International Journal of Pharmaceutics 374 (2009) 39–45

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

The influence of alcohol, propylene glycol and 1,2-pentanediol on the permeability of hydrophilic model drug through excised pig skin

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ARTICLE INFO

Article history:
Received 9 December 2008
Received in revised form 26 February 2009
Accepted 27 February 2009
Available online 14 March 2009

Keywords:
Percutaneous penetration
Porcine membrane
In vitro
Caffeine
Enhancement

ABSTRACT

Alcohol and glycol including 1,2-pentanediol, a new product in this field, were examined for their transdermal penetration enhancing in vitro properties using pig skin and caffeine as a model drug. In order to investigate a possible influence of these compounds, we followed diffusion from an aqueous solution with caffeine followed by a series of different vehicles, their compositions were: (1) in water as a control; (2) in propylene glycol/ethanol/water (25:25:48; v/v/v); (3) in 1,2-pentanediol/water (2.5:95.5, v/v); (4) in 1,2-pentanediol/water (5:93, v/v); in propylene glycol/water (5:93; v/v); and in ethanol/water (5:93; v/v). The *stratum corneum*/vehicle partition coefficients (K_m), maximum flux (J), enhancement factor (EF), 24-h receptor concentration (Q_{24h}) were determined and compared to control values (caffeine in water). Permeation was also expressed in percentage of the applied dose absorbed in the different compartments. In all test models, caffeine was released and penetrated into pig skin. The 1,2-pentanediol was presented as the most effective enhancer; with a low proportion of this compound (only 5%), caffeine penetrated the skin quicker and in a greater extent. While this compound showed promise as penetration enhancer, further study was required to determine its effectiveness with others drugs and its irritation potential.

1. Introduction

Transdermal drug delivery is gaining more and more interest in the pharmaceutical industry. It also represents the most successful and most innovative area of research in drug delivery. Transdermal drug delivery possesses several advantages and offers an attractive alternative to conventional oral and injection therapies. Drugs have to penetrate into the deeper skin layers or permeate the skin whereas human skin represents an effective, selective barrier to chemical permeation (Barry, 1983). Unfortunately, only a few drugs possess the physicochemical properties necessary for this route of delivery: most drugs are unable to cross the skin in quantities required for successful systemic therapy (Barry, 1983). The barrier to percutaneous drug penetration is presented by the upper layer of the skin, the stratum corneum (SC), which consists of a highly organized extracellular lipid compartment tightly joined to the corneocytes via desmosomes in a brick and mortar wall-like configuration (Barry and Bennett, 1987).

Different approaches including chemical enhancers (Barry, 1987; Walker and Smith, 1996), iontophoresis (Guy, 1998) and sonophoresis (Boucaud et al., 2001) were employed to lessen the barrier function of the skin. Numerous chemical compounds were evaluated for penetration-enhancing activity; these agents are chemical compounds which reversibly alter the barrier function of the skin. They allow an increasing rate of percutaneous permeation of drugs. Four main mechanisms of enhancement can be specified: (1) interactions with the intracellular keratin (denature it or modify its conformation causing swelling and increased hydration); (2) modification of the desmosomes that maintain cohesion between corneocytes; (3) interactions with the intercellular lipids to reduce the barrier resistance of the bilayer lipids; (4) alter the solvent nature of the SC to modify partitioning of the drug into the tissue (Barry, 1991; Goodman and Barry, 1989; Williams and Barry, 2004). To show the potential activity of an enhancer, two ways are possible:

(1) a skin pre-treatment is made with the selected enhancer; for example before being mounted in the in vitro diffusion cells, skins were immersed in a solution containing the enhancer (Bhatia et al., 1997; Monti et al., 2001) or aliquots pre-treatment solution were applied directly on the surface of epidermal (Panchagnula et al., 2001; Trottet et al., 2004);

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doi:10.1016/j.ijpharm.2009.02.021

(2) without pre-treatment, the chosen enhancer is incorporated in the vehicle which is then applied with "in-use" conditions.

