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European Journal of Pharmaceutical Sciences 24 (2005) 239–244
EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES
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Percutaneous absorption of cyclizine and its alkyl analogues

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Received 25 October 2004; received in revised form 25 October 2004; accepted 3 November 2004
Available online 15 December 2004

Abstract

Cyclizine (**I**) alkyl analogues (**II**–**IV**) were synthesized and their skin permeation parameters evaluated in vitro. It was hoped that these compounds would possess physicochemical properties more favourable for percutaneous delivery than (**I**). The identification and levels of purity for the compounds were confirmed by mass spectrometry (MS), nuclear magnetic resonance (NMR) spectrometry, and infrared spectrometry (IR) while melting points were determined by an electrothermal digital Bϋchi melting point apparatus. Aqueous solubilities (25 °C) and partition coefficients were determined and in vitro permeation studies were performed in buffer (37 °C) at pH 7.4 over a period of 24 h, using Franz diffusion cells fitted with human epidermal membranes. Generally, the analogues were more lipophilic, but nevertheless possessed higher aqueous solubilities as compared to (**I**). (**II**) and (**IV**) exhibited two- to three-fold increase in aqueous solubility and their melting temperatures dropped by more than 55 °C. Compound (**III**) had similar aqueous solubility to (**I**), but its melting point dropped by about 35 °C. Measured steady-state fluxes indicated that (**II**) is a far better penetrant ($J = 6.95\ \mu g/cm^2/h$) of human epidermis than (**I**). Although fluxes of (**III**) and (**IV**) drop off markedly from that of (**II**), they remained above the flux of (**I**), which is ($0.132\ \mu g/cm^2/h$). In conclusion, (**II**) was the best skin permeant and also exhibited the highest aqueous solubility and lowest level of crystallinity as compared to (**I**) and other analogues. (**III**) and (**IV**) were more lipophilic. The overall permeation data of this series indicated that the more water-soluble and the lowest melting point compound was the best skin permeant.

Keywords: Cyclizine; Alkyl analogues; Physicochemical properties; Percutaneous delivery

1. Introduction

Cyclizine is a piperazine derivative, which belongs to the anti-histamine group of drugs. It is described chemically as 1-(diphenylmethyl)-4-methylpiperazine. It acts both on the emetic trigger zones and by damping the labyrinthine sensitivity. Pharmacologically it has anti-histaminic, anti-serotonic, local anesthetic, and vagolytic actions (Susan et al., 1989). Therapeutically it is an anti-emetic agent, the normal dose being 50 mg for 4–6 h. It is recommended in the treatment and prevention of motion sickness, post-operative vomiting, and Menieres disease (Dundee and Jones, 1968). The synthesis of cyclizine was reported by Baltzly et al. (1949). Its anti-histaminic action was discovered by Castillo et al. (1949) and it was reported to be one-fourth as active as its congener chlorcyclizine in blocking the histamine-induced spasm of the tracheal chain preparation. The use of cyclizine hydrochloride for the prevention of seasickness and airsickness has been described by Chinn et al. (1952, 1953). Gutner et al. (1954), using microcaloric and galvanic stimulation methods, found that cyclizine notably decreased labyrinthine sensitivity in human subjects and that cyclizine alleviated post-operative nausea and vomiting. The same investiga-

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doi:10.1016/j.ejps.2004.11.001

tion also found that the drug partially antagonized vomiting induced by the administration of apomorphine to dogs.

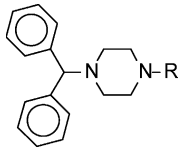
A number of drugs readily passes through the skin and the rate and extent to which this happens is influenced by the physicochemical properties of the drug (Beckett, 1982). Other factors may also have an influence, but if kept constant, it is possible to determine which physicochemical properties are most important in determining the rate and extent of absorption through or into the skin. Recent studies revealed that alkylation approach to improve the dermal delivery of drugs offers several advantages, since it changes the physicochemical properties of the drug (i.e. aqueous solubility, lipophilicity, and level of crystallinity). It is important to take into consideration both the relative potency of the analogue and its ability to permeate the skin. For example, it would be better to select an active with a 20-fold lower potency but a 100-fold better flux.

