA) for preventing solvent evaporation. Prior to the coating process, the final liquid formulation was checked for the absence of crystals by polarized microscopy. The coating machine performed the following steps: Coating the final liquid formulation with a variable knife onto the release liner, then transporting the film through the separate ovens for solvent evaporation, and finally laminating the dried film with the backing membrane. The ovens showed a length of 10 cm each and were programmed as follows: acrylate-based formulations 38°C and 76°C, silicone- and polyisobutylene-based formulations 34°C and 74°C, respectively. The transport speed of the film was set at 0.1 m/min in all cases. During the coating process, circular samples of 3.6 cm in diameter were die cut from the laminate by circular punches and weighed so that the height of the knife could be adjusted to a corresponding matrix weight of approximately 50 mg/sample. The matrix weight was determined by subtracting the mean weight of 10 samples sized 3.6 cm in diameter of the backing membrane from the total weight of matrix-backing laminate samples. The continuous manufacturing process under controlled conditions guaranteed homogeneous drug contents and matrix weights of the laminate.

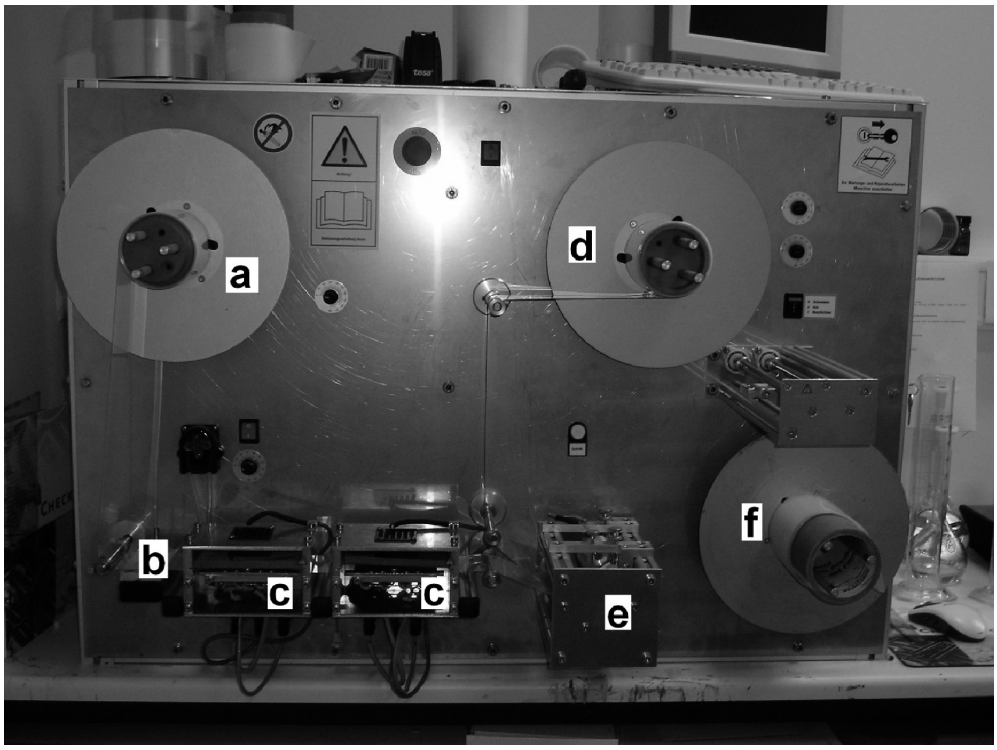


**FIGURE 2** Coating Machine (Check Tec, Braunschweig, Germany); (a) Release Liner; (b) Knife; (c) Oven; (d) Backing Membrane; (e) Transport Motor and Laminating Device; (f) Continuous Laminate.