The goal of this study is to identify potential new based penetration enhancers and particularly 1,2-pentanediol using an in vitro pig skin model and caffeine as the model drug (Kim et al., 2002). All selected enhancers were incorporated in vehicle containing caffeine and applied with in-use conditions. The penetration properties are determined by the SCCP (Scientific Committee on Consumer Product) opinion (SCCP, 2006) and OECD (Organisation for Economic Co-operation and Development) Guideline TG 428 (OECD, 2000a,b).

2. Materials and methods

2.1. Chemicals

Chemical products used for in vitro experimentation were: distilled water, methanol (Carlo Erba Reagents, France), 1,2-pentanediol (Hydrolite-5®, Symrise, France), propylene glycol (Prolabo, France), ethanol (Carlo Erba Reagents, France), water (Ecotainer®, Aqua B.Braun, Belgium), physiologic serum (Versol NaCl 0.9%, Aguettant, France). All reagents used for chromatography were of analytical-reagent grade. Ultra high quality water was obtained from Alpha-Q system (Millipore, France). Caffeine (Caf, 3,7-Dihydro-1,3,7-trimethyl-1H-purine-2,6-dione) was obtained from QuimDis France.

2.2. Instruments

For this investigation, static Franz glass diffusion cells were used (Legallais, France). These cells consist of donor and receptor chambers between which a piece of whole porcine skin is positioned. A Tewameter TM210® (Courage-Khasaka, Monaderm, Monaco) was used to determine the transepidermal water loss (TEWL) which reflects the skin integrity (Nangia et al., 1998). The full skin thickness was measured using dial thickness gauge (Mitutoyo, Japan, 0.01–10 mm).

2.3. In vitro permeability studies

Permeability studies were performed using methods previously described (Fernandez et al., 2000a,b). Porcine ears (three different donors) were obtained from freshly killed animals in a local slaughterhouse (Pézenas, France). After cleaning with cold tapwater, full-thickness, non-dermatomed skin (about 0.9–1.1 mm) was removed with a scalpel from the cartilage of the outer region. Only intact skin discs with an internal diameter of 3 cm were kept and sealed in plastic bags then stored at −20 °C until ready for use (Kurul and Hekimoglu, 2001), for a period that did not exceed 6 weeks. The skin samples were mounted in static diffusion cells in modified Franz diffusion cells (Franz, 1975) in such a way that the dermal side of the skin was exposed to the receptor fluid. The diffusion area was 0.95 cm^2. The precise volume of the acceptor compartment (approximately 9 ml) was measured for each cell and was included into the calculations. The continuously stirred receptor medium, physiologic serum Versol NaCl 0.9% solution to preserve skin conditions was maintained at 37 ± 1 °C by water circulation (Polystat CC1, Huber). In these circumstances, the skin disc temperature was 32 ± 1 °C (via heat dissipation) which corresponded to the skin surface temperature in vivo (measured with Thermocouple thermometer, ecoScan).

2.4. The donor solution

Six formulations with 2% of caffeine were compared; their compositions are presented in Table 1.

Solubility of caffeine was tested in each vehicle. Experiments were made on a long time contact (24 h) at 25 ± 1 °C with gentle homogenization with a magnet bar. We have considered that caffeine concentration at 2% corresponded to a range equal to 20% below the saturated concentration found in the vehicle with the lowest caffeine solubility (Table 2). To target the effect of potential enhancers we have chosen to work under the saturated concentration.

In these formulations, the 2% of caffeine were completely solubilized. The difference was based on the presence of different solvents, which are known for modifying the penetration flux (Daniels, 2004; Pugh et al., 2005) like ethanol (Krill et al., 1992; Yum et al., 1994), propylene glycol (Barry, 2001; Chan, 2005; Tata et al., 1994), and the study of 1,2-pentanediol (Fig. 1).

10 μl of the different formulation were applied on the surface of the skin through the donor compartment. Formulations were applied at a finite dose using a pipette. The solution film covered the entire skin surface with uniform and homogeneous spreadability over the whole skin area, but without determining its thickness.

Table 1
Composition of all vehicles studied. In order to investigate the effect of each enhancer we chose the simplest and most adapted formulations in term of concentrations, keeping in mind the "in-use" conditions.