Calpena et al. (1994) highlighted the possibility of delivering some anti-emetic drugs via the dermal route. Several of the anti-emetics were found to be likely candidates for formulation into transdermal delivery system. Thus, cyclizine (**I**) is one of the anti-emetic drug entities, which could be considered for possible transdermal delivery. This possibility, however, may be hindered by its low aqueous solubility and high melting point. It is, therefore, likely that the delivery characteristics of (**I**) can be improved by using its alkyl analogues, derivatives possessing both a high aqueous solubility and lipophilicity at physiological pH (pH 7–8) and also possessing a lower melting point than (**I**). Therefore, in the present study, cyclizine alkyl analogues were synthesized, their physicochemical properties determined and their in vitro skin permeation evaluated.

2. Materials and methods

Cyclizine analogues (**II**–**IV**) were synthesized according to the methods by Zikolova and Ninov (1972) and Zikolova et al. (1984). Cyclizine (**I**), 1-(diphenylmethyl)piperazine, ethyl iodide, propyl iodide, and butyl iodide were obtained from Sigma–Aldrich (UK). Identification and levels of purity were confirmed by electron impact mass spectra (MS) recorded on a micromass autospec ETOF mass spectrometer, nuclear magnetic resonance (^{1}H NMR and ^{13}C NMR) spectra recorded on a Varian Gemini 300 spectrometer operating at frequency of 300 MHz for ^{1}H and 75 MHz for ^{13}C using $CDCl_3$. The following abbreviations were used to describe the splitting pattern of ^{1}H signals: s: singlet, t: triplet, st: sextet, bs: broad singlet, and m: multiplet. Infrared spectra (IR) were recorded on a Nicolet 550 series II spectrometer using KBr pellets. Melting points were determined with an electrothermal digital Bϋchi B-540 melting point apparatus. For solubility studies, HPLC grade acetonitrile (Across Organic, NJ, USA), potassium dihydrogen phosphate and *ortho*-phosphoric acid (Merck, Johannesburg, South Africa), HPLC grade double deionized water and *n*-octanol (BDA laboratory suppliers, Poole, England) were used. For permeability studies, female human abdominal skin was obtained from Klerksdorp Surgical Clinic (South Africa).

2.1. General synthesis method



$R = CH_3$	1-(diphenylmethyl)-4-**methyl**piperazine	(**I**)
$R = CH_2CH_3$	1-(diphenylmethyl)-4-**ethyl**piperazine	(**II**)
$R = (CH_2)_2CH_3$	1-(diphenylmethyl)-4-**propyl**piperazine	(**III**)
$R = (CH_2)_3CH_3$	1-(diphenylmethyl)-4-**butyl**piperazine	(**IV**)

To 0.12 mole (30.28 g) of 1-(diphenylmethyl)piperazine in 20 ml dry benzene, 20.6 g anhydrous sodium bicarbonate was added. The reaction was stirred and heated under reflux. To the suspension, 0.12 moles of ethyliodide or propyl iodide or butyl iodide dissolved in 20 ml dry benzene was added dropwise over a period of 20 min. The reaction was refluxed until completion, as followed by TLC. It was filtered, washed with dry benzene, and the solvent was removed under vacuum. In each instance, an almost white powder (compounds **II**, **III**, or **IV**) was purified by column chromatography (ethyl acetate:dichloromethane:methanol, 7:2:1; silica gel PF_{254}) and recrystallised at room temperature.

2.1.1. 1-(Diphenylmethyl)-4-**ethyl***piperazine* (**II**)

6.71 g (44.73%) of almost white product were produced following the analysis by TLC and column chromatography (CC) (ethyl acetate:dichloromethane:methanol, 7:2:1). R_f value: 0.64; mp: 51 °C; *m*/*z* (EI+, %): M^+ 280 (91), 113 (100), 56 (58), 165 (75), 167 (89), 194 (84), 195 (68), 208 (56), and 70 (67); δ_H (300 MHz, $CDCl_3$): 1.1 (t, 3H, CH_3), 2.4 (t, 2H, CH_2), 2.5 (bs, 8H, piperazine protons), 4.21 (s, 1H, CH), 7.3 (m, 10H, aromatic protons); δ_C (75 MHz, $CDCl_3$): 11.7 (CH_3), 51.6 (CH_2), 52.2 (CH_2), 52.9 (CH_2), 76.2 (CH), 126.9 (CH), 127.9 (CH), 128.5 (CH), and 142.8 (C). ν_{max} (KBr, cm^{-1}): 725, 960, 1160, 1250, 1460, 2800, 2960, and 3460.