### Polarized Microscopy

The TTS were stored in sealed aluminium laminate bags for 30 days at two different controlled conditions: at ambient temperature in a storage room with temperature control (temperature between 18°C and 25°C) and at 40°C in an oven (Memmert UM 300, Memmert, Schwabach, Germany). Three circular patches sized 3.6 cm in diameter were examined for drug crystallization by polarized microscopy, using a Motic PM-2805 (Motic, Wetzlar, Germany), immediately after the manufacturing process as well as after the storage period. Polarized microscopy was described as the method of choice for the identification of crystals in matrix patches (Lipp & Müller-Fahrnow, 1999).

### Skin Adhesion

Placebo patches were manufactured as described above and applied to the lower inner forearms of four male human volunteers between the ages of 28 and 65 years and remained in position for 24 h. The skin adhesion of the patches was assessed on a scale of one (low skin adhesion) to five (high skin adhesion).

### Workup Procedure for the Determination of Proterguride in TTS Based on Acrylates or Silicone

Circular TTS (n=6), diameter 3.6 cm (corresponding area: 10.18 $cm^2$), were die cut from the laminate using circular punches, weighed, and then extracted with 40 mL acetonitrile for 40 min in an ultrasonic bath (Sonorex Super RK 106, Bandelin electronic, Berlin, Germany). Afterward, the extraction media were transferred into graduated flasks (50.0 mL) and filled up to the mark with acetonitrile. These solutions were subsequently analyzed by HPLC.

### Workup Procedure for the Determination of Proterguride in TTS Based on Polyisobutylene

Circular TTS (n=6), diameter 3.6 cm (corresponding area: 10.18 $cm^2$), were die cut from the laminate using circular punches, weighed, and then extracted with 40 mL n-hexane for 40 min in an ultrasonic bath (Sonorex Super RK 106, Bandelin electronic, Berlin, Germany). Afterward, the extraction media were transferred into graduated flasks (50.0 mL) and filled up to the mark with n-hexane. This solution was extracted with 15 mL acetonitrile in triplicate. The acetonitrile phases were collected in graduated flasks (50.0 mL) and filled up to the mark with acetonitrile. These solutions were subsequently analyzed by HPLC.

### Excised Hairless Mouse Skin

Freshly excised hairless mouse skin of 8–9-week-old male hairless mice was received from Taconic M&B (Lille Skensved, Denmark). After sacrificing the mice and excising the skin, the skin was allowed to equilibrate for 40 min in 10 mL of isotonic saline with the addition of 10% glycerol as a cryoprotective agent in a plastic bag. The skin was shipped on dry ice and stored below −4°C in a freezer. After thawing, it was gently shaken with 100 mL of bidistilled water for several minutes in triplicate. Then the skin was rinsed with plenty of bidistilled water to remove any glycerol from the skin tissue. This procedure was performed in accordance with the study by reference Babu et al., (2003), which showed a final glycerol concentration in the skin below 0.005%. Previous experiments showed no significant differences of drug flux and lag time (Student's *t*-test, $P<0.05$) from a reference formulation during storage periods of the skin for up to 7 weeks (data not shown).

### Skin Permeation Studies

Static Franz diffusion cells were used, showing a receptor volume of 8 mL and a diffusion area of 1 $cm^2$. The cells were maintained at 38.5±0.5°C by a circulating water bath, yielding a temperature of 32°C at the diffusion area. All experiments were performed at least in triplicate. The frozen hairless mouse skin was thawed in water of 37°C, then waved with 100 mL of bidistilled water for several minutes in triplicate, and finally rinsed with plenty of bidistilled water. The skin was freed from adhering subcutaneous fat tissue, cut into six pieces, and then allowed to equillibrate for 1 h. Subsequently, TTS sized 1.2 cm in diameter were stamped out of the laminate and applied to the stratum corneum. The skin pieces were mounted into the Franz diffusion cells containing a mixture of 20% polyethyleneglycol and 2% 2-hydroxypropyl-β-cyclodextrin in phosphate-buffered solution at pH 7.4 that served as receptor medium, guaranteeing sink conditions over 48 h. The receptor medium was stirred at 500 rpm with a magnetic bar. Samples of

