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RESEARCH PAPER

Development of Matrix Patches for Transdermal Delivery of a Highly Lipophilic Antiestrogen

Adrian Peter Funke,[1] Clemens Günther,[2] Rainer Helmut Müller,[3] and Ralph Lipp[1,*]

[1]Pharmaceutical Development, Schering AG, Berlin, Germany
[2]Preclinical Pharmacokinetics, Schering AG, Berlin, Germany
[3]Department of Pharmaceutics, Biopharmaceutics, and Biotechnology, Freie Universität Berlin, Berlin, Germany

ABSTRACT

The aim of this study was to develop matrix-type transdermal systems (TDSs) containing the highly lipophilic (log $P = 5.82$) antiestrogen (AE) and the permeation enhancers propylene glycol and lauric acid. For that purpose, permeation of AE from various adhesive matrices through excised skin of hairless mice was evaluated. It was found that pretreatment of the skin with permeation enhancers raised the transdermal flux of subsequently applied antiestrogen. Highest steady-state transdermal fluxes ($1.1\,\mu g\,cm^{-2}\,h^{-1}$) were obtained from Gelva®, polyacrylate adhesive, followed by $0.55\,\mu g\,cm^{-2}\,h^{-1}$ from Oppanol® polyisobutylene, $0.31\,\mu g\,cm^{-2}\,h^{-1}$ from BIO-PSA® silicone, and $0.12\,\mu g\,cm^{-2}\,h^{-1}$ from Sekisui polyacrylate matrices. In order to develop TDS with high content of fluid permeation enhancer propylene glycol, two different strategies were investigated. One strategy was the addition of hydroxypropyl cellulose (HPC) as thickening agent to Gelva matrices. This allowed for propylene glycol loading levels of up to 30%, resulting in transdermal AE fluxes of $0.09\,\mu g\,cm^{-2}\,h^{-1}$. On the other hand, a fleece-laminated backing foil was loaded with the described permeation enhancer formulation and laminated with polyacrylate adhesive layer, resulting in transdermal AE fluxes of $0.06\,\mu g\,cm^{-2}\,h^{-1}$. However, application of these TDSs on skin pretreated with permeation enhancers raised the fluxes to $2.6\,\mu g\,cm^{-2}\,h^{-1}$ from Gelva/HPC and $0.46\,\mu g\,cm^{-2}\,h^{-1}$ from fleece/Sekisui.

Key Words: Transdermal drug delivery systems (TDSs); Permeation enhancers; Propylene glycol; Lauric acid; Highly lipophilic drug; Antiestrogen.

*Correspondence: Ralph Lipp, Pharmaceutical Development, Schering AG, 13342 Berlin, Germany; Fax: +49 30 46 81 24 35; E-mail: ralph.lipp@schering.de.

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INTRODUCTION

The transdermal administration of drugs often provides several benefits.[1–4] For example, in some cases a hepatic first-pass effect is avoided, and nearly constant drug delivery during a long period of up to one week with a single patch can be achieved. However, the stratum corneum is a barrier against the permeation of drugs because of the rigid lamellar structure of the intercellular lipids in this skin layer. The most easily permeating drugs have small molecules of moderate lipophilicity. Often, a parabolic dependence is found between skin permeation and the octanol-water partition coefficient P of the applied drugs with an optimum value of log $P \approx 2$.[5,6] At low log P (hydrophilic molecules), the low permeability is due to low partitioning into the lipids of the stratum corneum. In this case, the partitioning into the stratum corneum can be improved[7] by increasing the thermodynamic activity of the drug in the transdermal formulation (push), by the use of permeation enhancers (pull), or by physical enhancement strategies, such as iontophoresis[8] or sonophoresis.[9,10] But also at high log P values (highly lipophilic molecules), the permeability often is low,[5,6] due to accumulation of lipophilic drugs in the stratum corneum and poor partitioning into hydrophilic layers of the skin. However, according to the literature, there have been fewer attempts to improve the permeation of these molecules than to improve the permeation of hydrophilic drugs.