2.1.2. 1-(Diphenylmethyl)-4-**propyl***piperazine* (**III**)

8.00 g (53.3%) of almost white product were produced following the analysis by TLC and column chromatography (CC) (ethyl acetate:dichloromethane:methanol, 7:2:1). R_f value: 0.71; mp: 70 °C; *m*/*z* (EI+, %): M^+ 294 (89), 127 (100), 167 (97), 194 (78), 195 (78) 208 (54), 165 (71), and 56 (55); δ_H (300 MHz, $CDCl_3$): 0.9 (t, 3H, CH_3), 1.5 (st, 2H, CH_2), 2.31 (t, 2H, CH_2), 2.49 (bs, 8H, piperazine protons), 4.21 (s, 1H, CH), 7.3 (m, 10H, aromatic protons); δ_C (75 MHz, $CDCl_3$): 11.8 (CH_3), 19.9 (CH_2), 51.8 (CH_2), 53.4 (CH_2), 60.6 (CH_2), 76.2 (CH), 126.9 (CH), 128 (CH), 128.5

(CH), and 142.9 (C). ν_{max} (KBr, cm^{-1}): 725, 1000, 1160, 1250, 1460, 2800, 2960, and 3460.

*2.1.3. 1-(Diphenylmethyl)-4-***butyl***piperazine (***IV***)*

5.12 g (34.1%) of almost white product were produced following the analysis by TLC and column chromatography (CC) (ethyl acetate:dichloromethane:methanol, 7:2:1). R_f value: 0.67; mp: 52 °C; *m/z* (EI+, %): M^+ 308 (90), 141 (98), 167 (99), 194 (89), 195 (85), 208 (62), 165 (76), and 56 (60); δ_H (300 MHz, $CDCl_3$): 0.9 (t, 3H, CH_3), 1.28 (m, 2H, CH_2), 1.42 (m, 2H, CH_2), 2.3 (t, 2H, CH_2), 2.41 (bs, 8H, piperazine protons), 4.2 (s, 1H, CH), 7.3 (m, 10H, aromatic protons); δ_C (75 MHz, $CDCl_3$): 13.9 (CH_3), 20.7 (CH_2), 28.9 (CH_2) 51.9 (CH_2), 53.5 (CH_2), 58.5 (CH_2), 76.3 (CH), 126.9 (CH), 128 (CH), 128.5 (CH), and 142.9 (C). ν_{max} (KBr, cm^{-1}): 725, 1000, 1160, 1250, 1460, 2800, 2960, and 3460.

2.2. Chromatographic procedure

The analytical HPLC system comprised of a Shimadzu LC-6A delivery system, Shimadzu SPA-6A UV detector, Shimadzu SCL-6B system controller with SIL-6B autosampler and Shimadzu CR6A chromatopac (integrator). A Lichrospher (4 mm × 250 mm), 100 Å pores – 5 μm, RP – 18 endcapped column (Machery–Nagel, Düren, Germany) was used. Compounds were analysed with a mobile phase comprising of acetonitrile: 0.05 M (pH 3) phosphate buffer (6:4) with UV detection at 200 nm. The pH was adjusted to 3 with 15% *ortho*-phosphoric acid solution. The flow rate was 1.0 ml/min and column temperature was maintained at 25 °C.

2.3. Aqueous solubility

The aqueous solubilities of (**I**) and its alkyl analogues were determined by equilibrating a large excess of each compound in HPLC water. The temperature (25 °C) was held constant by means of a water bath. To hasten the attainment of equilibrium, magnetic bars continuously stirred each slurry. Equilibrium was attained within 24 h. Samples were then filtered through a Millipore filter (0.45 μm) and the concentration of the compounds were determined by HPLC.