**TABLE 1** **Actual Drug Content and Matrix Weights [n = 6, Mean (Standard Deviation)]**

| PSA | Drug load [% w/w] | Matrix weight per 10.18 $cm^2$ [mg] |
|---|---|---|
| Eudragit® E 100 (+PVP) | 3.02 (0.03) | 45.6 (7.6) |
| Gelva® 7883 (+PVP) | 3.04 (0.17) | 45.4 (2.0) |
| BioPSA® 420-2 | 3.17 (0.39) | 58.4 (7.2) |
| Oppanol® B 15 SFN | 3.24 (0.23) | 43.0 (10.4) |
| Eudragit® E 100 (−PVP) | 2.65 (0.06) | 51.1 (2.2) |
| Gelva® 7883 (−PVP) | 2.53 (0.03) | 65.8 (1.1) |

500 μL were withdrawn at different time points and collected in HPLC vials. The sample volume was replaced by prewarmed receptor medium. This dilution was taken into account when calculating the permeation data.

### *Drug Quantification*

Analysis was done using HPLC, consisting of a Kontron MT2 datasystem, Kontron 420 pump, Kontron 460 autosampler, and Kontron 430 UV detector, Waters Symmetry Shield RP18 3 μm $3.9 \times 20$ mm guard column, and a Waters Symmetry Shield RP18, 3 μm, $4.6 \times 100$ mm analytical column. The detector was set at a wavelength of 222 nm. The flow rate was 0.9 mL/min. The mobile phase consisted of 55% 20 mM phosphate-buffered solution pH 7.1 and 45% acetonitrile, gradient grade. Proterguride showed a retention time of approximately 9.7 min. Quantification was done using the external standard method and the peak area as quantification criteria.

## RESULTS AND DISCUSSION

The transdermal permeation behavior of Proterguride across hairless mouse skin was investigated using drug in adhesive matrix patches as dosage forms. The matrix weights and the effective drug loads, analyzed by HPLC are given in Table 1. All formulations were free of drug crystals when controlled immediately after the manufacturing process. The formulations based on the acrylates were manufactured with and without an addition of 10% per weight with PVP, which is an effective inhibitor of drug crystallization (Kim & Choi, 2002). Because the hydrophilic polymer PVP did not yield homogeneous matrices when formulated with the lipophilic silicone or polyisobutylene polymers, the latter adhesives were formulated without addition of PVP. The permeation data obtained did not indicate any significant influence of PVP at the 10% concentration onto the steady-state flux of Proterguride in the acrylate-based matrices (Fig. 3). The permeation profiles obtained from the different formulations with a drug load of 3% by weight each are shown in Fig. 4. The transdermal drug delivery system based on the Eudragit® E 100 formulated with PVP showed a significantly higher steady state flux ($J_{ss}$) and average flux ($J_a$) and a significantly lower lag time than the system based on Oppanol®. The system based on the silicone pressure-sensitive adhesive delivered a significantly higher $J_a$ than the system based on the polyisobutylene Oppanol® (Student's

