Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmaceutics and Biopharmaceutics 66 (2007) 422–428
European Journal of Pharmaceutics and Biopharmaceutics
www.elsevier.com/locate/ejpb

Research paper

Single-layer transdermal film containing lidocaine: Modulation of drug release

Cristina Padula, Sara Nicoli, Paolo Colombo, Patrizia Santi *

Department of Pharmacy, University of Parma, Parma, Italy

Received 3 July 2006; accepted in revised form 21 November 2006
Available online 29 November 2006

Abstract

We have recently described an innovative drug delivery system, a water-based and vapor permeable film intended for dermal and/or transdermal delivery. The aim of this work was to modulate the delivery of the model drug lidocaine hydrochloride from the transdermal film across rabbit ear skin. The effect of drug loading, of film-forming polymer type and content, of adhesive and plasticizer on lidocaine transport across the skin was evaluated. Additional objective was to evaluate the effect of occlusion on the kinetics of lidocaine transport, by applying an occlusive backing on the surface of the transdermal film. From the data obtained it can be concluded that the transdermal film acts as a matrix controlling drug delivery. The film-forming polymer molecular weight had a negligible effect on drug penetration, while its content was more effective. The choice of the adhesive seems to be the most important variable governing drug transport. In particular, the presence of lauric acid combined with a basic drug, such as lidocaine, can produce a relevant improvement in permeation, because of the formation of an ion pair. Concerning the kinetics, drug depletion is responsible for the declining permeation rates observed in the late times of permeation.

Keywords: Transdermal; Patch; Permeation; Rabbit ear skin; Lidocaine

1. Introduction

Transdermal patches are innovative drug delivery systems intended for skin application in view of achieving a systemic effect. Among the different types of systems, the drug-in-adhesive products, in which the drug is included in the adhesive layer contacting the skin, are very commonly used, being thin, conformable and comfortable. More and more efficient systems are introduced into the market, with the advantage of reducing the size of the patch to the size of a stamp (DOT-Matrix®, Novogyne Pharmaceuticals).

Transdermal patches are generally occlusive, i.e., they do not allow water to be released from the skin surface, and this is often the reason for skin irritation [1]. On the other hand, occlusion generally increases drug transport because it augments the water content of the stratum corneum, although the effect is not the same for different permeants [2]. An alternative to water permeable patches [3] is the use of non-occlusive gels or, more recently, of quick-drying sprays [4]. The last approach has been used for isosorbide dinitrate [5], but poor bioavailability was observed, implying that a large surface area must be used. Metered-dose transdermal systems (MDTS®, Acrux Inc., Melbourne, Australia) are constituted of a solution of the drug in volatile and non-volatile solvents. Upon atomization, the volatile solvents evaporate quickly, leaving a concentrated drug solution in the non-volatile component that is taken up into the stratum corneum and forms a reservoir from which the drug can be released.

We have recently described an innovative drug delivery system, a water-based and vapor permeable bioadhesive film intended for dermal and/or transdermal delivery

* Corresponding author. Department of Pharmacy, University of Parma, Viale G.P. Usberti, 27/A, 43100 Parma, Italy. Tel.: +39 0521 905069; fax: +39 0521 905006.
E-mail address: patrizia.santi@unipr.it (P. Santi).

0939-6411/$ - see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejpb.2006.11.014

[6–8]. The transdermal film is not adhesive in the dry state but only when applied on wet skin. The permeation kinetics across the skin of model drugs included in the transdermal film, namely lidocaine and caffeine, was unusual, showing a sort of ''burst'' effect in the early times of permeation. In the case of caffeine, this was attributed to a certain degree of ''conserved supersaturation'' in the solid phase [8]. In the late times of the experiment the permeation across the skin was slower, and this was attributed to drug depletion from the transdermal film [6]. Overall, the permeation profiles became linear with the square root of time, suggesting a matrix-type control of drug delivery by the film.

The aim of this work was to modulate the delivery of the model drug lidocaine hydrochloride from the transdermal film across rabbit ear skin. The effect of drug loading, of film-forming polymer type and content, of adhesive and plasticizer on lidocaine transport across the skin was evaluated. Additional objective was to evaluate the effect of occlusion on the kinetics of lidocaine transport, by applying an occlusive backing on the surface of the transdermal film. Rabbit ear skin was used as barrier, because it has been shown to be a reasonable model for human skin in vitro, using lidocaine as model drug [9].