2.4. Partition coefficient

Cyclizine has ionizable functional groups and therefore it is important to know the pH at which partitioning is measured. ACD software was used to predict the effect of pH on the partitioning and the results of log *D* plotted as a function of pH are shown in Fig. 1. The figure shows a complex behaviour but it clearly demonstrates the differences in partitioning that occur around physiological pH.

Equal volumes of *n*-octanol and phosphate buffer (pH 7.4) were saturated with each other for at least 24 h before the experiment. Solutions of (**I**) and its alkyl analogues were prepared with the pre-saturated *n*-octanol phase as a solvent.

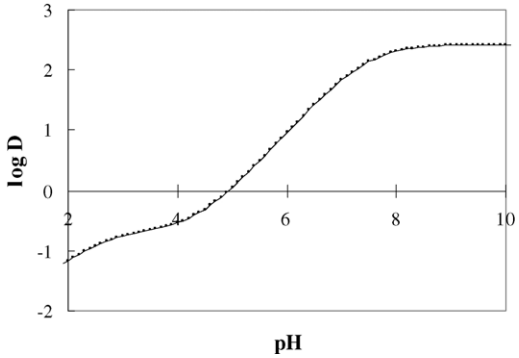


Fig. 1. log *D* as a function of pH.

Five millilitres of these solutions were transferred to a 10 ml test tube, each containing equal volumes (5 ml) of phosphate buffer. Three tubes of each compound were stoppered and agitated for 1 h and another set for 2 h. After centrifugation, the *n*-octanol and buffer phases were separated and appropriately diluted with methanol and mobile phase before injecting onto the HPLC column. Partition coefficients were calculated as the ratio of drug concentration in the *n*-octanol phase to that in the buffer phase. There was no difference in the values of K_{oct} when the tubes were agitated for 1 or 2 h.

2.5. Melting point

Melting points were taken in capillary tubes on an electrothermal digital Bϋchi B-540 melting point apparatus and are uncorrected.

2.6. In vitro skin permeation study

2.6.1. Preparation of donor solutions

Donor solutions of (**I**)–(**IV**) were obtained by equilibrating excess amounts of each compound with phosphate buffer (pH 7.4) into stoppered glass containers. The temperature was maintained at 37 °C by circulating water through the jackets from a constant temperature water bath. The slurries were vigorously and continuously mixed for 24 h using magnetic stirring bars. Saturated state was achieved well within 24 h.

2.6.2. Preparation of the skin

Full thickness female human abdominal skin tissue from the surgery clinic was sealed in evacuated plastic bags and frozen at −20 °C. The adipose tissue was removed by blunt dissection and immersion of the skin in 60 °C water for 1 min to separate the epidermis. The epidermis was then peeled away from the dermis using forceps (Harrison et al., 1984). The skin sections were cut into squares, wrapped in aluminium foil, sealed in plastic bags, and stored in a freezer at −20 °C until utilized (within 1 month of its receipt). The frozen skin pieces were thawed at room temperature and examined for defects before mounting them onto the Franz diffusion cells.

2.6.3. Skin permeation method

Vertical Franz diffusion cells with a 4 ml capacity receptor compartment and a 1.07 cm^2 diffusion area were used. The epidermal layer of the skin was mounted carefully onto the lower half of the diffusion cells with the stratum corneum facing the donor compartment. The donor compartments were fastened to the receptor compartments with clamps, the skin acting as a seal between the half-cells. The receptor compartments were filled with phosphate buffer (pH 7.4), taking care that there were no air bubbles left in the compartments. The diffusion cells were placed in a water bath at a constant temperature of 37 °C on a submersible magnetic stirring bed, a small magnetic stirring bar was placed at the bottom of the lower compartment and the system was allowed to equilibrate for 1 h before adding the saturated drug containing solution to the donor compartment. The experiment was initiated by charging the donor compartment with 700 μl of a freshly prepared saturated solution of the drug and immediately covering it with Parafilm® to prevent any significant evaporation from the donor compartment. At pre-determined intervals (2, 4, 6, 8, 10, 12, and 24 h), the entire contents of the receptor compartment were withdrawn and replaced with fresh buffer (37 °C). This ensured that sink conditions existed throughout the experiment. Two hundred microlitres of each sample was directly assayed by HPLC to determine the drug concentration in the receptor fluid. The duration of the skin permeation experiment was 24 h.