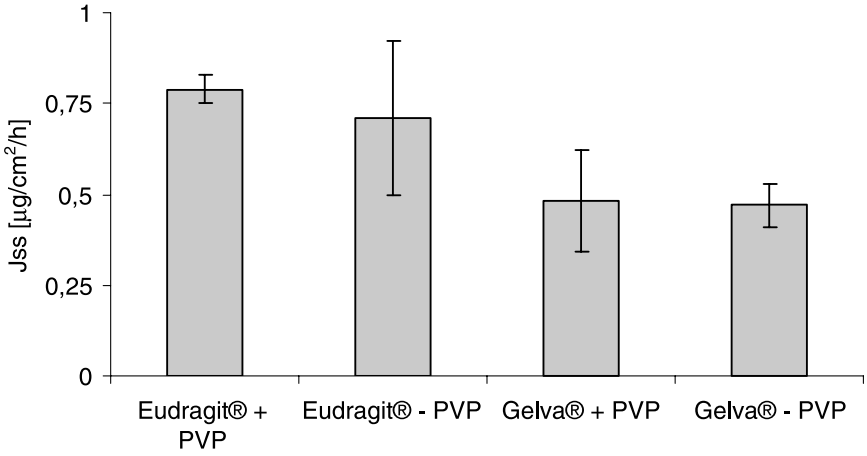


**FIGURE 3** **Influence of PVP at the 10% Level onto the Steady-State Flux of Proterguride from Acrylate Matrices Through Hairless Mouse Skin.**

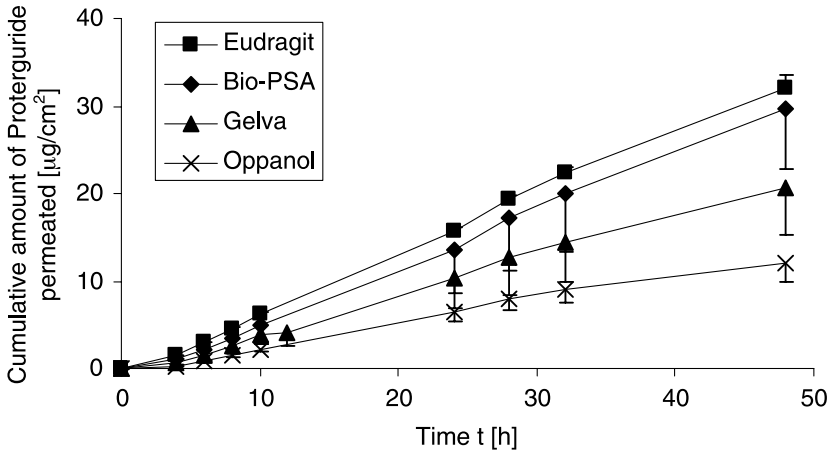


**FIGURE 4** **Permeation Profiles of Proterguride from Different Formulations with a Drug Load of Approximately 3% each, Acrylates Formulated with Additionally 10% by Weight of PVP. Each Point Represents the Mean (Standard Deviation) of at Least Three Experiments.**

*t*-test; $P = 95\%$). The permeation data are summarized in Table 2. Using Oppanol® or BioPSA® as adhesive, Proterguride tended to massive crystallization within the short storage period at ambient temperature and at 40°C. This is caused by the absence of PVP and the lipophilicity of these PSAs. Figure 5 shows Proterguride crystals in these lipophilic formulations formed during storage for 30 days at 40°C in sealed aluminium laminate bags. The batches produced with an acrylate as polymer and a drug load of 3% (w/w) did not show any crystals during storage for up to 90 days in sealed aluminium laminate bags at room temperature and at 40°C, respectively, if formulated with PVP. In case of absence of PVP, the acrylate-based formulations have also been stable for at least 30 days storage at both conditions. Another important parameter for the characterization of transdermal drug delivery systems is skin adhesion. Placebo patches of the different polymers were manufactured with a matrix weight of approximately 50 mg/10 $cm^2$ and applied to the lower inner forearm of four human volunteers for 24 h to evaluate the stickiness on a scale between one and five as described. The results (Table 3) indicated that there were only slight to no differences in skin adhesion in the case of the acrylates, whether or not PVP was added. Gelva®, Oppanol®, and BioPSA® polymer showed very good skin adhesion over at least 24 h, while the adhesion of the Eudragit® E 100 formulations was not sufficient. One volunteer reported the loss of the Eudragit® E 100 placebo patch formulated without PVP. Regarding the results of the in vitro skin permeation and the physical stability, the acrylates were chosen to investigate the influence of the drug load onto the steady-state flux of Proterguride. Additional formulations containing 10% by weight of PVP each and up to 10% by weight of Proterguride, respectively, were manufactured with both adhesives. The data for drug loads and matrix weights are given in Table 4. Figure 6 shows the steady-state flux of Proterguride as a function of the drug load in the acrylate-based formulations. The steady-state flux values showed linear increase as the drug load was increased up to approximately 4% in case of Gelva®-based patches. At drug concentrations beyond 4% in the formulation, the curve reached a plateau. In the case of Eudragit®-based patches, the maximum flux was reached at a concentration somewhat higher than in Gelva®-based formulations. This indicates that the thermodynamic activity, the driving force for the permeation process, reached its maximum at a drug load of approximately 4% (Gelva®) or 6% (Eudragit®), respectively, which is also