Number of the formulation	Formulation name	Components	% express in w of caffeine and v for solvent
1	Water	Caffeine	2
		Distilled water	98
2	Propylene glycol 25% + EtOH 25% (PG + EtOH 25:25)	Propylene glycol	25
		Ethanol	25
		Caffeine	2
		Distilled water	48
3	1,2-Pentanediol 2.5% (P2.5%)	1,2-Pentanediol	2.5
		Caffeine	2
		Distilled water	95.5
4	1,2-Pentanediol 5% (P5%)	1,2-Pentanediol	5
		Caffeine	2
		Distilled water	93
5	Propylene glycol 5% (PG5%)	Propylene glycol	5
		Caffeine	2
		Distilled water	93
6	Ethanol 5% (EtOH%)	Ethanol	5
		Caffeine	2
		Distilled water	93

Table 2
Saturated concentration of caffeine in all vehicles.

Number of the formulation	Formulation name	Caffeine saturation (g/l)
1	Water	31.4 ± 0.7
2	Propylene glycol 25% + EtOH 25% (PG + EtOH 25:25)	41.5 ± 4.3
3	1,2-Pentanediol 2.5% (P2.5%)	26.2 ± 1.0
4	1,2-Pentanediol 5% (P5%)	37.7 ± 1.8
5	Propylene glycol 5% (PG5%)	32.0 ± 0.6
6	Ethanol 5% (EtOH%)	25.3 ± 6.7

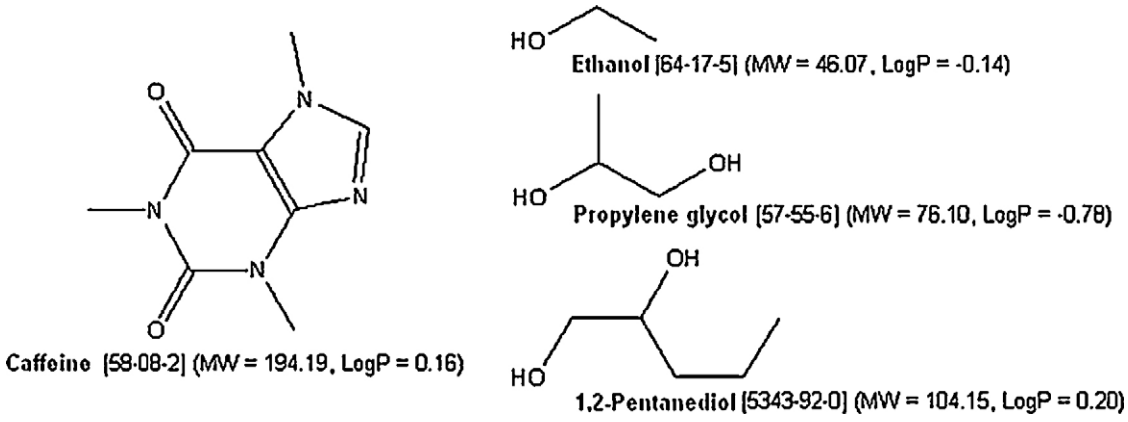

Fig. 1. The molecular structure of caffeine, ethanol, propylene glycol and 1,2-pentanediol. Physical properties used in percutaneous penetration are reported as molecular weight and the log *P* values which were obtained from KowWin® (Meylan and Howard, 1995).

Diffusion cells were occluded with a layer of Parafilm® immediately after application of the test compounds in order to minimise evaporation. In this case, Parafilm® is not directly applied on the skin but on the top of the donor compartment of the Franz cell. With these conditions, no crystallization of caffeine was observed during all the experiment. Samples of the acceptor phase were withdrawn at predetermined intervals over 24 h, each time being replaced with fresh acceptor phase, and analyzed by HPLC.