3. Results and discussion

3.1. Synthesis of cyclizine alkyl analogues

The analogues were successfully synthesized according to the methods by Zikolova and Ninov (1972) and Zikolova et al. (1984). The molecular mass of each compound was determined experimentally with mass spectroscopy and by empirical calculation. The value of molecular mass was the same in both cases. The structures and purities of the analogues were confirmed by MS, NMR, and IR.

3.1.1. Spectral data of cyclizine analogues

The MS data for the compounds confirmed the presence of the molecular ions (M^+) at *m*/*z* 280, 294, and 308, corresponding to the molecular formula $C_{19}H_{24}H_2$ (**II**), $C_{20}H_{26}N_2$ (**III**), and $C_{21}H_{28}N_2$ (**IV**), respectively. M^+ 113, 127, and 141 correspond to the *N*-alkyl piperazine fragment for (**II**), (**III**), and (**IV**), respectively, and the signal at 167 represents the aromatic portion without the alkyl piperazine radical. Signals at 194, 195, and 208 represent the rearrangement and fragmentation of the alkyl piperazine moiety.

In addition to the ^{1}H NMR and ^{13}C NMR signals of cyclizine (**I**), compound (**II**) has a triplet from the methyl group at δ 1.1 in the ^{1}H NMR spectrum and a signal at δ 11.7 in the ^{13}C NMR spectrum. The ^{1}H NMR spectrum of (**III**) shows in addition to signals of (**I**) a sextet at δ 1.5 due to the methylene protons and a triplet at δ 0.9 due to the methyl group of the propyl moiety. ^{13}C NMR spectrum of (**III**) shows signals due to methylene carbon atom at δ 19.9 and at 11.8 from the methyl group of the propyl moiety. The ^{1}H NMR spectrum of (**IV**) shows in addition to signals of (**I**) a multiplet at δ 1.28 and 1.42 due to the methylene protons and a triplet at δ 0.9 due to the methyl group of the butyl moiety. ^{13}C NMR spectrum of (**IV**) shows signals due to methylene carbon atoms at δ 20.7 and at 28.9; whereas, the methyl group of the butyl moiety resonates at δ 13.9.

Table 1
Physicochemical properties of (**I**) and its alkyl analogues

Compound	Molecular weight (g/mol)	ACD log *D* pH 7.4	Melting point (°C) ± S.D.
I	266.4	2.09	107
II	280.4	2.58	51
III	294.4	3.11	70.1
IV	308.5	3.64	52.1

3.2. Physicochemical properties

Table 1 summarizes the physicochemical properties of (**I**) and its alkyl analogues. The melting point of (**I**) was the same as reported in literature. The trend in melting point as a function of alkyl chain length can be seen in Table 1. Although there is irregularity in the pattern, overall the melting points decrease as the alkyl chain is extended. Compound (**I**) had a melting point of 107 °C. Increasing chain length to $–CH_2CH_3$ and $–CH_2CH_2CH_2CH_3$ resulted in compounds (**II**) and (**IV**) with melting points of about 55 °C lower than (**I**). Increasing the chain to $–CH_2CH_2CH_3$ resulted in a melting point higher than that of (**II**) and (**IV**), however, the melting point was lower than that of (**I**). Yalkowsky et al. (1972) studied alkyl chain length series and found that melting points decreased overall, but not linearly. This indicates that extra alkyl functionalities disrupt the intracrystalline cohesion of the drug.

It is interesting to compare the predicted log *D* values, as determined using ACD software, with the experimentally measured ones. This is shown in Fig. 2. There is a linear relationship between the experimental and predicted values for the four analogues. However, the predicted ones are not as high as those measured. The precise reasons for this are unknown but it should be remembered that log *D* values are dependent on the ionic nature of the aqueous medium and the absolute values may depend on different amount of ion pairs that are present. This will be affected by the nature of the counter ions and the ionic strength of the solution.