2. Materials and methods

Silicone membranes (thickness 0.25 mm) were obtained from Perouse Plastie, Bornel, F, while lidocaine hydrochloride (M_w 270.2, $pK_a = 7.9$) was a gift from Lisapharma (Erba, I). Eudragit® E100 was obtained from Rofarma (Gaggiano, Milan, Italy) while polyvinyl alcohol (PVA) of molecular weights of 29,400, 83,400 and 115,200 (degree of hydrolysis 87%) from Nippon Ghosei (Osaka, J). Polyvinyl pyrrolidone K30 (PVP) was a gift from BASF (Ludwigshafen, D). All other chemicals used were of analytical grade.

Plastoid® E35H was prepared according to the protocol of Rofarma: Eudragit® E100 (15.9% w/w), lauric acid (9.2% w/w), and adipic acid (1.8% w/w) were added to hot water (72.1% w/w, temperature ~80 °C). The mixture was stirred, maintaining the temperature at ~80 °C, until a clear solution was formed. The solution was cooled to 60 °C and glycerol (1.0% w/w) was added. The mixture was then gradually cooled to room temperature while stirring.

2.1. Film preparation

Films containing lidocaine hydrochloride were prepared as previously described [6]. The composition of the mixtures to be laminated is reported in Table 1. A solution of lidocaine hydrochloride in water/plasticizer was added to PVA water solution and to the adhesive Plastoid® E35H or to PVP 16% w/w solution. The resulting mixture was slowly stirred overnight using a magnetic bar. All mixtures were laminated on siliconized paper using a film casting knife (BYK Gardner, Silverspring, MD, USA; gap 200 μm) and oven-dried at 80 °C. After drying for 30 min to final water content of approx. 10% w/w (as determined by Karl Fisher titration), the films (10 × 20 cm) were covered with a second siliconized paper and individually sealed in aluminum pouches.

2.2. Film characterization

Once dried, 3 circles 26 mm in diameter were cut from each film. Each circle was measured for weight and thickness (Absolute Digimatic 547-401, Mitutoyo, Milan, I, resolution 0.001 mm) and then was dissolved in 100 ml of water under sonication for 1 h. The solutions obtained were analyzed by HPLC in order to determine the amount of lidocaine contained in the transdermal film. The results were expressed as percentage of lidocaine (w/w) and as mg/cm^2 (see Table 1).

2.3. In vitro transport experiments

Permeation experiments were conducted in vertical Franz-type diffusion cells (Disa, Milan, I), with an exposed surface area of either 3.9 cm^2 (when patches were used as donor) or 0.6 cm^2 (when solutions were used as donor).

Table 1
Composition of the mixtures used for film preparation (% w/w on wet basis)

	L29S2H	L29S2	L83S2	L83G2	L83S8	L115S2	L83S2PVP
PVA 29	18.6	12.4	–	–	–	–	–
PVA 83	–	–	12.4	12.4	11.2	–	12.4
PVA 115	–	–	–		–	12.4	–
Plastoid® E35H	27.0	27.0	27.0	27.0	27.0	27.0	–
PVP 16% solution	–	–	–	–	–	–	27.0
Sorbitol	4.0	4.0	4.0	–	4.0	4.0	4.0
Glycerin	–	–	–	4.0	–	–	–
Lidocaine HCl	2.0	2.0	2.0	2.0	8.0	2.0	2.0
Water	48.4	54.6	54.6	54.6	49.8	54.6	54.6
Lidocaine content[a]							
% w/w	5.2 ± 0.1	7.1 ± 0.1	5.6 ± 0.1	5.7 ± 0.1	19.6 ± 0.1	5.9 ± 0.1	7.1 ± 0.1
mg/cm^2	0.28 ± 0.01	0.27 ± 0.01	0.25 ± 0.01	0.21 ± 0.01	1.06 ± 0.01	0.38 ± 0.01	0.54 ± 0.01

[a] As base on finished product.

Preliminary experiments have shown that the size and geometry of the cells does not modify the results obtained. Rabbit ear skin or silicone membrane was used as barrier. Rabbit skin was excised post-sacrifice from the inner part of rabbit ears (6 months old) obtained from a local slaughter's house. When not used immediately, the skin was kept refrigerated (2–5 °C) and used within 3 days.

The donor compartment was filled with the following formulations:

(i) Lidocaine hydrochloride solutions (2% w/w alone or with Plastoid® E35H or with PVP): 1 ml was applied on 0.6 cm^2;
(ii) Film: the prepared film (3.9 cm^2) was applied on a 3.9 cm^2 area. Since the film is adhesive only in the presence of water, the exposed skin area was wetted with a measured volume of water (about 15 $\mu l/cm^2$) before film application.

