Available online at www.sciencedirect.com
SCIENCE DIRECT®
International Journal of Pharmaceutics 269 (2004) 121–129
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

A mathematical approach to predicting the percutaneous absorption enhancing effect of sodium lauryl sulphate

Joaquín Borrás-Blasco [a], Octavio Díez-Sales [b], Alicia López [c], Marina Herráez-Domínguez [b,*]

[a] *Servicio de Farmacia, Hospital General Universitario de Elche, 03202 Elche, Spain*
[b] *Departament de Farmacia i Tecnología Farmacéutica, Facultat de Farmacia, Universitat de Valencia, Avd. Vicente Andrés Estellés s/n, 46100 Burjassot, Spain*
[c] *Departmento de Farmacología y Tecnología Farmacéutica, Universidad Cardenal Herrera-CEU, 46113 Moncada, Spain*

Received 14 April 2003; received in revised form 23 July 2003; accepted 1 September 2003

Abstract

A study has been made of the effect of sodium lauryl sulphate (SLS) at several concentrations from 0.24 to 5% (w/w) on skin permeability. Seven model drugs were selected for this study on the basis of their lipophilicity as represented by their log P_{oct} values (from −0.95 to 4.2). Skin pre-treatment with aqueous solutions of SLS does not increase the permeability coefficient of the most lipophilic compounds (log $P_{oct} \geq 3$). For the other compounds assayed the increase in the permeability coefficients depends on the concentration of SLS used in the skin pre-treatment, and on the lipophilicity of the compounds tested.

The correlation between the inverse of SLS efficacy as an enhancer (1/ER) and the lipophilicity (log P_{oct}) of the model permeants was established via a hyperbolic equation. This model makes it possible to predict the percutaneous absorption enhancing effect of SLS, expected for a compound of specific lipophilicity, according to the concentration used in skin pre-treatment. An excellent accuracy ($r^2 > 0.94$) for the linear relationship between the experimental ($n = 15$) and theoretical (ER) values predicted by the equation was obtained. The model proposed was also useful for experimental data obtained previously using Azone® and compounds with the same range of lipophilicity.
© 2003 Elsevier B.V. All rights reserved.

Keywords: Percutaneous absorption; Sodium lauryl sulphate; Azone®; Penetration enhancers; Lipophilicity

1. Introduction

The transdermal route offers many advantages when administering drugs in local and systemic therapy. However, the outermost layer of skin, the stratum corneum or horny layer, forms a strong barrier to most external substances, including drugs. Several strategies can be employed to reduce the barrier effect of skin, such as the use of chemical enhancers (Ogiso et al., 1995) and physical methods (Byl, 1995; Banga et al., 1999). Chemical enhancers can be used to improve both local topical therapy and transdermal delivery. Terpenes, urea, fatty acids, short- and long-chain alcohols, pyrrolidones, several surfactants and laurocapram (Azone®) have been shown to behave as penetration enhancers (Williams and Barry, 1991).

Sodium lauryl sulphate (SLS) is an anionic, amphiphilic surfactant extensively used in various consumer products and for industrial purposes. Due to its widespread topical use, the skin is often exposed to

* Corresponding author. Tel.: +34-96-3544912; fax: +34-96-3544911.
E-mail address: marina.herraez@uv.es (M. Herráez-Domínguez).

0378-5173/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2003.09.021

SLS. The SLS skin-interactions have been analysed in many studies; in some of them the impairment of the skin barrier function caused by SLS has been attributed to removal of intercellular hydrophobic lipids, thus leading to an increase in transdermal water loss (Froebe et al., 1990). SLS also binds extensively to intracellular keratin, which explains some of its irritant effects such as tightness and roughening of skin (Leveque et al., 1993). Furthermore, SLS inserts between the lipid sheets and fluidizes the lipid bilayers in the stratum corneum (Ribaud et al., 1994).