2.5. Determination of caffeine in the skin

After an exposure time of 24 h, the diffusion cells were dismounted and the skin surface washed twice with 1.0 ml of distilled water and eight times with 1.0 ml of methanol to remove the residual donor samples. To separate superficial layers of the SC the procedure known as 'tape stripping' was used (Clarys et al., 2001; Rougier et al., 1983; Weigmann et al., 2001). For this purpose, the SC of the treated area was removed by 15 successive tape-strippings using D-Squam™ (φ = 14 mm) (Monaderm, Monaco) with a constant pressure (225 g cm^{-2}) for 5 s. After eliminating SC from skin samples by the tape-stripping procedure, the viable epidermis was separated from the dermis with dissection after immersing in water at 60 °C for 2.5 min (Jiang et al., 1999; Jimenez et al., 2004; Kligman and Christophers, 1963). The viable epidermis and dermis samples were separately chopped into small pieces and the test substances were extracted with 2 ml of methanol for 24 h under constant shaking. Then, the skin pieces were removed and the organic solvent was filtered through a 0.22 μm membrane filter (Millex-GV4, Millipore, France) before the HPLC analysis.

2.6. Sample analysis

For the quantification of caffeine in donor formulations, skin surface, skin layers (SC, viable epidermis, dermis) and in receptor fluid have been developed and validated by a direct, very sensitive, simple, and rapid high performance liquid chromatographic (HPLC) analytical method. HPLC analysis was performed using a Hewlett-Packard 1050 system which consisted of an automatic sampling system, a 1050 quaternary pump, and a variable wavelength diode UV 6000 LP detector. Caffeine was analyzed using a reversed-phase C_{18} column (Nucleosil, Macherey-Nagel, 5 μm, 250 mm × 3 mm) kept at 40 °C. Caffeine was detected at 273 nm with a retention time of approximately 6.65 ± 0.01 min using a mobile phase of 10:90 acetonitrile:water at a flow rate of 0.8 ml min^{-1}.

The samples studies were of two types: solutions (receptor fluids, washing solutions), and solids (SC on tapes, epidermis, dermis). Consequently they required different treatments to obtain the best analytical solution to be injected. Adequate concentration range, satisfactory recovery and good stability had to be achieved, in a standardized general operating procedure. The receptor fluids were injected directly and the washing solutions were high, corresponding to the excess of caffeine presence in formulation which had not penetrated within the skin. So each washing solution was diluted with 10 ml of methanol for HPLC measurement. In contrast, the concentrations of the chemical compounds studied in skin compartments were low. Thus, for these latter samples, the volume of solvent had to be as low as possible and compatible with the detectability of the chromatographic measurement.

2.7. Data analysis

The cumulative amount of caffeine (μg cm^{-2}) permeating per unit skin surface area was plotted against time (hours). The flux (J_s, μg cm^{-2} h^{-1}) was derived from the linear portion of the concentration–time profiles. The permeability coefficient (K_p, cm h^{-1}) was calculated as in (Cole and Heard, 2007):

$$K_p = \frac{J_s}{C_v} \quad (1)$$

C_v was the total donor concentration of the solute. The time to maximum rate (apparent lag time), the percentage of the dose recovered in the receptor fluid in 24 h, the percentage in the skin membrane and the percentage total recovery were also calculated. The amount in the surface swabs plus in the strips was defined