**TABLE 2** **In Vitro Skin Permeation Data of Proterguride from Formulations Based on Different Types of Adhesives with a Drug Load of Approximately 3% by Weight**

| | Eudragit® | BioPSA® | Gelva® | Oppanol® |
|---|---|---|---|---|
| $J_a$ [µg/$cm^2$/h] | 0.67 (0.03) | 0.62 (0.15) | 0.49 (0.14) | 0.25 (0.07) |
| $J_{ss}$ [µg/$cm^2$/h] | 0.79 (0.04) | 0.66 (0.26) | 0.44 (0.10) | 0.36 (0.05) |
| lagtime [h] | 2.19 (0.15) | 2.71 (0.54) | 2.41 (0.65) | 3.78 (0.75) |

Note: Acrylates formulated with PVP. Mean (standard deviation) of at least three experiments.

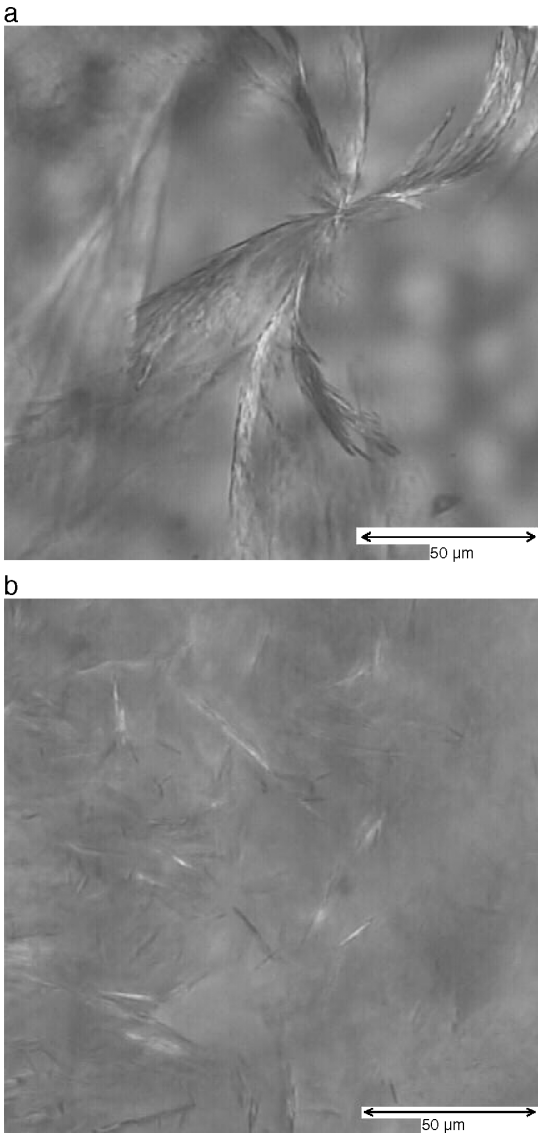


**FIGURE 5** **(a) Proterguride Crystals in a Formulation Based on BioPSA® After Storage for 30 Days at 40°C. (b) Proterguride Crystals in a Formulation Based on Oppanol® After Storage for 30 Days at 40°C.**