We have previously studied the effect of SLS on the in vitro percutaneous absorption of compounds of different lipophilicities (Borrás-Blasco et al., 1997). The results obtained in that work showed the effect of SLS to depend on the lipophilicity of the permeant used. This is a typical observation in penetration enhancement studies: larger (relative) effects are much more likely to be found with penetrants that transport poorly under control (no enhancer) conditions. The present work adds new experimental data concerning the influence of SLS concentration on the skin effects of this surfactant. In addition, enhancer effect–lipophilicity relationships are established based on a procedure which seems to afford an approach for reliable interpretation of the data. Attempts are likewise made to establish a model of predictive value.

2. Materials and methods

2.1. Materials

SLS was purchased from Merck (Madrid, Spain) and had a stated purity of >98%. The penetrants used in this study, i.e. 5-fluorouracil, pentoxifylline, salicylamide and indomethacin (all from Sigma Chemical Co., Madrid, Spain) were used as received with a stated purity of >99%. In order to obviate depletion of penetrants from the donor solutions, they were prepared as saturated solutions (added with an excess of compound) in buffered medium at pH 6.2. At this pH value, all compounds are essentially non-ionised.

2.2. SLS skin pre-treatment

The skin was pre-treated for 12 h with aqueous solutions of SLS at the concentrations assayed (0.24 and 0.5%, w/w). The 0.24% (w/w) concentration corresponds to the critical micellar concentration (CMC) of SLS (Lodén, 1990). It is clear that when the skin is pre-treated with 0.5% (w/w), SLS is at a supramicellar level. The time of skin pre-treatment with SLS is the same as the one used with Azone® in previous work (Díez-Sales et al., 1996) in order to compare the behaviour of both molecules provided with the same C-12 alkyl chain.

2.3. Diffusion experiments

All permeation experiments were performed on full-thickness skin excised from the abdomen of Wistar rats (females aged 20–25 days) obtained from our laboratory colony. The surface of rat skin has been denuded of hair with an electric razor. These animal models are frequently used in studies of percutaneous absorption, and were chosen here for their ready availability and homogeneity and because good parallelism was observed between in vitro permeability across human and rat skin in previous work (Díez-Sales et al., 1991).

The in vitro methodology and the analytical procedure were described in earlier work (Borrás-Blasco et al., 1997).

Eq. (1) was used to fit the experimental data (Scheuplein, 1967):

$$Q(t) = A \times P \times L \times C \times \left[D \times \frac{t}{L^2} - \frac{1}{6} - \frac{2}{\pi^2} \sum_{n=1}^{\infty} \frac{(-1)^2}{n^2} \times \exp\left(\frac{-D \times n^2 \times \pi^2 \times t}{L^2} \right) \right] \quad (1)$$

where $Q(t)$ is the quantity which passes through the membrane and reaches the receptor solution at a given time t: this amount was quantified by HPLC as previously reported (Borrás-Blasco et al., 1997), A represents the actual diffusional surface area (4.52 cm^2), P is the partition coefficient of the permeant between the membrane and the donor vehicle, L is the membrane thickness, D is the diffusion coefficient of the permeant in the membrane, and C is the concentration (here solubility) of the permeant in the donor solution. The terms $P \times L$ and D/L^2 were replaced in Eq. (1) by p_1 and p_2, respectively, and calculated using a non-linear least squares computer program (Okamoto

et al., 1988). The permeability coefficients (k_p) were calculated from the following equation:

$$k_p = p_1 \times p_2 \quad (2)$$

Finally, the enhancement ratio (ER) was determined from the following equation (Williams and Barry, 1991):

$$\mathrm{ER} = \frac{k_p \text{ after application of penetration enhancer}}{k_p \text{ before application of penetration enhancer}} \quad (3)$$

The values reported are mean ratios from a minimum of five replicates.

2.4. Fitting of models to data

To better understand the interactions between enhancer, permeants and skin, and also to obtain where possible a model to predict the value of the enhancement ratio from the physicochemical parameters of permeants (especially partition coefficient), the calculated ER and the P_{oct} values (partition coefficients in octanol/water) were correlated through the double logarithmic linear equation:

$$\log \mathrm{ER} = a \log P_{oct} + b \quad (4)$$

where a and b are constants which can be experimentally calculated.