It has been demonstrated previously[11] that highly lipophilic molecules such as antiestrogen (AE) are able to permeate excised skin of hairless mice, if propylene glycol and lauric acid are used in combination as a permeation enhancer in liquid transdermal formulations. Furthermore, it has been shown that liquid transdermal formulations should contain 3.3–10% lauric acid and 30–90% propylene glycol for optimal permeation enhancement.[11] These liquid formulations were made up to 100% with dimethyl isosorbide (DMI), which served as an inert solvent.

The aim of this study was to develop a more attractive and convenient dosage form, namely a matrix transdermal system (TDS) containing AE and the two aforementioned permeation enhancers in sufficient amounts. For that purpose a suitable pressure-sensitive adhesive matrix had to be selected. The most important features of this adhesive should be sufficiently high drug release and high partitioning of the drug from the resulting matrix patch to the skin. Furthermore, a high-loading capacity for drugs and enhancers, especially for the fluid permeation-enhancer propylene glycol, is needed. Therefore, AE-matrix TDS without enhancer should be manufactured using adhesives from three different classes—polyacrylate, silicone, and polyisobutene. In vitro release of AE from these TDSs and the in vitro permeation of excised skin of hairless mice after pretreatment with enhancers have to be investigated. Enhancer capacity of these adhesive types should be evaluated, too. The most suitable adhesive type has to be selected for the subsequent development of TDSs with a high permeation enhancer content.

MATERIALS

Antiestrogen (11β-fluoro-7α-[5-(methyl-{3-[(4,4,-5,5,5-pentafluoropentyl)-sulfanyl]-propyl}-amino)-pentyl]-estra-1,3,5(10)-triene-3,17βdiol) was manufactured by Schering AG, Berlin, Germany.

Gelva® multipolymer solution 7883, a solution of a vinylacetate acrylate copolymer in ethyl acetate (solids 50%) was bought from Solutia, Springfield, MA. TSR adhesive solution, a solution of 2-ethylhexyl-acrylate *N*-vinyl-2-pyrollidone copolymer in ethyl acetate (solids 35.7%) was obtained from Sekisui Chemical Co., Osaka, Japan. BIO-PSA® X7-4502 medical grade silicone pressure-sensitive adhesive solution (solvent: ethyl acetate, solids 60%) was supplied by Dow Corning Medical, Midland, Michigan. Oppanol® B12SF, a pure polyisobutene (mean molecular weight 30,000 Dalton) was obtained from BASF AG, Ludwigshafen, Germany. Before application, Oppanol® was dissolved in hexane. ScotchPak® 1022 polytetrafluoroethylene-coated polyester liner and CoTran® 9720 polyethylene film (backing) were bought from 3M Medica, Borken, Germany. Fleece-laminated polyester backing was obtained from VanLeer packaging worldwide, 4P Folie, Forchheim, Germany.

Propylene glycol was bought from Sigma-Aldrich-Chemie GmbH, Steinheim, Germany. Lauric acid, (2-hydroxypropyl)-β-cyclodextrin (molecular weight ≈ 1380, degree of substitution ≈ 0.6, melting point $\approx 275^{\circ}C$), sodium dodecyl sulfate, and benzylpenicilline potassium salt were purchased from Fluka Chemie AG, Buchs, Switzerland. Hydroxypropyl cellulose (HPC 75,000) was supplied by Aqualon, Düsseldorf, Germany. Phosphate buffered saline (PBS) (137 mM sodium chloride and 2.7 mM potassium chloride in 10 mM phosphate buffer pH = 7.4) was prepared from tablets, bought from Fluka Chemie AG, Buchs, Switzerland. Water

was double distilled. All other chemicals were of analytical grade.

METHODS

Drug Absorption Studies

Sections of full-thickness skin of male, hairless mice (MF 1 h/h, supplied by Harlan-Winkelmann, Borchen, Germany) were placed into modified, flow-through Franz diffusion cells (effective diffusion area 2 cm^2, Schering AG, Berlin, Germany). Transdermal drug delivery system (2 cm^2, matrix weight between 5 and 30 mg) were applied onto the stratum corneum side of each skin section after removing the release liner. In selected studies, skin was pretreated by filling the donor compartment with 20 μL of a fluid-permeation enhancer formulation 16 h before TDS application.