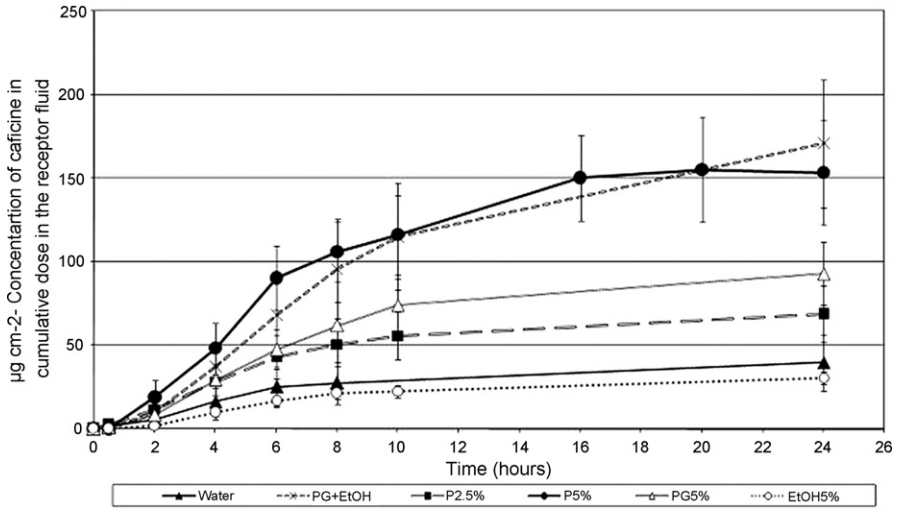

Fig. 2. Concentration–time profiles of caffeine through excised pig-ear full-thickness skin. Data presented as mean ± SE. In vitro studies following application of 10 µl of 2% caffeine in water ($n = 7$) compared with five vehicles with enhancers. PG + EtOH 25:25% ($n = 7$), P2.5% ($n = 8$), P5% ($n = 9$), PG5% ($n = 7$) and EtOH5% ($n = 7$).

as unabsorbed dose. The quantities in epidermis and dermis represent the absorbable dose. And the amount of test compound in the receptor fluid was defined as absorbed dose. Experimental data represented mean values ($n > 5$) ± standard deviation (SD) unless otherwise stated. An enhancement factor (EF) was calculated by dividing the flux from the formulation with enhancer by the flux from the enhancer free formulation (control formulation in water (1)) (Cole and Heard, 2007; Wu et al., 1997):

$$\mathrm{EF} = \frac{J_{\mathrm{Enhancer}}}{J_{\mathrm{control(Water)}}} \quad (2)$$

Statistical analysis was conducted using the non parametric Kruskal–Wallis ANOVA test to determine differences between data sets with Statgraphic logiciel (2001).

3. Results and discussion

3.1. Validation of the analytical procedure

An external calibration of caffeine (0.1 to 10 mg l^{-1}) was used to validate the analytical method in terms of linearity, precision, accuracy and limits of detection and quantification. The repeatability was established by the relative standard deviation (CV%) calculated from the ten injections of high (1.0 mg l^{-1}) concentration. The detection limit was calculated as the concentration that led to a signal three times the noise level, the quantification limit as 10 times the noise level (Harmonised tripartite guideline, 1996).

Testing the linearity of the validation plot from 0.1 to 10 mg l^{-1} revealed a correlation coefficient (r^2) of 0.996. The standard deviation was about 0.34%. The limits of detection (LOD = 0.13 mg l^{-1}) and limit of quantification (LOQ = 0.43 mg l^{-1}) were low enough to appreciate the quantity of product contained in each sample.

3.2. Determination of skin integrity: TEWL measurement

After a first visual observation of skin pieces, TEWL was recorded on each site. The rate of percutaneous penetration and TEWL was greatly increased when the barrier function of the SC was compromised. In practice with conditions mentioned above, TEWL values of less than 10 ± 5 g m^{-2} h^{-1} (for whole skin coming from the pig's ear) made it possible to accept the membrane, and any important increase would reflect a loss of intactness for the sample being tested. The skin in which the barrier was disrupted was not used in the study.

All TEWL values were less than 15 g m^{-2} h^{-1}: 7.1 ± 3.4 for water, 6.0 ± 3.0 for PG + EtOH, 9.6 ± 2.8 for P2.5%, 8.8 ± 6.0 for P5%, 6.1 ± 1.9 for PG5% and 9.2 ± 3.8 for EtOH 5%. This reflected the intactness of the pig skin.

3.3. Kinetic diffusion of caffeine

Permeation profiles of caffeine, i.e. cumulative amounts of caffeine permeated through full-thickness porcine skin plotted against time, are shown in Fig. 2.

The J_s, K_p, T_{Lag} values for permeation of 2% caffeine from the donor vehicles are summarized in Table 3.

Reference experiments had run with only caffeine in water without enhancer. Reference values for steady state

Table 3
Skin permeation parameters for caffeine.