Because no good correlations were observed for some concentrations of SLS used, we additionally employed a hyperbolic-type function:

$$\frac{1}{\mathrm{ER}} = \frac{a \times P}{b + P} \quad (5)$$

where (1/ER) is the inverse of the enhancer ratio obtained for each compound under different experimental conditions. Thus, all possible values were included within the limits $\to 0$ (maximum ER) and $\to 1$ (minimum ER). P represents the partition coefficient values of the compounds tested, a is the asymptotic value established and corresponding to the absence of ER (when $a = 1$) and b is an experimental parameter deduced from the fit. Fitting was done using a non-linear regression computer program (Sigma Plot 8.0).

2.5. Statistical analysis

Two-way analysis of variance (ANOVA) was used prior to the Scheffe test; $P < 0.05$ was considered significant. The statistical criterion for assessing the quality of the fits was the correlation coefficient (r^2) between experimental and calculated values.

Akaike's information criterion (AIC) (Akaike, 1976), as well as the correlation coefficient (r^2) between experimental and model-predicted ER values, were used to assess to goodness of the fits.

3. Results and discussion

In order to analyse the effect of SLS concentration on skin permeability, the in vitro percutaneous penetration of compounds with different lipophilicities ($\log P_{oct}$ from -0.95 to 4.42) was investigated using different concentrations of SLS.

The values of p_1 (partition parameter) and p_2 (diffusion parameter) were estimated by curve fitting of Eq. (1) to each set of experimental in vitro permeation data (given in Table 1). As can be seen, with the exception of indomethacin—the most lipophilic compound—pre-treatment of the skin with SLS seems to induce modifications in both p_1 and p_2 values for the other compounds (5-fluorouracil, pentoxifylline and salicylamide). These modifications depend on the SLS concentration used in the pre-treatment of skin and also on the lipophilicity of the compounds tested. These results could be explained by considering that the enhancer effect of SLS is a consequence of two simultaneous mechanisms: firstly, SLS fluidizes the lipid bilayers in the stratum corneum (Ribaud et al., 1994), increasing the diffusion parameter (p_2). In addition, SLS can induce increased hydration of the stratum corneum and viable epidermis (Rhein et al., 1986), which could explain the increases in partitioning parameter (p_1). Both mechanisms could contribute to increase skin penetration by hydrophilic compounds, but they cancel each other out for the most lipophilic compound.

According these observations, and in order to analyse the influence of the variables (concentration of SLS used in skin pre-treatment and lipophilicity of the permeants) upon the global skin permeation process, the permeability coefficients for each compound and condition assayed were calculated from Eq. (2) and are shown in Table 2 together with those obtained for 1 and 5% (w/w) SLS skin pre-treatment in previous work (Borrás-Blasco et al., 1997). The statistical analysis

Table 1
Values of the parameters p_1 ($\times 10^3$ cm) and p_2 ($\times 10^3\,h^{-1}$) estimated by curve fitting of the theoretical Eq. (1) to the individual in vitro permeation data, shown as mean ± S.D. ($n = 5$) for the series of drugs assayed under different conditions