The receptor phase was 0.9% w/v sodium chloride solution (lidocaine solubility 6.54 mg/ml [6]), thermostated at 37 °C and magnetically stirred (100 rpm) in order to prevent any boundary layer effects. At predetermined time intervals the receptor solution was sampled and analyzed by HPLC for the determination of lidocaine permeated.

Each permeation experiment was replicated at least 4 times, on skin samples obtained from different animals.

In the experiments from solutions, the permeation profiles were fitted to the equation given below:

$$Q = (KH)C_{veh}\left[\frac{D}{H^2}t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{n=7}\frac{(-1)^n}{n^2}\exp\left(\frac{-Dn^2\pi^2 t}{H^2}\right)\right] \quad (1)$$

where Q is the cumulative amount of drug permeated per unit area at time t, C_{veh} is the concentration of the drug in the donor vehicle, K is the stratum corneum/vehicle partition coefficient, D is the diffusion coefficient and H is the diffusion path-length. The permeability coefficient P was calculated as the product between KH and D/H^2. The fitting was performed using KaleidaGraph® 3.6.2 (Synergy Software) running on a MacIntosh Power Book G4. The average error associated with each fitted value was in the range 3–20%.

2.4. Lidocaine analysis

The amount of lidocaine in the samples was quantified by high pressure liquid chromatography (HPLC) using a Perkin-Elmer liquid chromatograph (Perkin-Elmer, Norwalk, CT, USA) which included a UV detector, set to 216 nm and an analytical column μBondapak® C18 300 × 3.9 mm (Waters, Milford, MA, USA). A mixture (14/86, v/v) of acetonitrile and potassium dihydrogen phosphate 0.05 M (brought to pH 4.0) was used as mobile phase, at a flow rate of 1.3 ml/min. Injection volume was 50 μl. In these conditions the retention time was about 9 min. The method has been previously validated [6].

2.5. Statistical analysis

Each experiment was replicated at least four times. The significance of the differences between values was assessed using ANOVA (KaleidaGraph 3.6.2 software on a Macintosh PowerBook G4) followed by Bonferroni's test.

3. Results and discussion

Table 1 reports the composition of the mixtures used for transdermal film preparation, together with the respective values of lidocaine content in the finished product. The films prepared were identified with an alphanumerical code: the first letter stands for lidocaine, the following two numbers refer to the molecular weight of PVA, the fourth letter refers to the plasticizer (S for sorbitol and G for glycerin), the fifth digit refers to lidocaine hydrochloride content on wet basis and the sixth digit refers for total PVA content (H stands for high content), or to the replacement of Plastoid with PVP (PVP).

Lidocaine loading ranged from 5.0% to 19.6% w/w. The effect of polymer type and content was examined using PVA with different molecular weight (29,400–115,200) in differing amounts (12.4% or 18.6% w/w on wet basis). Sorbitol or glycerin was used as plasticizer and PVP or Plastoid® as adhesive.

3.1. Effect of polymer molecular weight and content

The polymer PVA represents the structuring agent of the transdermal film and can play a role in determining drug release. Three different molecular weights of PVA were used, namely 29,400 (PVA29), 83,400 (PVA83) and 115,200 (PVA115) (Table 1). PVA29 was tested at two different concentrations, i.e., 18.6% and 12.4% w/w on wet basis, while the other PVAs were kept at 12.4%. The rationale behind the use of PVAs with different molecular weights was that it could modify drug transport, because the mechanism involved in drug release is diffusion. In a previous paper [6] we have shown that lidocaine release from the transdermal film is conditioned to the hydration of the polymeric component by the water used in its application. In other words, the transdermal film – applied on the wet skin surface – absorbs water, swells and then drug release takes place. The use of different molecular weights of the same polymer can modify the extent/kinetics of swelling and/or the diffusive mobility of the drug in the polymeric network. The change of polymer content in the finished product can, in principle, modify swelling and/or diffusive mobility as well. Fig. 1 shows the permeation profiles obtained. In analogy with the data reported previously [6], all profiles were not linear with time, but showed a fast initial permeation, followed by a reduced flux in the late times. From the observation of the profiles it is quite evi-