The receptor fluid, consisting of PBS (phosphate buffered saline) with 3% w/v (2-hydroxypropyl)-β-cyclodextrin as solubility enhancer and 1 Mio I.U./L benzylpenicilline potassium salt as microbiological stablilizer, was pumped through the diffusion cell by a pneumatic pump (model IPN 12 or IPN 16, Ismatec, Glattbrugg-Zürich, Switzerland) at a flow rate of approximately 1 mL/h. The receptor fluid was collected in glass vials (Algroupwheaton, Millville, NJ) during a period of 48 h, changing the vials every two hours over the first eight hours of each study and every eight hours thereafter (automatic sample collector, model retriever III or IV, Isco, Lincoln, Nebraska). In the case of skin pretreatment, the receptor fluid was collected over the additional period of 16 h before the application of the TDS. Selected vials were weighed before and after sampling to control receptor fluid flow rate through Franz cells. The whole system was maintained at 32°C by a thermostatic water pump (model S/F3, Haake, Karlsruhe, Germany). All acceptor solution fractions were stored at −18°C until high-performance liquid chromatography/ultraviolet (HPLC/UV) and gas chromatography/flame ionization detector (GC/FID) analysis, in order to minimize microbiological contaminations and chemical drug degradation.

For each skin section, cumulatively permeated amounts of drugs, enhancers, and solvents were plotted against time, using Microsoft Excel. These curves typically exhibit a linear section during the first 12–24 h, followed by a flattening (see Fig. 3). The linear sections of the curves were individually extrapolated to determine steady-state fluxes (slope) and lag time (point of intersection with time axis). As a third parameter, the total amount of drug permeated (in most cases during 48 h) was calculated.

Manufacturing of Transdermal Systems

Transdermal drug delivery systems were produced in a discontinuous manner by means of an Erichsen coater (Hemer/Westfalen, Germany) model 335/1. The solid drug AE and the solid enhancer lauric acid were dissolved in a part of the solvent. Hydroxypropyl cellulose was dispersed in the fluid-permeation enhancer propylene glycol. Polyisobutene adhesive was dissolved in hexane, and the other three adhesives were obtained as ready-to-use solutions in ethyl acetate. The mixtures of drugs, enhancers, HPC, and solvent were added to the pressure-sensitive adhesive solution. Amounts and concentrations are given in Tables 1, 4, and 5. The resulting wet mixes were coated onto fluoropolymer-treated polyester liner by means of a 400 μm knife. Solvents were removed by oven drying at 70°C. The drying time was adjusted between 20 to 45 min, in order to reach the individually desired content of the partly volatile permeation enhancer propylene glycol.[12] Lamination with polyethylene backing was performed immediately after oven drying. The resulting three-layered sheets were used to die-cut circular TDSs of 2 cm^2 (for in vitro permeation studies) or 10 cm^2 area (for analytical characterization and in vitro release testing).

Analytical Characterization of TDSs

Polyacrylate and silicone matrix TDSs were extracted directly with acetonitrile (40 mL per 10 cm^2 TDSs) by means of an ultrasound bath (30 min, model Sonorex Super RK 103H, Bandelin Electronic, Berlin, Germany) and made up to 50.0 mL for assay. Polyisobutene matrix TDS were dissolved in hexane (30 mL per 10 cm^2 TDSs). These solutions were extracted four-times with 20 mL acetonitrile. Acetonitrile fractions were combined and made up to 100.0 mL for assay. The search for crystals and the investigation of propylene glycol droplet size within TDS matrices was performed with a Laborlux S microscop (Leitz, Bensheim, Germany). After removal of the release liner, the TDSs (10 cm^2) were applied to an object slide. Linear polarization equipment combined with a LAMBDA-plate was used to distinguish crystalline structures from the amorphous adhesive matrix.

In Vitro Release of AE from Transdermal Systems

In vitro release of AE from TDSs was evaluated by means of a dissolution tester (Erweka DT6 Dissolutiontester, Erweka, Heusenstamm, Germany or Prolabo Dissolutest, Firma Janke & Kunkel, Staufen, Germany), using the paddle-over-disk method according to USP 24, ⟨724⟩ Apparatus 5. Transdermal systems (10 cm^2) were fixed with the backing side onto round metal plates by means of 355 Medical silicone adhesive (Dow Corning Medical, Midland, MI). Fleece TDSs were sealed at the lateral side by means of 355 Medical silicone adhesive, in order to avoid lateral drug release from the soaked fleece backing. After removal of the release liner, the specimens were put into the vessels (900 mL 1% aqueous solution of sodium dodecyl sulfate, 32°C) of dissolution tester (50 rpm). One mL samples were taken after 1, 2, 4, 6, 24, and 48 h, and AE content was determined by HPLC/UV.