Physicochemical parameters, such as aqueous solubility and lipophilicity, have shown to influence membrane flux, therapeutic activity, and pharmacokinetic profiles of medicines (Goosen et al., 1998). The aqueous solubilities and lipophilicities of (**I**) and its alkyl analogues are listed in Table 2. Further alkylation of the piperazine ring results in compounds that are more lipophilic but also possess higher aqueous solubility than (**I**). Although the first member of the

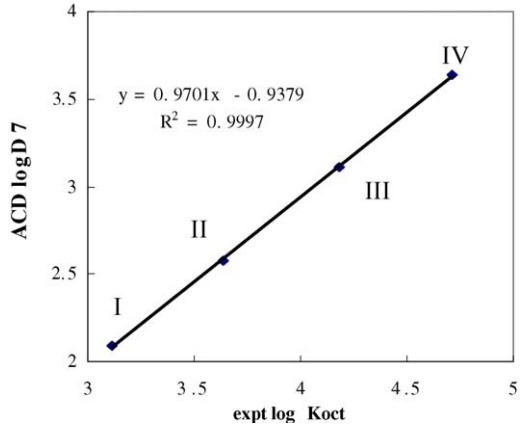


Fig. 2. The relationship between the experimental log *D* and those predicted using ACD software.

series (**II**) was about three times more soluble than (**I**), compound (**III**) had aqueous solubility almost equal to that of (**I**). Compound (**IV**) was found to be more than 2.5 times more soluble than (**I**). It clearly appears that compounds (**II**) and (**IV**) are more soluble than compound (**III**) despite the fact that the aqueous solubility of (**IV**) is limited by its extra methylene group. The changes in aqueous solubilities of these analogues mirror the changes in crystallinity seen through the melting points. The low solubility of (**III**) can be attributed to the higher melting point as compared to (**II**) and (**IV**).

Comparing the *n*-octanol/water partition coefficient as a function of alkyl chain length in Table 2, it can be seen that longer chain analogues are more lipophilic. Bundgaard and Falch (1985) indicated that the increase in lipophilicity is generally accompanied by a decrease in water-solubility, but inspection of the data in Table 2 reveals that the aqueous solubility increased relative to (**I**) despite the higher log K_{oct} value of the compounds.

Based on the physicochemical properties of the analogues (Tables 1 and 2), it can be seen that compounds (**II**) and (**IV**) have higher aqueous solubilities and higher lipophilicities as compared to (**I**). It can, therefore, be predicted that these analogues should have the highest skin flux in this series. Compound (**I**) and (**III**) have lower aqueous solubilities and higher melting points. This might have a less favourable effect on their skin permeability. Compound (**III**) possesses higher log K_{oct}, that could result in the compound being more skin permeable than (**I**). A prediction of the order of penetration of compounds through the skin would be: (**II**) > (**IV**) > (**III**) > (**I**) as the result of the fact that the flux determining physico-

Table 2
Aqueous solubility and partition coefficient for (**I**) and its alkyl analogues

Compound	Aqueous solubility (25 °C) (μg/ml ± S.D.)	log K_{oct} ± S.D.
I	185.5 ± 0.20	3.11 ± 0.4
II	569.6 ± 5.39	3.64 ± 0.4
III	189.9 ± 3.30	4.18 ± 0.2
IV	481.8 ± 11.8	4.71 ± 0.5

Table 3
Permeation parameters of (**I**) and its alkyl analogues through human skin

Compound	J ± S.D. (μg/cm²/h)	T_L (h)	k_p ± S.D. (cm/h) 32 °C	D (cm²/h) × 10^{-3}
I	0.132 ± 0.04	0.15	0.003 ± 0.01	25.0
II	6.952 ± 0.38	0.21	0.044 ± 0.18	17.9
III	0.250 ± 0.02	0.28	0.0044 ± 0.09	13.4
IV	0.686 ± 0.06	0.40	0.005 ± 1.05	9.38

chemical properties, partitioning and solubility, are both in the same direction.