near the saturation concentration. The acrylate-based formulations loaded with 6% or 10% by weight with Proterguride showed crystals formed in the matrices during storage at 40°C for 30 days in sealed aluminium laminate bags (Fig. 7). Immediately after the manufacturing process, no crystals in the formulations, supersaturated by the rapid solvent evaporation during the manufacturing process, could be observed using the method as described above. However, data obtained indicated that the drug crystallization process occurred subsequently. Crystallization was not observed in placebo patches or in low-dose acrylate-based patches after storage, so the conclusion that the crystals consisted of Proterguride can be considered as safe. Taking into account that the crystallization process is accelerated at higher temperatures, and the skin permeation experiments were conducted at 32°C at the diffusion area, drug crystallization is also encouraged and leads to a decrease in thermodynamic activity. A similar dependency from the drug load in matrix patches onto the steady-state flux was also shown by Gondaliya and Pundarikakshudu (2003), who investigated the transdermal permeation behavior of Bupropion from Eudragit® E. Also, Roy et al. (1996) showed a linear increase of the steady-state flux of fentanyl from polyisobutylene matrices through human cadaver skin for drug loads up to the saturation concentration and a plateau of the curve at higher drug concentrations in the formulation. Roy et al. (1996) identified drug crystals in the high loaded matrices, which are responsible for no further increase of the thermodynamic activity, resulting in no further increase in the flux values.

This study demonstrated that drug in adhesive matrix patches containing Proterguride were successfully formulated based on Gelva® polymer, which showed good skin adhesion, physical stability (if

**TABLE 3** **Evaluation of the Skin Adhesion of Placebo Patches in Human Volunteers**

| Pressure sensitive adhesive | Skin adhesion |
|---|---|
| Oppanol® B 15 SFN | +++++ |
| Bio PSA® 7-4202 | ++++ |
| Gelva® 7883+PVP | +++++ |
| Gelva® 7883−PVP | +++++ |
| Eudragit® E100+PVP | ++(+) |
| Eudragit® E100−PVP | +++ |

Note: +low skin adhesion; +++++ good skin adhesion.

**TABLE 4** **Actual Drug Content and Matrix Weights [n=6, Mean (Standard Deviation)]**

| PSA | Drug load [% w/w] | Matrix weights per 10.18 $cm^2$ [mg] |
|---|---|---|
| Eudragit® E100 | 1.21 (0.03) | 49.9 (7.9) |
| Eudragit® E100 | 5.81 (0.08) | 53.1 (4.0) |
| Eudragit® E100 | 11.05 (0.39) | 17.9 (1.2) |
| Gelva® 7883 | 1.05 (0.04) | 47.0 (3.5) |
| Gelva® 7883 | 3.84 (0.08) | 49.1 (3.6) |
| Gelva® 7883 | 5.54 (0.15) | 59.3 (2.9) |
| Gelva® 7883 | 10.43 (0.18) | 50.3 (3.4) |