Compound	Untreatment of the skin	Pre-treatment of the skin with SLS (%, w/w)			
	Control	0.24 (CMC)	0.5	1	5
5-Fluorouracil					
p_1 ($= P \times L$)	9.16 (1.19)	17.48 (6.23)	25.60 (4.43)	20.18 (3.14)	22.99 (4.65)
p_2 ($= D/L^2$)	60.02 (20.96)	66.98 (26.54)	162.01 (42.10)	211.59 (52.32)	199.04 (44.40)
Pentoxifylline					
p_1 ($= P \times L$)	37.05 (6.01)	39.82 (5.97)	84.37 (17.32)	120.79 (23.80)	115.85 (38.17)
p_2 ($= D/L^2$)	65.86 (7.35)	68.30 (11.22)	89.13 (19.11)	90.32 (16.50)	92.45 (27.31)
Salicylamide					
p_1 ($= P \times L$)	677.59 (134.16)	668.99 (125.22)	688.16 (136.98)	898.51 (144.95)	895.66 (156.98)
p_2 ($= D/L^2$)	46.68 (12.65)	48.73 (12.98)	47.62 (11.97)	64.10 (13.17)	65.62 (13.26)
Indomethacin					
p_1 ($= P \times L$)	6689.48 (1245.31)	6449.55 (1301.65)	6937.93 (1190.83)	6930.22 (1176.92)	7325.4 (1287.91)
p_2 ($= D/L^2$)	11.69 (1.96)	11.75 (1.15)	11.23 (1.67)	11.74 (0.89)	11.05 (3.18)

of the permeability coefficients obtained through the membrane without (control) and with pre-treatment (SLS) are also included in the same table.

As can be seen, for the most lipophilic compounds (4-butylaniline and indomethacin) no differences were observed between the k_p values for control and k_p values for each of the SLS concentrations assayed. For the other compounds ($\log P_{oct}$ from −0.95 to 1.97) it can be seen that as the lipophilicity of the compound increased, the concentration required for the SLS effect on skin permeability likewise increased. In accordance with the results obtained, the minimum concentration required for the enhancer effect corresponds to the CMC (0.24%, w/w) in the case of 5-fluorouracil, versus 0.5% (w/w) for pentoxifylline and 1% (w/w) for salicylamide.

Moreover, with the exception of 5-fluorouracil, no differences were observed between the permeability coefficients obtained for 1 and 5% (w/w). This would seem to indicate the possible existence of a limit in the capacity of the surfactant to alter the function of the skin as a barrier. Saturation of enhancer effects has been previously described from the studies conducted with other enhancers such *n*-nonane and *n*-nonanol (Hori et al., 1991). Judging from the results obtained in the present work, this limit seems to be found in the condition corresponding to pre-treatment of the skin with a 1% (w/w) SLS solution. In any case, as we have previously reported for other enhancers (Díez-Sales et al., 1996; López et al., 2000), the influence of enhancer concentration on skin permeability depends on the lipophilicity of the permeants.

In order to compare and quantify the effect of SLS according to the lipophilicity of the penetrants and the concentration of the surfactant used in the solution employed for membrane pre-treatment, the ER for each compound and condition were calculated. These data are given in Fig. 1 jointly with those calculated previously for 1 and 5% (w/w) SLS skin pre-treatment. As can be seen, for any particular condition of skin pre-treatment, the greatest enhancer effect observed corresponded to the lowest lipophilicity value of the penetrant (5-fluorouracil).

Initially, a linear relationship between $\log P_{oct}$ and the efficacy of the enhancer (represented by the calculated log ER) was established (Table 3). Although this type of relationship could be considered of value for the greater SLS concentrations (1 and 5%, w/w) according to their respective r^2 values, no good correlation is observed in the case of the lesser concentrations (0.24 and 0.5%, w/w). Consequently, for this range of SLS concentrations, this equation does not seem to be useful as a tool for predicting the magnitude of ER that can be expected for a particular compound with a given lipophilicity.

This behaviour initially shows certain similarities, but also differences, with that observed for Azone® in previous works (López et al., 2000; Díez-Sales et al.,

Table 2
Lipophilicity values ($\log P_{oct}$) and permeability coefficients experimentally found for the tested compounds through full thickness Wistar rat skin without (control) and with SLS treatment at different concentrations ($n = 5$, mean ± S.D.)