3.3. In vitro skin permeation study

The percutaneous permeation of (**I**) and its alkyl analogues was studied by an in vitro technique using a Franz diffusion cell mounted with the epidermal layer of human skin as the diffusion membrane. The permeation parameters (flux, J; lag time, T_L; permeability coefficient, k_p; and diffusion coefficient, D of (**I**)) and its alkyl analogues from their saturated aqueous solutions (pH 7.4) are summarized in Table 3. The steady-state flux of each compound was determined from the slope of the linear portion of the cumulative amount versus time plot and their mean steady-state flux is presented as a bar chart in Fig. 3. The compounds attained steady state diffusion in the skin within 0.4 h. The lag times were determined by extrapolating the linear portion of the curve to its intersection with the *x*-axis. There was no significant difference in the lag times.

The diffusion experiment showed that there is a varying degree of permeation between (**I**) and its alkyl analogues. Generally, the analogues resulted in higher permeation than (**I**). Fig. 3 shows the permeation profiles of (**I**) and its alkyl analogues. It clearly indicates that, relative to (**I**), there is an increase in the steady-state flux of the analogues. The highest flux is observed with (**II**) followed by (**IV**). This could be attributed to their high aqueous solubility and low

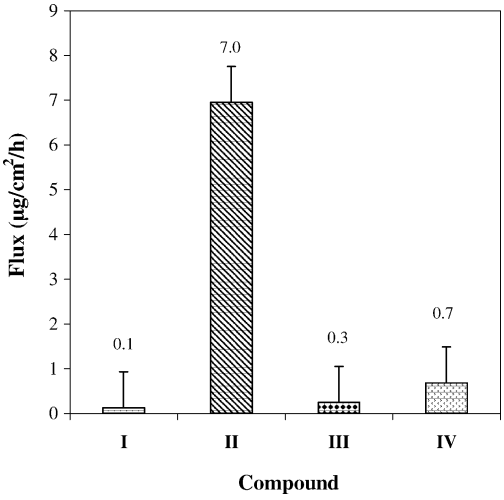


Fig. 3. Mean steady-state flux (μg/cm²/h) ± S.D. of (**I**) and its alkyl analogues from saturated aqueous solutions (n = 6).

level of crystallinity, as is evident from their low melting points. (**I**) and (**III**) exhibited lower flux, a reflection of their higher melting points and low aqueous solubility. Flynn and Yalkowsky (1972) studied the effects of alkyl chain length on the flux across a synthetic membrane. They found that a plot of the logarithm of the steady-state flux from saturated solution against chain length gave a parabolic curve. The results obtained in this study, show that the series is capable of odd–even alternation in aqueous solubility, melting point and in percutaneous permeation. This kind of behaviour is attributed to the dependence of these physicochemical properties upon the sum of the energy required to disrupt the crystal and the intermolecular interactions between like and unlike species in solution. The linearity of partition coefficient with alkyl chain length is because the partition coefficient is a property of the solute and therefore is not dependent on the crystal structure. It is only dependent upon the interactions occurring in solution. There is a correlation between aqueous solubility, melting point and percutaneous permeation of the compounds. (**II**) Showed high percutaneous permeation hence increased aqueous solubility and low melting point. Low percutaneous permeation of (**I**) and (**III**) is attributed to their low aqueous solubility and high melting point. Thus, the more water-soluble member of the series is the most penetrating member through the human epidermis.

The partitioning behaviour of cyclizine and its derivatives as a function of pH is interesting. In this study the donor phase was buffered at pH 7.4 at which value partitioning is quite favourable. In unbuffered conditions the solution at the skin surface will be at approximately pH 5, the estimated pH of the skin surface. At this pH, the portioning is much less favourable and less efficient fluxes may be anticipated. However, this would need verifying experimentally.

The results of this study suggest that alkylation is a potential useful approach to enhance percutaneous penetration. The following rank order of penetration of compounds was established: (**II**) > (**IV**) > (**III**) > (**I**). In conclusion, it is clearly demonstrated that further alkylation of the piperazine ring in 1-(diphenylmethyl)piperazine molecule beyond a methyl group results in compounds that are more hydrophilic and less crystalline. These physicochemical properties favour percutaneous delivery of drugs. From all the permeability data, compound (**II**) showed the best permeation results of the series and it was clear from experimental data that aqueous solubility and level of crystallinity played an important role in the skin permeation process.

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