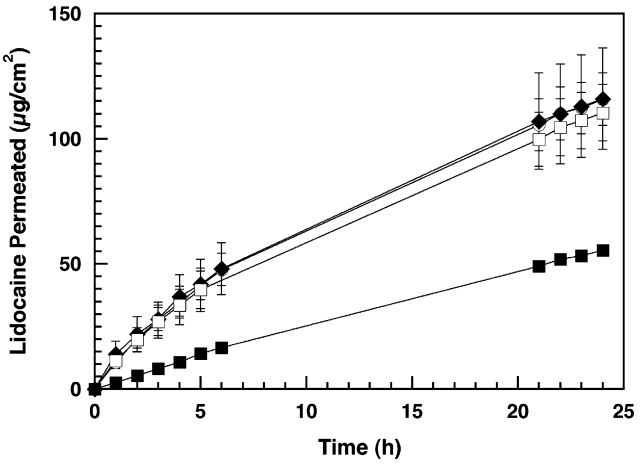

Fig. 1. Permeation profiles of lidocaine across rabbit ear skin from different films (see Table 1): L83S2 (○), L115S2 (◆), L29S2 (□), L29S2H (■). Average values ± SEM; $n \geqslant 4$.

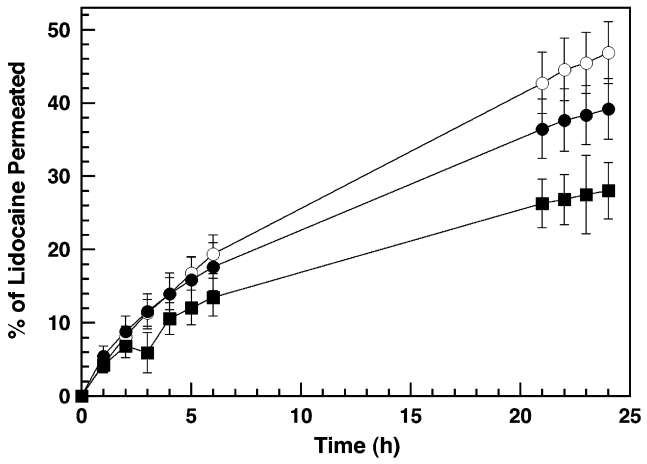

Fig. 2. Percentage of lidocaine permeation across the skin from films L83S2 (○), L83S8 (■) and L83G2 (●). Average values ± SEM; $n \geqslant 4$.

dent that changing the molecular weight of the polymer from 29,400 (L29S2) to 115,200 (L115S2) did not modify drug release, either in terms of amount permeated or in terms of kinetics. In the three cases (L29S2, L83S2 and L115S2) the profiles were almost super-imposable, despite slight differences in drug content (see Table 1). On the contrary, the increase in PVA content in the formulation from 12.4% to 18.6% (L29S2 vs. L29S2H) lowered in a significant way the permeation profile obtained (statistical analysis on the amount permeated at 24 h: $p < 0.01$). The polymer content in the finished product, on dry basis, was 61% w/w for L29S2H and 52% w/w for L29S2. The reduction of permeation rate can be due, at least in part, to the different lidocaine loading (5.2% vs. 7.1% w/w), but also to the polymer concentration. In fact, it is well known that in swellable matrices, the use of a higher amount of polymer can produce a more "dense" polymeric network upon hydration with water, responsible for the reduced diffusivity of the drug included [11].

Overall these results suggest that it is the percentage of polymer more than its molecular weight the determinant for drug release from the film.

3.2. Effect of type of plasticizer

Fig. 2 shows the percentage of lidocaine permeated from films containing either sorbitol or glycerin. A previous report [12] on the effect of amount and type of plasticizer on the mechanical properties of the transdermal film (tensile strength and elongation at break) showed that glycerin gave higher flexibility to the film than sorbitol. Concerning drug transport, sorbitol and glycerin seem to be equivalent, because the permeation profiles obtained were not significantly different. However, this result cannot be generalized, because the effect of plasticizer on drug transport is probably related to the physico-chemical properties of the permeant, in particular to its solubility in the plasticizer. As described earlier (see Fig. 1), the profiles were not linear with time, but showed a fast initial permeation, followed by a reduced flux in the late times. Considering the high percentage of lidocaine permeated, the reason for the declining permeation rate is probably drug depletion from the film.

It is important to underline that the percentage of lidocaine permeated across the skin from the transdermal film was unusually high for a patch. In fact, 50% of the amount loaded had permeated the skin after 24 h. This aspect represents a novelty for this type of delivery system and can be of particular importance for the safety of the exhausted system and when dealing with a very expensive active.

3.3. Effect of drug loading

The increase in drug loading from 5.6 (L83S2)% to 19.6 (L83S8)% w/w, using sorbitol as plasticizer and PVA83 as film-forming agent, produced an obvious increase in the amount of lidocaine permeated, although the percentage permeated did not change so much, as can be observed in Fig. 2.