Compound	$\log P_{oct}$	Permeability coefficients (k_p) ($\times 10^{-3}$ cm h^{-1})					Statistical differences				
		Control[a]	SLS 0.24% (w/w)	SLS 0.5% (w/w)	SLS 1% (w/w)[a]	SLS 5% (w/w)[a]	C/I	C/II	C/III	C/IV	III/IV
5-Fluorouracil	−0.95[b]	0.55 (0.03)	1.17 (0.16)	4.15 (0.20)	4.27 (0.19)	4.56 (0.20)	S	S	S	S	S
Antipyrine	0.23[c]	0.28 (0.03)	nd	nd	1.51 (0.29)	1.43 (0.16)	nd	nd	S	S	NS
Pentoxifylline	0.72[d]	2.44 (0.05)	2.72 (0.10)	7.52 (0.40)	10.91 (0.39)	10.71 (1.11)	NS	S	S	S	NS
Salicylamide	1.23[e]	31.63 (1.85)	32.60 (1.71)	32.77 (1.64)	57.60 (1.93)	58.77 (2.10)	NS	NS	S	S	NS
4-Ethylaniline	1.97[f]	116.76 (4.54)	nd	nd	134.26 (7.16)	140.85 (12.85)	nd	nd	S	S	NS
4-*n*-Butylaniline	3[f]	165.43 (17.22)	nd	nd	157.74 (15.06)	160.06 (15.38)	nd	nd	NS	NS	NS
Indomethacin	4.42[a]	78.18 (2.62)	75.75 (1.58)	77.92 (2.05)	81.34 (3.51)	80.91 (4.15)	NS	NS	NS	NS	NS

Statistical analysis of permeability coefficients found for the tested compounds under different conditions is included. C: control; I: SLS 0.24% (w/w); II: SLS 0.5% (w/w); III: SLS 1% (w/w); IV: SLS 5% (w/w); nd: not determined; S: significantly different; NS: not significantly different.

[a] Borrás-Blasco et al. (1997).
[b] Leo et al. (1971).
[c] Díez-Sales et al. (1996).
[d] Cheon Koo et al. (1994).
[e] Hansch and Anderson (1967).
[f] Yano et al. (1986).

Table 3
Statistical figures and equation parameters, according to Eqs. (4) and (5), found for data fittings, corresponding to the different experimental conditions for SLS used in this work, and for data obtained with Azone®

Model equations	Equation and statistical parameters	SLS (%, w/w)				Azone® (%, w/w)[a]		
		0.24	0.5	1	5	1	5	10
Linear	r^2	0.6061	0.6728	0.8136	0.8321	0.7028	0.7524	0.7938
	AIC	−1.06	0.49	−0.77	−0.95	−0.21	0.18	0.42
	a	−0.054 (±0.031)	−0.155 (±0.076)	−0.191 (±0.049)	−0.192 (±0.039)	−0.152 (±0.057)	−0.207 (±0.068)	−0.260 (±0.076)
	b	0.168 (±0.074)	0.553 (±0.181)	0.659 (±0.092)	0.666 (±0.087)	0.442 (±0.136)	0.624 (±0.163)	−0.775 (±0.182)
Hyperbolic	r^2	0.9672	0.8613	0.9698	0.9698	0.9931	0.9367	0.8430
	AIC	−2.39	−0.16	−3.43	−3.48	−4.18	−1.69	−0.44
	a	0.978 (±0.034)	1.074 (±0.196)	1.009 (±0.049)	0.994 (±0.048)	0.962 (±0.018)	0.906 (±0.060)	0.926 (±0.111)
	b	0.124 (±0.030)	6.292 (±4.781)	14.351 (±3.531)	14.512 (±3.549)	0.734 (±0.142)	1.616 (±0.886)	3.232 (±2.204)

[a] Díez-Sales et al. (1996).