Assay of Propylene Glycol and Lauric Acid

Hewlett-Packard 5890 Series II gas chromatograph with HP7673A automatic sampler (Agilent Technologies, Palo Alto, (CA), was used with the following: CPSil 5 CB column (Varian Chrompack, Darmstadt, Germany), length: 10 m, ID: 0.53 μm, carrier: helium, injector: 280°C, 1 μL split injection (0.5 min splitless), detector: FID, 280°C, external standard; oven temperature program: 0–4 min: 70°C, 5.4–11.4 min: 170°C, 12.9–21.9 min: 270°C, 24.7–25.7 min: 70°C, heating/cooling rate: 70°C/min; retention times: 1.2 min (propylene glycol) and 8 min (lauric acid).

Aqueous solutions of (2-hydroxypropyl)-β-cyclodextrin contain small amounts of propylene glycol, resulting from hydrolytical side-chain cleavage. Therefore, a blank permeation study was conducted, replacing the skin with a sheet of parafilm. The determined amounts of propylene glycol in acceptor fluid fractions were used as zero values for in vitro permeation studies.

Assay of AE

The following were used: HPLC system, consisting of Degasys DG 1310 degaser, Gynkotec GINA 160 automatic sampler and two Gynkotec high precision pumps, model 300 (Dionex, Sunnyvale, CA), Kontron Instruments M800 gradient mixer (Biotek Kontron Instruments, Neufahrn, Germany); 783A programmable absorbance detector (Applied Biosystems, Weiterstadt, Germany); Perkin Elmer Nelson 900 Series interface and ACCESS*CHROM software (Perkin Elmer, Überlingen, Germany), column: RP 18 Hypersil ODS 3 μm, length 125 mm, inner diameter 4.6 mm (VDS optilab, Montabaur, Germany), injection volume 50 μL, eluent: acetonitrile–water–0.3% w/v trifluoroacetic acid, gradient (acetonitrile:water): 0–0.5 min: 20:80, 1–10 min: 52:48, 11–14 min: 92:8, 16–20 min: 20:80, flow 1.2 mL/min, detection: UV 230 nm, external standard; retention time: 8.5 min (AE).

RESULTS AND DISCUSSION

AE Release and Skin Permeation from Adhesive Matrices

Antiestrogen containing matrix TDSs based on adhesives from three different adhesive classes, polyacrylate (Gelva, Sekisui), silicone (BIO-PSA) and polyisobutene (Oppanol), were manufactured as described in Table 1. Antiestrogen was present in dissolved form in all TDSs, and no crystals could be detected by microscopic examination immediately after manufacturing as well as after three months of

Table 1. Matrix weight and content of various TDS formulations.

Formulation	Adhesive type	Matrix weight (mg/cm^2)	Content AE (%) in relation to matrix weight
1	Gelva polyacrylate	6.93 ± 0.42	1.82 ± 0.05
2	Sekisui polyacrylate	4.91 ± 0.37	1.51 ± 0.05
3	BiO-PSA silicone	7.19 ± 2.70	1.59 ± 0.36
4	Oppanol polyisobutene	5.99 ± 0.38	1.26 ± 0.13

Mean ± standard deviation ($n = 6$).

storage at 25°C and 40°C, respectively. AE release results investigated by in vitro dissolution test are shown in Figs. 1 and 2. Until release of up to 50% of drug, the release profile (Fig. 2) follows the theoretical dependence on the square root of time.[13] Polyacrylate matrices provided fastest release, followed by silicon adhesive matrix; slowest release was obtained from polyisobutene matrix (Fig. 1). These results were not statistically significant.