Number of formulation	Donor vehicle[a]	Number of tests	J_s (µg cm^{-2} h^{-1})[b]	EF[c]	$K_p \times 10^{-5}$ (cm h^{-1})[d]	T_{lag} (h)	Cumulated dose Q_{24h} (µg)[e]
(1)	Water = reference	7	4.90 ± 2.10	1.0	24.5 ± 1.0	1.1 ± 0.5	39.81 ± 16.73
(2)	PG + EtOH 25:25%	7	14.20 ± 4.27	2.9	71.0 ± 2.1	1.3 ± 0.2	170.72 ± 38.32
(3)	P2.5%	8	7.33 ± 2.77	1.5	36.7 ± 1.4	1.1 ± 0.6	68.72 ± 17.06
(4)	P5%	9	15.49 ± 2.58	3.2	77.4 ± 1.29	1.1 ± 0.2	153.46 ± 31.44
(5)	PG5%	7	8.92 ± 1.61	1.8	44.6 ± 0.8	0.9 ± 0.4	92.97 ± 18.89
(6)	EtOH5%	7	3.46 ± 0.85	0.7	17.3 ± 0.42	1.2 ± 0.4	30.76 ± 3.65

[a] The concentration of caffeine in all formulations was 2% (w/v).
[b] J_s steady state fluxes obtained from the linear portion of the concentration-time profiles.
[c] Enhancement factor (EF) = J_s across skin in vehicle with enhancer/J_s across skin in water control.
[d] K_p (cm h^{-1}), permeability coefficient = J (µg cm^{-2} h^{-1})/drug concentration (mg ml^{-1}).
[e] Cumulative dose in receptor compartment, 24-h post-application.

Table 4
Distribution data for caffeine 24-h following application of 10 μl of formulations containing 2% of caffeine with and without enhancers.

Number of formulation	Donor vehicle	Washing solution (rinced surface)	Stratum corneum[a]	Epidermis[b]	Dermis	Receptor fluid	Total recovery
(1)	Water	68.6 ± 15.6	2.6 ± 0.9	0.2 ± 0.5	5.0 ± 2.7	18.9 ± 8.0	95.4 ± 8.1
(2)	PG + EtOH 25:25%	13.9 ± 7.1	1.5 ± 1.4	0.8 ± 0.8	8.8 ± 3.6	81.1 ± 18.2	106.2 ± 8.9
(3)	P2.5%	47.6 ± 12.5	4.5 ± 1.9	0.2 ± 0.2	0.9 ± 0.2	32.5 ± 8.7	85.8 ± 10.3
(4)	P5%	34.1 ± 19.9	1.9 ± 1.6	<LD	5.1 ± 2.7	65.4 ± 17.1	102.6 ± 11.3
(5)	PG5%	53.5 ± 6.1	0.9 ± 0.7	<LD	2.0 ± 0.7	44.2 ± 8.9	100.7 ± 8.9
(6)	EtOH5%	81.6 ± 6.9	2.4 ± 1.2	0.2 ± 0.3	1.9 ± 1.3	14.6 ± 1.7	100.7 ± 6.3

[a] SC corresponding to 15 strips.
[b] Viable epidermis without SC.

flux was $4.90 \pm 2.10\ \mu g\,cm^{-2}\,h^{-1}$, permeability coefficient was $24.5 \pm 1.0 \times 10^{-5}\ cm\,h^{-1}$, and Q_{24h} $39.81 \pm 16.73\ \mu g$. These results showed the capacity of caffeine to permeate the skin, which was already shown in the literature (Dias et al., 1999; Greaves et al., 2002; van de Sandt et al., 2004; Wilkinson et al., 2006).

The concentration in caffeine for each vehicle was compared and the Kruskal–Wallis test was performed. This test tests the null hypothesis that the median within each of the six vehicles was the same. In our study, the *P*-value was less than 0.05, thus there was a statistically significant difference between the medians at 95% confidence level.

The statistical analysis of flux values showed a possible formation of 3 groups: Water (1) + EtOH5% (6); P2.5% (3) + PG5% (5); PG/EtOH (2) + P5% (4). These groups reflected the enhancement of the permeation of caffeine through pig skin.

Formulation (6) presented the same order of flux value like the formulation reference (1). EtOH used at 5% did not improve the caffeine flux. The proportion of this solvent was too low to show a significative effect on the permeation flux.

Formulations (3) and (5) presented same values of flux. 1,2-pentanediol at 2.5% had the same effect on the permeation of caffeine than PG at 5%. It represented an interesting approach in order to decrease the proportion of the solvent to improve the flux in the same extent. According to previous reports the enhancement of propylene glycol was related to the proportion of this solvent in the formulation (Hadgraft, 1999; Moser et al., 2001).