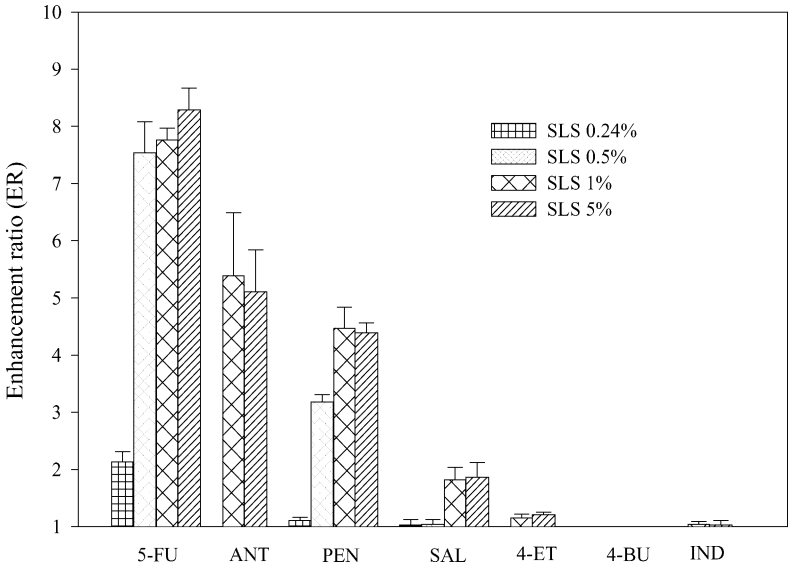

Fig. 1. The penetration enhancing activity of SLS for different concentrations (0.24, 0.5, 1 and 5%, w/w) expressed as enhancement ratios. 5-FU, 5-fluorouracil; ANT, antipyrine; PEN, pentoxifylline; SAL, salicylamide; 4-ET, 4-ethylaniline; 4-BU, 4-*n*-butylaniline; IND, indomethacin.

1996). In one such study (López et al., 2000), the relation between log ER and log P_{oct} appeared to be linear, with a correlation coefficient of $r^2 = 0.9103$ (Azone® 1%, w/w) and 0.687 (Azone® 5%, w/w). It is important to note that the lipophilicity range of the compounds tested in the mentioned study (log P_{oct} from −0.95 to 2.33) is lower than in the present work. However, when the compounds included in the experiments (Díez-Sales et al., 1996) comprise a broad lipophilicity range (log P_{oct} from −0.95 to 4.42) similar to that found in the present work, this linear relationship between log P_{oct} and log ER does not yield good correlation coefficients (Table 3). In other words, this linear equation does not seem to be of general applicability in predicting the magnitude of ER that can be expected for a particular compound with a given lipophilicity.

In order to develop a model capable of predicting the percutaneous absorption enhancing effect according to the concentration of SLS used in the pre-treatment of the skin and the lipophilicity (log P_{oct}) of the compound, a hyperbolic equation has been tested (Eq. (5)). The results obtained are summarised in Table 3. As can be seen, under all our experimental conditions good correlation coefficients were obtained, superior to those of the linear model. The value of a obtained is almost equal to 1, as expected (absence of ER), whereas the value of b increases with the concentration of SLS until a maximum is reached (corresponding to skin pre-treatment with SLS 1%, w/w), i.e. the b value for 5% (w/w) SLS skin pre-treatment is similar to that obtained with 1% (w/w) skin pre-treatment. This is in agreement with the observations made above, which indicate that the maximum effect of SLS on skin permeability is achieved after skin pre-treatment with 1% (w/w) SLS. Based on this fact, we proceeded to determine the relationship between parameter b and SLS concentration. A linear relationship with a good correlation coefficient ($r^2 > 0.99$) was observed, and the equation representing the straight line obtained was the following:

$$b = 18.44\,(\pm 1.83) \times C - 3.76\,(\pm 1.21) \quad (6)$$

In view of the linear relationship obtained between parameter b and SLS concentration, we proceeded to use this parameter as representative of the effect of SLS on skin permeability. Substituting the value of b in the hyperbolic equation used (Eq. (5)), we obtain the following expression:

$$\frac{1}{\mathrm{ER}} = \frac{P}{18.44\,(\pm 1.83) \times C - 3.76\,(\pm 1.21) + P} \quad (7)$$