There are three very important steps during the absorption of drugs from transdermal systems: first the diffusion of the drug out of the TDS, then the partitioning of the drug between the TDS and the stratum corneum, followed by the diffusion of the drug through the stratum corneum. To investigate the partitioning of AE from the adhesive matrix into the skin, in vitro permeation studies of excised skin of hairless mice were performed after pretreatment (16 h) with enhancer combination propylene glycol–lauric acid (9 + 1; 20 µL per 2 cm^2 skin section), thus reducing the barrier function of the stratum cornuem. Results are given in Fig. 3, and Table 2 summarizes steady-state fluxes as well as totally permeated amounts. Steady-state flux of AE from Gelva polyacrylate TDSs was as high as 1 $\mu g\,cm^{-2}\,h^{-1}$. As reported previously,[11] the unhindered permeation rate of AE from fluid formulations through skin without stratum corneum is not more than 6 $\mu g\,cm^{-2}\,h^{-1}$. Therefore, an excellent partitioning of AE from Gelva polyacrylate to the skin was concluded. Other adhesive matrices provided lower AE fluxes. It is noteworthy that the permeation rates did not correlate with the release data from the in vitro dissolution test. In vitro dissolution tests are widely used in quality control for TDS, especially in order to detect batch-to-batch variations.[14,15] They can also be useful in transdermal formulation development to exclude systems that do not release sufficient amounts of drug at all. However, normally in vitro dissolution tests cannot be used to predict transdermal drug fluxes.[14,15]

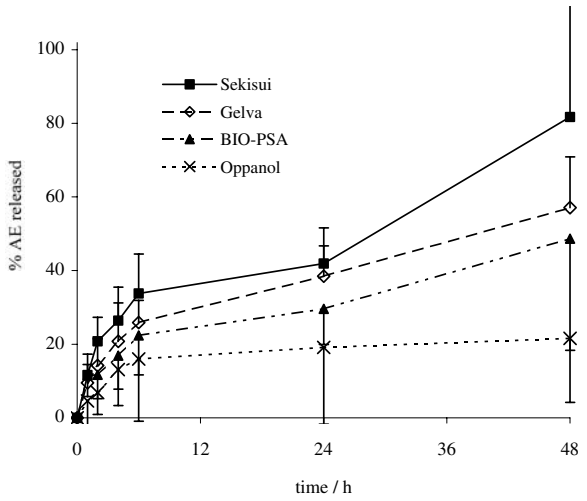

Figure 1. In vitro release of AE from various pressure-sensitive adhesive matrices (mean ± standard deviation; $n = 6$).

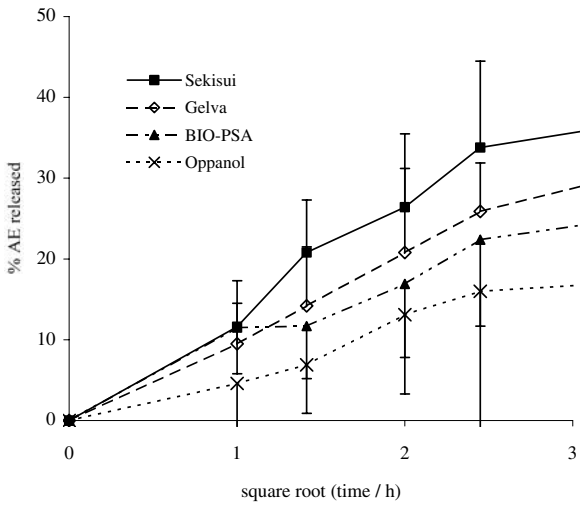

Figure 2. In vitro release of AE from various pressure-sensitive adhesive matrices, plotted against square root of time (mean ± standard deviation; $n = 6$).

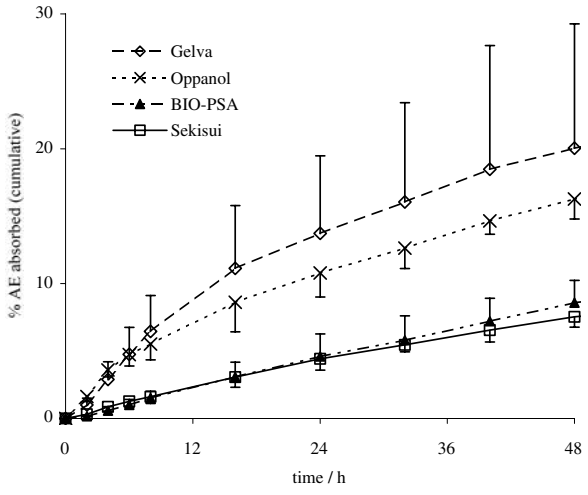

Figure 3. Cumulated transdermal absorption of AE from various pressure-sensitive adhesive matrices through excised skin of hairless mice (mean ± standard deviation; $n = 3$).