3.4. Effect of occlusion

Previous studies have shown that the application of an occlusive backing on the transdermal film object of the present work, loaded with progesterone, can increase to a significant extent the amount of drug permeated across the skin [13]. The same approach was used for lidocaine and the result is reported in Fig. 3, in comparison with the non-occluded film. Occlusion seems to increase slightly the amount of lidocaine permeated, although the difference was not statistically significant (statistical analysis on the amount permeated at 24 h $p = 0.45$). The difference between the results obtained with progesterone and lidocaine hydrochloride is probably due to the different physico-chemical properties of the two drugs, in particular the

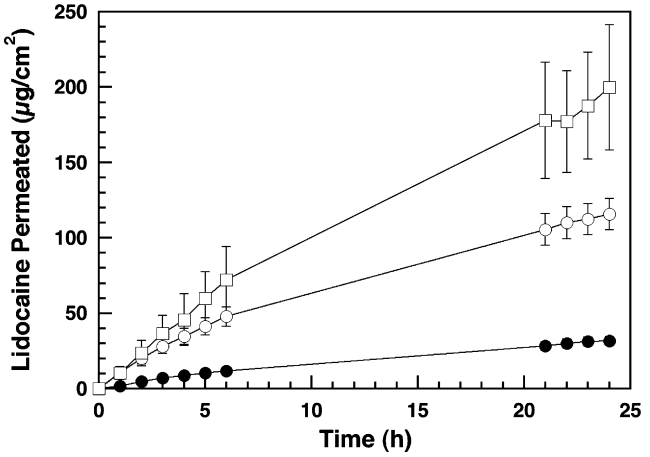

Fig. 3. Permeation profiles of lidocaine across rabbit ear skin from films L83S2PVP (●) and L83S2 in non-occlusive (○) and occlusive condition (□). Average values ± SEM; $n \geqslant 4$.

lower lipophilicity of lidocaine hydrochloride compared to that of progesterone. In fact, previous studies [2] have shown that occlusion produces a different effect depending on the physico-chemical properties of the drug, in particular it is more efficient for lipophilic permeants.

3.5. Effect of adhesive

Finally the effect of adhesive was examined. Two typical adhesives for transdermal drug delivery, namely Plastoid® E35H (L83S2) and PVP (L83S2PVP), were tested using PVA83 as film-forming agent and the results are reported in Fig. 3. Despite the small difference in drug loading (7.1% vs. 5.6% w/w) the permeation profiles were notably different, the film containing PVP (7.1% w/w of lidocaine) being much less efficient in delivering lidocaine. PVP can alter the solubility of lidocaine into the film, because it is a known solubilizing agent for poorly soluble drugs [14]. Increased drug solubility in the vehicle produces a reduction of the thermodynamic activity of the drug in the formulation, which in turns reduces the flux of the drug [15]. Moreover, Plastoid® E35H is a mixture of an acrylic polymer, namely dimethylaminoethyl methacrylate (Eudragit® E100), with lauric and adipic acids. It is well known that lauric acid can act as penetration enhancer for transdermal drug delivery, because it is able to penetrate into the stratum corneum and alter its lamellar structure, decreasing the overall lipid order [16–20]. Additionally, lauric acid can form ion pairs with organic bases including lidocaine [21], thus increasing their lipophilicity.

With the aim of verifying the underlying reasons for the difference observed between Plastoid® E35H and PVP, solution experiments were carried out. Solutions of lidocaine hydrochloride in water (2% w/w) were prepared: Solution 1 contained only the drug, Solution 2 contained lidocaine and Plastoid® E35H (27% w/w) and Solution 3 contained lidocaine and PVP (27% w/w of a 16% w/w solution). Fig. 4a reports the permeation profiles obtained and