Formulations (2) and (4) presented formulation interest because the permeation of caffeine was improved in great extent in these cases. The enhancing factor (EF) for formulation (2) was about 2.9 and 3.2 for formulation (6), which represented this increase of caffeine permeation. Finally by comparing with caffeine in water-solution, these last formulations presented a promoting effect for caffeine about 3 times superior.

Lag times were statistically the same with mean values of 1.3 and 0.9 h. The lag time (*t*-lag) reflects a complex sequence of events including the release of the drug from its vehicle, the reorganization of the skin barriers and the diffusion of caffeine through this time-varying medium. The different vehicles did not influence the *t*-lag which was in all cases near 1 h, in dermal route this value already corresponds to a short time of absorption.

The values obtained after the 24 h time application will be discussed with the compartment analysis in the following section.

3.4. Compartmental study

In the cosmetic field, the SCCP (SCCP, 2006) mentioned that amounts of the test compound must be determined in: the washing solution, the SC (e.g. adhesive tape strips), the epidermis without SC, the dermis and in the receptor fluid which corresponds to the systemic compartment. It was necessary to check for substance in the equipment. Moreover, the mass balance of the applied dose must be determined; it should be within the range of 85–115%. The amount of caffeine found in the receptor fluid was considered to be systemically available. The amounts found in the epidermis (without SC) and dermis were considered as potentially absorbed doses. The amount retained by the SC was not considered to be dermally absorbed, and thus did not contribute to the systemic dose.

Analyses in each layer of skin were performed after 24-h of exposition and all results were reported in Table 4.

The total recovery of caffeine at the end of the experiment was always as high as required by the guidelines ($100 \pm 10\%$ for OECD (2000a,b) and $100 \pm 15\%$ for SCCP (2006)).

Statistically, there was no difference in the level of caffeine in each layer of the skin; in general, the large part of caffeine in the skin was in the dermis. The great difference was at the level of what remained on the surface and what reached the receptor fluid.

In regards to the Q_{24h} values in receptor fluid, which correspond to direct systemic exposition it was possible to determine 3 homogeny groups (Fig. 3).

The first group was composed of formulations (1) and (6) where caffeine is solubilized in water and in water with 5% of ethanol. The presence of EtOH in the formulation did not increase the proportion of caffeine in receptor fluid and results were similar that those obtained with the control. At 5% in a water solution ethanol have not demonstrated an enhancing effect, the evaporative loss of this volatile solvent, from the donor phase during 24-h and the dilution effect may explain this situation. Effect of EtOH at 10% (Heard and Screen, 2008), at 25–50% (Kim et al., 2008) was studied by several authors but there is no literature for EtOH at 5%. Secondly at the same concentration PG and *P* which are not volatile solvents act as enhancer. This was demonstrated with the second group which was composed of P2.5% and PG 5% (formulations 3 and 5). Finally, the formulation PG + EtOH 25:25% (2) with a Q_{24h} about 171 μg and the formulation P5% (4) with a Q_{24h} of 153 μg presented important proportion of caffeine in the receptor fluid after the 24-h experiment.

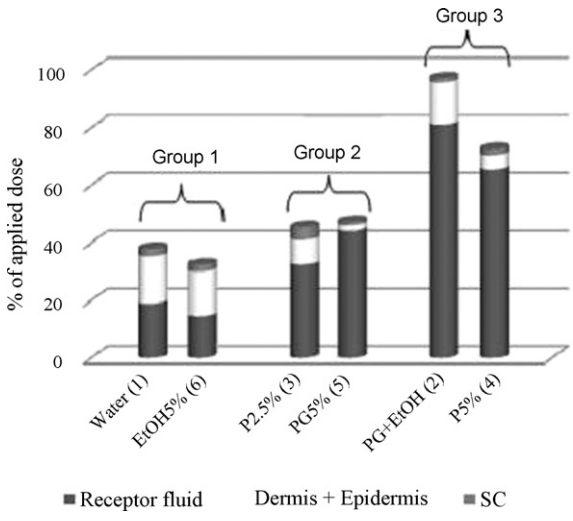

Fig. 3. Skin distribution of caffeine (% recovered material) 24 h following application of 10 μl of formulations containing 2% of caffeine with and without enhancers.