Table 2. In vitro permeation of AE through excised skin of hairless mice after pretreatment with propylene glycol–lauric acid (9 + 1) from TDS based on various adhesive materials (concentration AE: 2%).

Formulation		Steady-state flux ($\mu g\,cm^{-2}\,h^{-1}$)	Lag-time (h)	Amount permeated μg (48 h, 2 cm^2)
1	Gelva polyacrylate	1.08 ± 0.35	0.9 ± 0.2	48 ± 19
2	Sekisui polyacrylate	0.12 ± 0.01	0	11 ± 1
3	BIO-PSA silicone	0.31 ± 0.08	1.3 ± 1.2	26 ± 5
4	Oppanol polyisobutene	0.55 ± 0.09	0	26 ± 3

Mean ± standard deviation ($n = 3$).

Table 3. Enhancer capacity of pressure-sensitive adhesive matrices.

	Reachable content propylene glycol (%)			
Adhesive type	Wet mix	Emulsion type	Solvent	TDS
Gelva polyacrylate	35	Droplets, diameter 50 μm	Ethyl acetate	20
Sekisui polyacrylate	35	Microscopic homogen	Ethyl acetate/isopropanol	20
BIO-PSA silicone	20	Droplets, diameter 10–20 μm	Ethyl acetate/hexane	10
Oppanol polyisobutene	20	Droplets, diameter 50 μm	Ethyl acetate/hexane	1[a]

[a]After manufacturing, propylene glycol leached out of the polyisobutene matrix and formed a thin layer between the matrix and the backing.

Enhancer Capacity of Adhesives Matrices

Lauric acid is freely soluble in ethyl acetate. Therefore, this compound can be dissolved (content ≥ 5 %) in each of the adhesive solutions studied. Propylene glycol is a fluid, partly volatile, permeation enhancer, and it is not miscible with ethyl acetate. For these reasons, propylene glycol has to be dispersed in the adhesive solutions. During the heat-drying step of the TDS manufacturing process, the content of propylene glycol decreases. As a consequence, the drying time has to be chosen individually for each formulation (in the range between 20 and 45 min) in order to totally evaporate solvent while keeping propylene glycol content as high as possible.[12]

Emulsions containing propylene glycol and Gelva adhesive solution in ethyl acetate were sufficiently stable for further manufacturing steps. However, emulsions containing other adhesive solutions were not sufficiently stable when pure ethyl acetate was used as solvent. Therefore, these wet mixes were prepared using binary mixtures of solvents as specified in Table 3. The capacity of adhesive matrices for the fluid-permeation enhancer propylene glycol is also given in Table 3. Polyacrylate matrices showed highest capacity for propylene glycol (20%), and silicone pressure-sensitive adhesive provided only 10% propylene glycol capacity. Although propylene glycol could be dispersed in polyisobutene adhesive solution, there was found no more than 1% propylene glycol in the polyisobutene matrix, due to separation of propylene glycol from matrix and deposition between matrix and backing layer.

Enhancer-Loaded TDSs Based on Polyacrylate Adhesives

Due to its high enhancer loading capacity and the good partitioning of incorporated AE to the skin, Gelva polyacrylate adhesive was chosen for further development. In a previous study,[16] transdermal systems with varying AE content (in relation to matrix weight) in the range from 2.5–19%, lauric acid content from 2.5–13%, and propylene glycol content from 14–27% were described. Antiestrogen and lauric acid were present in the TDSs in dissolved form, and propylene glycol was dispersed in the form of droplets of approximately 50 μm diameter. If propylene glycol content did not exceed 20%, these systems had good adhesive properties and sufficient cohesive strength. In vitro permeation of these enhancers through excised skin of hairless mice was increased by higher enhancer contents in the respective TDS formulations. However, even enhancer concentrations as high as 20% were too low to promote sufficient enhancer penetration of the skin, and in consequence, to disturb the barrier.