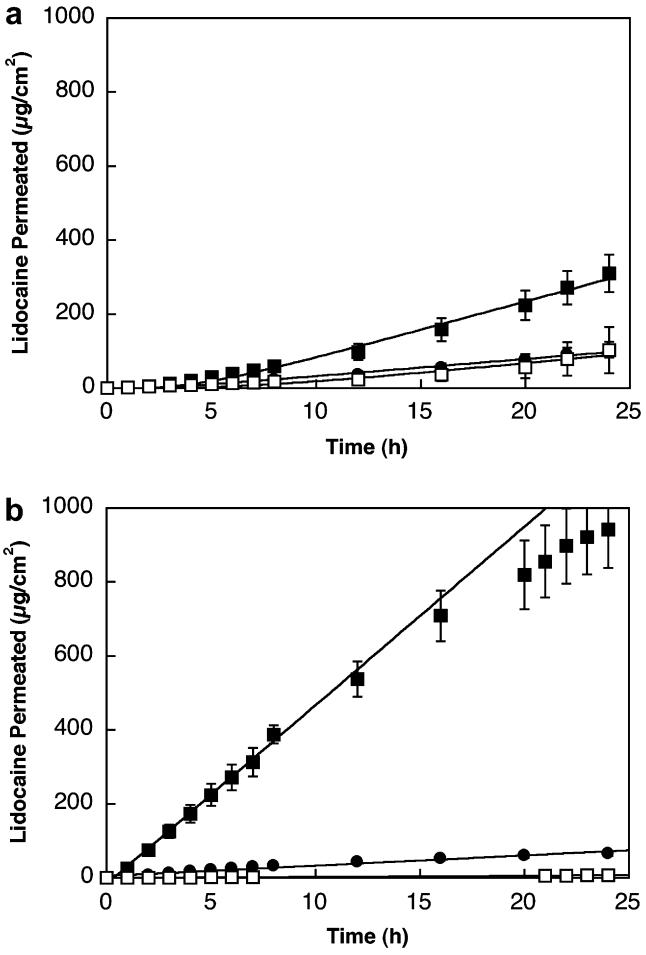

Fig. 4. Permeation profiles of lidocaine across rabbit ear skin (a) and silicone membrane (b) from solutions of lidocaine HCl 2% w/v: neat solution (●), Plastoid® E35H (■) and PVP (□). Average values ± SEM; $n \geqslant 4$. Lines represent the fitting of the data to Eq. (1), made on all data points except for Plastoid® E35H (b) for which only the first 8 h were included in the fitting.

shows that PVP had no effect on lidocaine permeation, while Plastoid® E35H increased in a significant way the amount of lidocaine permeated, compared to the neat solution in water. The permeation profiles were fitted to the appropriate solution of Fick's law for non-steady conditions [10] (Eq. (1)), to calculate the relevant permeation parameters, which are reported in Table 2. The fitting was made on all data points, except for Plastoid® E35H across silicone membrane for which only the first 8 h was included. The parameter KH gives indications as to the partitioning characteristics of the molecule, while D/H^2 represents the diffusive parameter. These parameters yield information about the effect of formulation, in particular the vehicle and penetration enhancer, on partition and diffusion of the permeant in and across the stratum corneum [22,20]. Data analysis reveals that Plastoid® E35H acts on the partitioning parameter, increasing it, while the diffusive parameter, although very variable, is not affected. Lauric acid (contained in Plastoid® E35H) is a known permeation enhancer. Artusi et al. [20] have shown that lauric acid,

Table 2
Permeation parameters of lidocaine across rabbit ear skin and silicone membranes from 2% w/w solutions (mean values ± SEM)

	$KH \times 10^3$ (cm)		$D/H^2 \times 10^3$ (h^{-1})		$P \times 10^4$ ($cm\,h^{-1}$)	
	Skin	Silicone	Skin	Silicone	Skin	Silicone
Neat Solution	8.6 ± 2.9	0.71 ± 0.2	64.2 ± 18.4	472 ± 106	3.0 ± 0.5	2.7 ± 0.3
Sol. Plastoid®	31.5 ± 4.6**	7.5 ± 0.6**	33.7 ± 5.9	423 ± 68	9.5 ± 1.2**	29.8 ± 4.0**
Sol. PVP	8.3 ± 6.4	0.35 ± 0.01	47.3 ± 14.9	71 ± 0.5*	2.9 ± 2.8	0.25 ± 0.01**

Significantly different from neat solution (*$p < 0.05$; **$p < 0.001$).

at 4% w/v, increased the partitioning parameter of the hydrophilic molecule thiocolchicoside across rabbit ear skin. Additionally, it has been shown that lauric acid can interact with cationic drugs such as sumatriptan [23], naphazoline [16] or lidocaine [21] forming ion pairs that are more lipophilic than the cationic drug and produce higher transdermal fluxes. To further confirm that Plastoid® E35H acts mainly on the permeant rather than as penetration enhancer on the skin, the experiments with solutions were performed also using an inalterable membrane such as a silicone membrane, on which a penetration enhancer such as lauric acid cannot produce direct effects. The results obtained are reported in Fig. 4b, where it can be observed that the effect of Plastoid® was the same as on the skin. The analysis of the permeation parameters (Table 2) confirms that the presence of Plastoid® produces a considerable (tenfold) increase of the partitioning parameter, while the diffusive parameter did not change. The use of PVP produced a decrease of lidocaine permeation across the artificial membrane, which resulted from a considerable reduction of the diffusive parameter, as can be seen in Table 2.