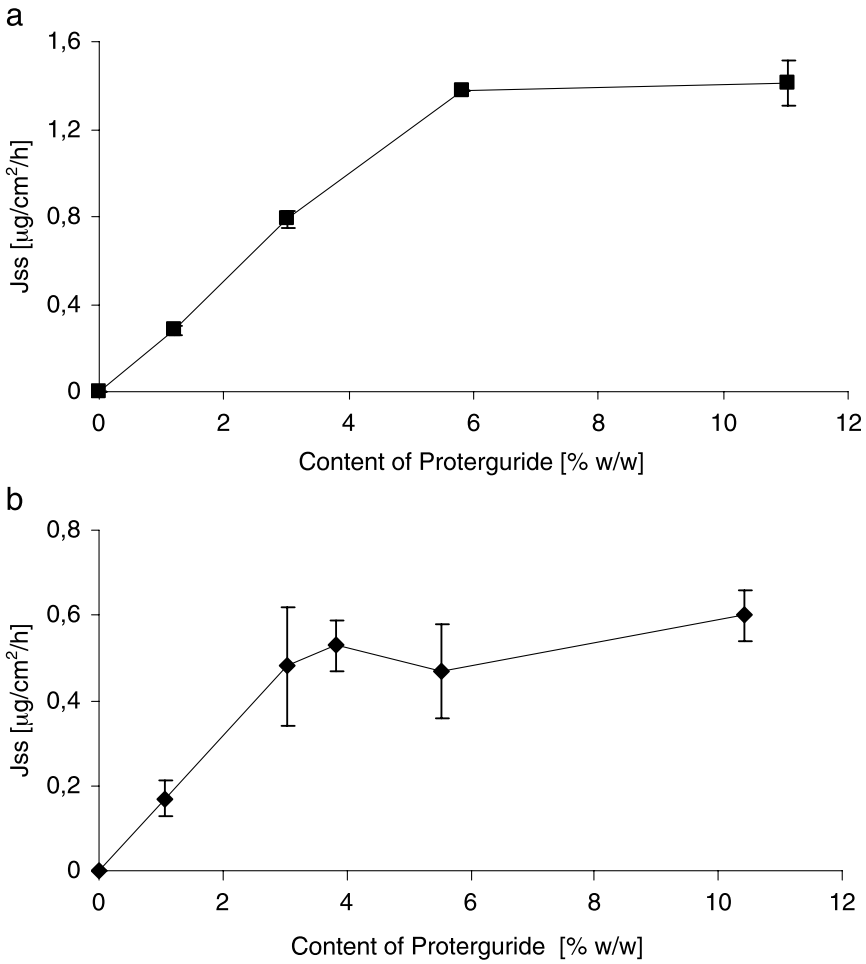


**FIGURE 6** **(a) Steady-State Flux of Proterguride Dependent on the Effective Drug Load for Formulations Based on Eudragit®. (b) Steady-State Flux of Proterguride Dependent on the Effective Drug Load for Formulations Based on Gelva®.**

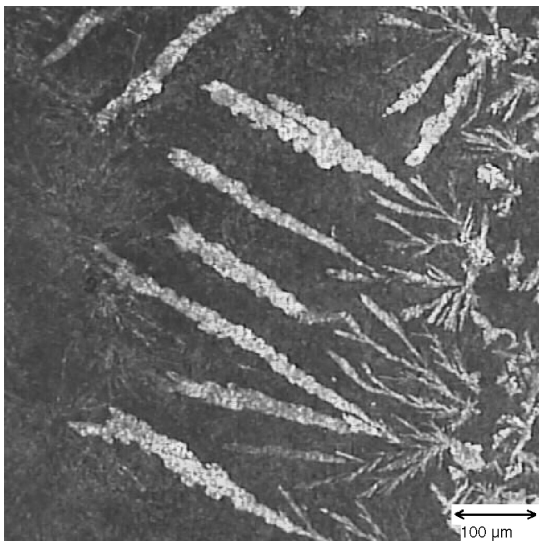


**FIGURE 7** **Crystals of Proterguride as Formed After Storage an Eudragit® Formulation with an Effective Drug Load of 11.05% (w/w) for 30 Days at 40°C.**

formulated with an addition of 10% by weight of PVP), and moderate flux values though hairless mouse skin in vitro. The optimal drug concentration was determined to 4% by weight in respect to physical stability of the patches and steady-state flux values.

## CONCLUSION

This paper deals with the transdermal administration of Proterguride from drug in adhesive matrix formulations. Hydrophilic Eudragit® E 100 showed the best flux values but also the lowest skin adhesion. The lipophilic polymers (silicone and polyisobutylene) facilitated drug crystallization already within short storage periods. Furthermore, the polyisobutylene showed only slow drug release. A drug load of 4% (w/w) in the case of Gelva®-based patches containing 10% PVP is near the saturation concentration. At this level, stable and crystal-free patches with notable steady-state flux values of Proterguride and good skin

adhesion could be formulated. Presently, Proterguride appears to be a promising candidate for further development of a transdermal dosage form to achieve continuous dopaminergic stimulation.

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