In order to further increase capacity of the TDS for the fluid-permeation enhancer propylene glycol, two different attempts were selected. Firstly, a thickening agent was added to the Gelva polyacrylate matrix in order to improve cohesive strength and adhesive properties. The second strategy was the use of a fleece-laminated backing foil that was soaked with a liquid formulation and then laminated with a thin adhesive layer.

Polyacrylate TDSs with a Thickening Agent

The propylene glycol loading capacity of Gelva polyacrylate TDSs is limited by the poor adhesive properties of these systems above 20% propylene glycol content. This can be overcome by thickening the adhesive solution. Since a basic drug and the permeation enhancer lauric acid are used in the same formulation, the nonionic hydrophilic thickening agent hydroxypropylcellulose (HPC) was selected. The addition of at least 10% (in relation to propylene glycol content) HPC to Gelva multipolymer solution allowed the increase of propylene glycol content in the wetmix up to 45% (per solids). In this case the droplet diameter was reduced to 6 μm, indicating a markedly more stable emulsion. The resulting emulsion macroscopically appeared transparent, in contrast to the whitish appearance of the emulsion without HPC. However, when concentrations above 10% HPC were used, the viscosity become too high for the coating process. For the manufacture of TDSs, an adhesive solution with the following contents in relation to solids was prepared: 40% propylene glycol, 10% lauric acid, 10% drug, and 4% HPC (i.e., 10% in relation to propylene glycol content). Coating was carried out by a 400 μm knife, and drying time was 25 min. Table 4 shows the composition of the resulting TDS. No crystals could be found by microscopic examination. Propylene glycol was dispersed in the matrix in the form of droplets of approximately 6 μm diameter.

TDSs with a Soaked Fleece-Laminated Backing

The second strategy to increase the enhancer load of TDSs provided a reservoir system which was manufactured in nearly the same way as a standard monolithic matrix TDS. For this purpose a fleece-laminated backing foil was used. The fleece was filled with a liquid formulation (15 mg/cm^2), consisting of 10% AE solution in the transdermal permeation-enhancer combination propylene glycol–lauric acid (9 + 1). In order to apply this soaked fleece onto skin, an adhesive layer is requested, which, on the one hand, has good adhesive properties to the fleece as well as to the skin and on the other hand, a good permeability for the enhancers and the drug. In preliminary studies, various polyacrylate type adhesives were tested, but only Sekisui showed sufficient adhesion to the soaked fleece. Therefore, pure Sekisui adhesive solution was coated on a liner using a 300 μm knife, and then dried at 70°C for 20 min. After cooling down to room temperature, the soaked fleece-laminated backing was carefully joined to this laminate. Resulting composition of TDSs is given in Table 5.

Table 4. Composition of TDS with hydroxypropylcellulose (HPC) as thickening agent based on Gelva polyacrylate adhesive.

Formulation	HPC/Gelva
Matrix weight (mg/cm^2)	7.64 ± 0.95
Content (%), in relation to matrix weight	
AE	10.4 ± 1.0
Lauric acid	10.1 ± 0.6
Propylene glycol	31.3 ± 6.9
HPC[a]	4.0

Mean ± standard deviation ($n = 6$).
[a]HPC: required value, content was not determined.

Table 5. Composition of TDS with soaked fleece backing and Sekisui polyacrylate adhesive.

Formulation	Fleece/Sekisui
Content (mg/cm^2)	
AE	1.11 ± 0.09
Lauric acid	1.12 ± 0.10
Propylene glycol	11.4 ± 0.76
Polyacrylate adhesive	4.03 ± 0.33

Mean ± standard deviation ($n = 6$).