In order to verify that this equation (Eq. (7)) is able to reproduce good estimates of the values of ER for all the compounds assayed, we carried out a linear fit between the experimental values (1/ER) obtained for all the compounds tested under the different treatment conditions of the membrane (0.24, 0.5, and 1%, w/w) and the theoretical values deduced from this equation ($n = 15$). The equation obtained is

$$\frac{1}{\mathrm{ER}_{\mathrm{theoretical}}} = \frac{1}{\mathrm{ER}_{\mathrm{experimental}}} \times 1.04\,(\pm 0.08) - 0.068\,(\pm 0.061) \quad (r^2 > 0.94) \qquad (8)$$

As can be seen, the slope is approximately equal to 1, and the ordinate at the origin is practically equal to 0. Both these observations, together with the correlation coefficient obtained, confirm the practical usefulness of the mathematical model proposed. Therefore, the equation proposed (Eq. (7)) can be applied to predict ER (in the range of concentrations used), which in the case of SLS is to be expected for a specific compound, the lipophilicity of which is known ($\log P_{\mathrm{oct}}$) and that is intended for use on the skin.

In order to verify whether this new form of operating is applicable to the behaviour observed with Azone®, the enhancer effect of which—as has been pointed out—depends on the lipophilicity value of the permeant, we performed the same procedure with the experimental data obtained in the study carried out with compounds with a wide range of lipophilicity (Díez-Sales et al., 1996). The results obtained are also summarised in Table 3. It should be noted that the correlation coefficient obtained, for any particular condition of membrane treatment with the enhancer, is better than when double logarithmic linear regression between the values of ER and lipophilicity was applied. Once again, the equation relating the parameter b with the concentration of enhancer used in the assays is linear, with a good correlation coefficient:

$$b = 2.83\,(\pm 0.78) \times C - 4.37\,(\pm 5.06) \quad (r^2 > 0.94) \qquad (9)$$

On substituting this equation for parameter b in Eq. (6) we obtain the following expression:

$$\frac{1}{\mathrm{ER}} = \frac{P}{2.83\,(\pm 0.78) \times C - 4.37\,(\pm 5.06) + P} \qquad (10)$$

Using Eq. (10), we calculated the theoretical values corresponding to each compound and treatment condition of the membrane. The linear fit between the experimental values ($n = 21$) and theoretical values yields the following equation (Eq. (11)), with an acceptable correlation coefficient:

$$\frac{1}{\mathrm{ER}_{\mathrm{theoretical}}} = \frac{1}{\mathrm{ER}_{\mathrm{experimental}}} \times 0.86\,(\pm 0.10) - 0.08\,(\pm 0.08) \quad (r^2 > 0.77) \qquad (11)$$

Therefore, the applicability of the equation proposed to describe the ER of Azone® in relation to the concentration used and to the lipophilicity of the permeants seems to be verified.

In conclusion, SLS and Azone® have been used as enhancers. Both of them have a hydrophobic C-12 tail but the hydrophilic ends are quite different. This fact could imply differences in their respective molecular interactions with the stratum corneum components. However, their effects on the in vitro percutaneous absorption of compounds with a wide range of lipophilicity values were qualitatively similar. For both enhancers the mathematic model proposed could predict the percutaneous absorption enhancing effect according to the concentration of the enhancer used in the pre-treatment of the skin and the lipophilicity ($\log P_{\mathrm{oct}}$) of the compound assayed.

Acknowledgements

The present work is part of a research project (PM 92-0149) carried out with a grant from the DGICYT (Spanish Ministry of Education and Science).

References

Akaike, H., 1976. An information criterion (AIC). Math. Sci. 14, 5–6.

Banga, A.K., Bose, S., Ghosh, T.K., 1999. Iontophoresis and electroporation: comparisons and contrasts. Int. J. Pharm. 179, 1–19.

Borrás-Blasco, J., López, A., Morant, M.J., Díez, O., Herráez, M., 1997. Influence of sodium lauryl sulfate on in vitro percutaneous absorption of compounds with different lipophilicity. Eur. J. Pharm. Sci. 5, 15–22.