Propylene glycol and ethanol were widely known and employed as chemical enhancers (Williams and Barry, 2004). These solvents enter the SC, change its solution properties by altering the chemical environment, and thus dissolve the barrier capacity of this cutaneous layer (Bach and Lippold, 1998; Barry, 2001). The binary combination influences the penetration in accordance with previous works, in which a synergistic effect with these two solvents was observed (Ho et al., 1998; Hori et al., 1990; Ota et al., 2003; Potts et al., 1991). Panchagnula et al. (2001) supported that this combination was very interesting; both enhanced the solubility of caffeine in the membrane (Moser et al., 2001), and EtOH induced the reduction in the barrier property of SC (Bommannan et al., 1991). Tata et al. (1994) showed that the penetration was greater when the proportion of ethanol in the mixture was increased. At low concentration 1,2-pentanediol could improve the permeation of caffeine in the same extent of the binary combination PG/EtOH at 25:25. At this concentration, the binary mixture was known to irritate skin and delipidate the surface membranes (Bommannan et al., 1991; Finnin and Morgan, 1999; Hadgraft, 1999; Scheuplein and Blank, 1973). So to avoid toxicity and to improve the penetration of caffeine in a greater extent, the development of a formulation with 1,2-pentanediol was interesting.

These results showed the dose effect of pentanediol on the delivery of caffeine. At 2.5%, 32% of caffeine reached the receptor fluid. Although, at 5%, 65% of the hydrophilic drug penetrated the skin; it seems to show a dose-dependent activity. Like propylene glycol, pentanediol penetrated the SC, partition into this layer and increase permeant solubility in and thus permeant flux through the SC. From this, the flux of both pentanediol and caffeine should be related. Smith and Maibach (1995), in a review of penetration enhancers, have been concerned that apparent effects of penetration enhancers could be dependent upon their dose. For propylene glycol, Trottet et al. (2004) described that the flux of loperamide hydrochloride was determined by the percentage of PG in the formulation. Herkenne et al. (2008) found similar results for ibuprofen delivery.

4. Conclusions

Transdermal drug delivery is achieving preference over other forms of drug delivery due to its potential advantages. However, high molecular weight and low permeating drugs cannot permeate easily through the SC. An approach to break this skin barrier is by using chemical penetration enhancers. The selection of an enhancer in general or a new product for a transdermal product should be based on its efficacy, lack of toxicity, and compatibility with other components (Skelly et al., 1987). An ideal enhancer should be pharmacologically inert, odorless, colorless, non-toxic, non-irritating, no allergenic, and compatible with most drugs and excipients (Ranade, 1991). It is essential that these compounds are safe and are used in low quantities.

In this paper, the diffusion of caffeine was studied with propylene glycol, ethanol and a new product in this field the 1,2-pentanediol in order to enhance the rate of penetration of this hydrophilic molecule. Decreasing order of enhancement activity for caffeine is: water with PG + EtOH 25:25% = water with 1,2-pentanediol 5% > water with 1,2-pentanediol 2.5% = water with propylene glycol 5% > water with EtOH 5% = water. The results obtained showed the great interest in the addition of a small concentration (5%) of 1,2-pentanediol in the formulation in order to improve the penetration rate, 3-time superior to caffeine in water solution. The use of PG/EtOH at 25:25 showed a same enhancement, but concentrations of these solvents were very high. The benefit of penetration enhancement in this case was counterbalanced by the fact that at this range of concentration, the use of these solvents can harm the skin. So, 1,2-pentanediol represents an effective penetration enhancer for caffeine; with a low concentration of this diol, it is possible to enhance dermal delivery of this hydrophilic compound, with a dose effect. However, further elucidation of the mechanism of action of permeation enhancement has to be made. And further studies will be necessary to determine its enhancing properties for more lipophilic model drugs.

Acknowledgement

We would like to thank the slaughterhouse (Pézenas, France) for kindly donating pig ears and the veterinary section too.

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