AE Release and Skin Permeation from TDSs with High Enhancer Content

Results from in vitro dissolution tests are shown in Fig. 4. Until release of up to 50% of the drug the release profile follows the theoretical dependence on the square root of time. The release of AE through polyacrylate (Sekisui) adhesive layer was fast and

therefore should not limit transdermal permeation. In order to investigate transdermal permeation of AE and enhancers, an in vitro permeation study through excised skin of hairless mice was carried out, applying each formulation onto three native skin sections and onto three pretreated (20 μL propylene glycol–lauric acid (9 + 1)) skin sections, respectively. Results are given in Tables 6,7. Both transdermal permeation of AE and enhancers through intact skin were in the range of passive permeation of these compounds from transdermal fluid formulations without enhancers.[11] Obviously no barrier-reducing activity of permeation enhancers could be detected in this case. In the case of the TDS with soaked-fleece backing, this is probably due to low permeation of the enhancers through the Sekisui adhesive layer. However, skin pretreatment resulted in a marked rise in transdermal permeation of both AE and lauric acid. Especially the HPC-thickened polyacrylate TDS provided high AE fluxes of 2.6 μg cm^{-2} h^{-1} through pretreated skin.

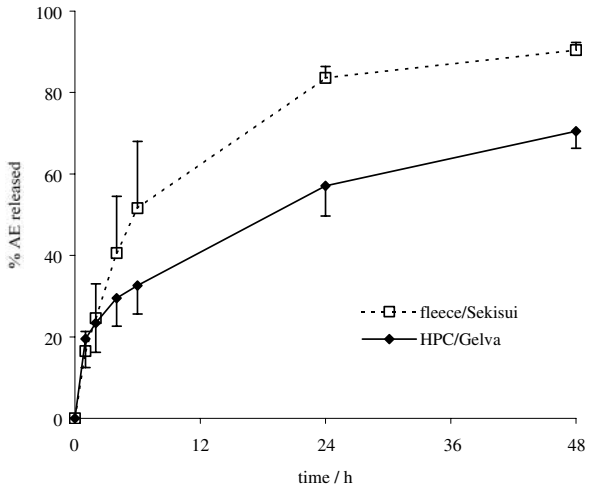

Figure 4. In vitro release of AE from TDS with high propylene glycol contents (mean ± standard deviation; $n = 3$).

CONCLUSIONS

From the data presented above, it is concluded that permeation of the highly lipophilic drug AE is limited by the stratum corneum barrier function.

Table 6. In vitro permeation of AE, lauric acid, and propylene glycol from polyacrylate matrix TDS with hydroxypropylcellulose as thickening agent.

Compound	Steady-state flux (μg cm^{-2}h^{-1})	Lag time (h)	Amount permeated μg (48 h, 2 cm^2)
Native skin without pretreatment			
AE	0.09 ± 0.04	3 ± 2	9 ± 4
Lauric acid	2 ± 0.1	0	175 ± 22
Propylene glycol	100 ± 53	1 ± 1	3380 ± 350
Skin pretreatment: propylene glycol–lauric acid (9 + 1)			
AE	2.62 ± 0.62	3 ± 1	170 ± 80
Lauric acid	17 ± 10	0	360 ± 267
Propylene glycol	196 ± 121	0	2600 ± 1690

Mean ± standard deviation ($n = 3$).

Table 7. In vitro permeation of AE, lauric acid, and propylene glycol from TDS with soaked fleece backing.

Compound	Steady-state flux (μg cm^{-2} h^{-1})	Lag-time (h)	Amount permeated μg (48 h, 2 cm^2)
Native skin without pretreatment			
AE	0.06 ± 0.02	3.8 ± 2.1	4 ± 1
Lauric acid	4 ± 2	2.4 ± 0.7	154 ± 62
Propylene glycol	225 ± 44	2.2 ± 0.4	9370 ± 1720
Skin pretreatment: propylene glycol lauric acid (9 + 1)			
AE	0.46 ± 0.31	2.9 ± 0.3	33 ± 29
Lauric acid	17 ± 2	0	584 ± 264
Propylene glycol	318 ± 118	0	10960 ± 3510

Mean ± standard deviation ($n = 3$).

Although enhancer content of TDSs was markedly increased by thickening the adhesive matrix and by using a fleece-laminated backing as well, enhancer release from these systems was not yet sufficient to reach marked enhancer penetration into the skin, and consequently, to disturb the barrier. Further development should focus on a reservoir/membrane type TDS, which provide higher enhancer content.

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