Byl, N.N., 1995. The use of ultrasound as an enhancer for transcutaneous drug delivery: phonophoresis. Phys. Ther. 75, 539–553.

Cheon Koo, L., Takahiro, U., Kazahosa, K., Akira, Y., Nak-Seo, K., Shigeru, G.J., 1994. Skin permeability of various drugs with different lipophilicity. J. Pharm. Sci. 83, 562–565.

Díez-Sales, O., Guzmán, D., Cano, D., Martín, A., Sánchez, E., Herráez, M., 1991. A comparative in vitro study of permeability with different synthetic and biological membranes. Eur. J. Drug Metab. Pharmacokin. 16, 441–446.

Díez-Sales, O., Watkinson, A.C., Herráez-Domínguez, M., Javaloyes, C., Hadgraft, J., 1996. A mechanistic investigation of the in vitro human skin permeation enhancing effect of Azone®. Int. J. Pharm. 129, 33–40.

Froebe, C.L., Simion, F.A., Rhein, L.D., Cagan, R.H., Kligman, A., 1990. Stratum corneum lipid removal by surfactants: relation to in vivo irritation. Dermatologica 181, 277–283.

Hansch, C., Anderson, S.J., 1967. The effect of intramolecular hydrophobic bonding on partition coefficients. J. Org. Chem. 32, 2583–2585.

Hori, M., Satoh, S., Maibach, H.I., Guy, R.H., 1991. Enhancement of propanolol hydrochloride and diazepam skin absorption in vitro: effect of enhancer lipophilicity. J. Pharm. Sci. 80, 32–35.

Leo, A.J., Hansch, C., Elkins, D., 1971. Partition coefficients and their uses. Chem. Rev. 71, 525–531.

Leveque, J.L., De Rigal, J., Saint-Leger, D., Billy, D., 1993. How does sodium lauryl sulfate alter the skin barrier function in man? A multiparametric approach. Skin. Pharmacol. 6, 111–115.

Lodén, M., 1990. The simultaneous penetration of water and sodium lauryl sulphate through isolated human skin. J. Soc. Cosmet. Chem. 41, 227–232.

López, A., Llinares, F., Cortell, C., Herráez, M., 2000. Comparative enhancer effects of Span® 20 with Tween® 20 and Azone® on the in vitro percutaneous penetration of compounds with different lipophilicities. Int. J. Pharm. 202, 133–140.

Ogiso, T., Iwaki, M., Paku, T., 1995. Effect of various enhancers on transdermal penetration of indomethacin and urea, and relationship between penetration parameters and enhancement factors. J. Pharm. Sci. 84, 482–488.

Okamoto, H., Hashida, M., Sezaki, H., 1988. Structure–activity relationship of 1-alkyl- or 1-alkenylazacycloalkanone derivatives as percutaneous penetration enhancers. J. Pharm. Sci. 77, 418–424.

Rhein, L.D., Robbins, C.R., Fernee, K., Cantore, R., 1986. Surfactant structure effects on swelling of isolated human stratum corneum. J. Soc. Cosmet. Chem. 37, 125–139.

Ribaud, C.H., Garson, J.C., Doucet, J., Lévêque, J.L., 1994. Organization of stratum corneum lipids in relation to permeability: influence of sodium lauryl sulfate and preheating. Pharm. Res. 11, 1414–1418.

Scheuplein, R.J., 1967. Mechanism of percutaneous absorption. II. Transient diffusion and the relative importance of various routes of skin penetration. J. Invest. Dermatol. 48, 79–88.

Williams, A.C., Barry, B.W., 1991. Terpenes and the lipid–protein-partitioning theory of the skin penetration enhancement. Pharm. Res. 8, 17–24.

Yano, T., Nakagawa, A., Tsuji, M., Noda, K., 1986. Skin permeability of various nonsteroidal anti-inflammatory drugs in man. Life Sci. 39, 1043–1050.