Then, the adhesive seems to play an important role in determining drug release.

3.6. Kinetics

On the basis of our previous conclusions on lidocaine [6], the first elaboration was done by simply plotting the amount of lidocaine permeated across the skin against the square root of time. A good data fitting was obtained in all cases (R^2 was always higher than 0.95), suggesting a common mechanism of drug release for all transdermal films. To better understand drug release mechanism, the permeation experiments using the film were also performed using silicone membrane as barrier. The percentage of lidocaine permeated from the film and from water solution of lidocaine is presented in Fig. 5, in comparison with the respective data obtained across rabbit ear skin. The permeation profile from the film across both barriers showed a high permeation rate in the early time of the experiment, more pronounced for silicone than for the skin. After 24 h, the percentage permeated was the same across the two barriers, approx. 50% of the amount loaded. The higher initial permeation across silicone barrier can be justified by the higher diffusivity of lidocaine across silicone barrier, demonstrated also by the higher permeation from solution.

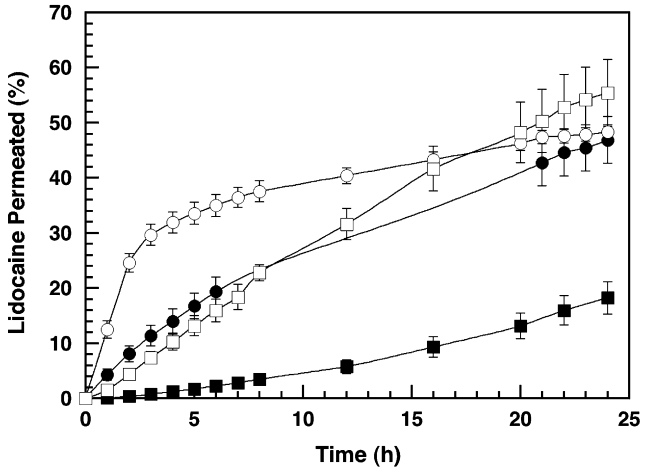

Fig. 5. Percentage of lidocaine permeated across rabbit ear skin (full symbols) and silicone membranes (empty symbols) from solution containing Plastoid® E35H (squares) and film L83S2 (circles). Average values ± SEM; $n \geqslant 4$.

The decline in permeation observed with the film – regardless of the barrier used – is due to drug depletion in the region of the film in contact with the barrier itself.

The results obtained with the two barriers, silicone membrane and rabbit ear skin, suggest that the element of control of lidocaine permeation across the skin was the release of the drug from the formulation. In particular, the film shows a matrix-type control of drug release, with initial high flux followed by a decline in flux due to drug depletion.

4. Conclusions

From the data obtained it can be concluded that the transdermal film acts as a matrix controlling lidocaine delivery, as shown by the shape of the permeation profiles across the skin. Using lidocaine as model drug, we have shown that drug permeation across the skin can be modulated, by changing the type or the amount of constituents. The film-forming polymer molecular weight had a negligible effect on drug release, while its content was more important. The choice of the adhesive seems to be the most important variable governing drug transport. In particular, the presence of lauric acid combined with a basic drug, such as lidocaine, can produce a relevant improvement in permeation, because of the formation of an ion pair. Using

a silicone membrane as barrier, it was possible to show that drug depletion is responsible for the declining permeation rates observed in the late times of permeation. Overall, up to 50% of the drug included crossed rabbit ear skin after 24 h of application.

Acknowledgements

S.p.A. Lisapharma (Como, I) is gratefully acknowledged for supporting this work. BASF Italia (Cesano Maderno. I) is acknowledged for supplying PVP.

References

[1] H. Zhai, H.I. Maibach, Occlusion vs. skin barrier function, Skin Res. Technol. 8 (1) (2002) 1–6.
[2] P. Treffel, P. Muret, P. Muret-D'Aniello, S. Coumes-Marquez, P. Agache, Effect of occlusion on in vitro percutaneous absorption of two compounds with different physicochemical properties, Skin Pharmacol. 5 (1992) 108–113.
[3] P. Minghetti, F. Cilurzo, V. Liberti, L. Montanari, Dermal therapeutic systems permeable to water vapour, Int. J. Pharm. 158 (2) (1997) 165–172.
[4] T.M. Morgan, B.L. Reed, B.C. Finnin, Enhanced skin permeation of sex hormones with novel topical spray vehicles, J. Pharm. Sci. 87 (10) (1998) 1213–1218.
[5] H. Laufen, M. Leitold, Bioavailability and metabolism of isosorbide dinitrate from a transdermal spray, Arzneimittelforschung 42 (7) (1992) 931–935.
[6] C. Padula, G. Colombo, S. Nicoli, P.L. Catellani, G. Massimo, P. Santi, Bioadhesive film for the transdermal delivery of lidocaine: in vitro and in vivo behavior, J. Control Release 88 (2) (2003) 277–285.
[7] S. Nicoli, V. Amoretti, P. Colombo, P. Santi, Bioadhesive transdermal film containing caffeine, Skin Pharmacol. Physiol. 17 (3) (2004) 119–123.
[8] S. Nicoli, P. Colombo, P. Santi, Release and permeation kinetics of caffeine from bioadhesive transdermal films, AAPS J. 7 (1) (2005) E218–E223.
[9] S. Nicoli, M. Cappellazzi, P. Colombo, P. Santi, Characterization of the permselective properties of rabbit skin during transdermal iontophoresis, J. Pharm. Sci. 92 (7) (2003) 1482–1488.
[10] K. Moser, K. Kriwet, A. Naik, Y.N. Kalia, R.H. Guy, Passive skin penetration enhancement and its quantification in vitro, Eur. J. Pharm. Biopharm. 52 (2) (2001) 103–112.
[11] R.W. Korsmeyer, R. Gurny, E. Doelker, P. Buri, N.A. Peppas, Mechanisms of solute release from porous hydrophilic polymers, Int. J. Pharm. 15 (1983) 25–35.
[12] C. Padula, P. Colombo, F. Pirot, P. Santi, Evaluation of the effect of type and amount of plasticizer on mechanical properties of Patch-non-Patch® films. in: I. Controlled Release Society (Ed.), 32 Intern. Symp. Control. Rel. Bioact. Mater, vol. 32, Miami (FL), 2005, p. 177.
[13] V. Aversa, P. Colombo, G. Massimo, P. Santi, Transdermal delivery of progesterone from isopropylmyristate-based microemulsions, in: 15th International Symposium on Microencapsulation, Parma (Italy), 2005, pp. 409–410.
[14] N. Zerrouk, N. Mennini, F. Maestrelli, C. Chemtob, P. Mura, Comparison of the effect of chitosan and polyvinylpyrrolidone on dissolution properties and analgesic effect of naproxen, Eur. J. Pharm. Biopharm. 57 (1) (2004) 93–99.
[15] F.P. Schwarb, G. Imanidis, E.W. Smith, J.M. Haigh, C. Surber, Effect of concentration and degree of saturation of topical fluocinonide formulations on in vitro membrane transport and in vivo availability on human skin, Pharm. Res. 16 (6) (1999) 909–915.
[16] P.G. Green, R.H. Guy, J. Hadgraft, In vitro and in vivo enhancement of skin permeation with oleic and lauric acid, Int. J. Pharm. 48 (1988) 103–111.
[17] C. Lee, T. Uchida, K. Kitagawa, A. Yagi, N. Kim, S. Goto, Relationship between lipophilicity and skin permeability of various drugs from an ethanol/water/lauric acid system, Biol. Pharm. Bull. 17 (10) (1994) 1421–1424.
[18] S.W. Smith, B.D. Anderson, Human skin permeability enhancement by lauric acid under equilibrium aqueous conditions, J. Pharm. Sci. 84 (5) (1995) 551–556.
[19] S. Nicoli, S. Rimondi, P. Colombo, P. Santi, Physical and chemical enhancement of transdermal delivery of triptorelin, Pharm. Res. 18 (11) (2001) 1634–1637.
[20] M. Artusi, S. Nicoli, P. Colombo, R. Bettini, A. Sacchi, P. Santi, Effect of chemical enhancers and iontophoresis on thiocolchicoside permeation across rabbit and human skin in vitro, J. Pharm. Sci. 93 (10) (2004) 2431–2438.
[21] R.A. Nash, D.B. Mehta, J.R. Matias, N. Orentreich, The possibility of lidocaine ion pair absorption through excised hairless mouse skin, Skin Pharmacol. 5 (3) (1992) 160–170.
[22] J. Hadgraft, M. Whitefield, P.H. Rosher, Skin penetration of topical formulations of ibuprofen 5%: an in vitro comparative study, Skin Pharmacol. Appl. 16 (3) (2003) 137–142.
[23] P. van der Bijl, L. Penkler, A.D. van Eyk, Permeation of sumatriptan through human vaginal and buccal mucosa, Headache 40 (2) (2000) 137–141.