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International Journal of Pharmaceutics 279 (2004) 59–66
international journal of pharmaceutics
www.elsevier.com/locate/ijpharm

Percutaneous delivery of carbamazepine and selected *N*-alkyl and *N*-hydroxyalkyl analogues

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Received 4 December 2003; received in revised form 22 March 2004; accepted 4 April 2004

Available online 2 June 2004

Abstract

Advantages associated with the transdermal delivery route are well documented, but in the past scientists have concentrated primarily on means of decreasing the barrier function of the skin for improved permeability. Pro-drugs, which possess more favourable physicochemical properties for improved transdermal permeability may have considerable potential. These have been considered in the past but recent information concerning structure activity relationships in dermal penetration has prompted increased interest. During this study, *N*-methyl (**2**), *N*-ethyl (**3**) and *N*-(2-hydroxyethyl) carbamazepine (**4**) analogues were synthesised for transdermal evaluation.

Keywords: Carbamazepine; *N*-alkyl analogues; *N*-hydroxyalkyl analogues; Transdermal; Percutaneous delivery

1. Introduction

The benefits associated with transdermal drug delivery have been widely described and include the bypassing of first pass drug metabolism, quick interruption of treatment and a non-invasive treatment regimen (Naik et al., 2000). These advantages result in lower therapeutic drug concentrations being required and greater patient compliance. This has prompted an interest in the transdermal route of drug delivery. The skin, however, provides the scientist with a great challenge for transdermal delivery. It is a highly efficient barrier, which protects the internal plasma successfully from the harsh exterior (Flynn, 1993). In the past, most transdermal research has concentrated upon means of increasing the transdermal flux of compounds by decreasing the barrier function of the skin, with the aid of penetration enhancers and/or specially designed vehicles to promote transdermal permeability (Beckett, 1982; Williams and Barry, 2004). The synthesis of analogues with more favourable physicochemical properties for improved transdermal delivery has gained favour in recent times.

Carbamazepine has been employed for the treatment of trigeminal neuralgia since the 1960s and was approved as an antiseizure agent in the USA in 1974. Presently, it is considered to be a primary drug for the treatment of partial and tonic–clonic seizures (Bonina et al., 2001). Carbamazepine was selected for this study in order to determine the effect of its *N*-alkylation and *N*-hydroxyalkylation on transdermal permeability and to investigate any relationships that

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doi:10.1016/j.ijpharm.2004.04.007

may exist between the physicochemical properties of the *N*-alkyl and *N*-hydroxyalkyl analogues and transdermal permeation.

Optimal transport through the skin requires a drug to possess lipophilic as well as hydrophilic properties (Pefile and Smith, 1997). An increase in lipophilicity increases the permeability coefficient but this is usually accompanied by a decrease in water solubility. Optimum delivery is often produced using a compromise between increased $\log K_{oct}$ and decreased solubility. The work reported here describes the preparation of the *N*-methyl, *N*-ethyl and *N*-hydroxyethyl analogues of carbamazepine with higher lipophilicity than carbamazepine itself, in order to determine the effects of these groups upon the physicochemical properties and transdermal permeability of the parent drug. This work is furthermore a continuation of our ongoing studies that enlarge the current database on the dermal delivery of compounds (Guy and Hadgraft, 1992; Goosen et al., 2002).

2. Materials and methods

Carbamazepine (**1**) (Aldrich, Milwaukee, USA) was used as starting material to synthesise the *N*-methyl (**2**), *N*-ethyl (**3**) and *N*-hydroxyethyl (**4**) analogues (Fig. 1). The following chemicals were used for synthesis: ethyl iodide, methyl iodide and 1-bromoethanol (Sigma–Aldrich, UK); reagent grade anhydrous benzene, magnesium sulphate and sodium hydride (Merck, Midrand, South Africa) and tetrabutylammonium hydrogen sulphate (Fluka, Buchs). *n*-Octanol (BHD Laboratory Supplies, Poole, UK) was used for the partition coefficient determinations. The following chemicals were used in HPLC analyses: HPLC grade acetonitrile, methanol and potassium dihydrogen phosphate (Merck, Midrand, South Africa). Double distilled deionised water was obtained from a Milli-Q water purification system (Millipore, Milford, USA).

2.1. Synthesis

N-Methyl carbamazepine (**2**) and *N*-(2-hydroxyethyl) carbamazepine (**4**) were synthesised by the addition of 62.5 ml anhydrous benzene to 0.015 mol sodium hydride and 0.013 mol carbamazepine in an anhydrous nitrogen atmosphere. The mixtures were stirred and refluxed under nitrogen for 24 h. The temperature was adjusted to 25 °C and 0.04 mol methyl iodide was added in the synthesis of *N*-methyl carbamazepine and 0.017 mol 1-bromoethanol was added in the synthesis of *N*-(2-hydroxyethyl) carbamazepine. The mixtures were refluxed for a further 8 h. The resultant hot mixtures were filtered and the solvents were removed by evaporation (McNamara, 1996). The reactions were followed by TLC. *N*-Methyl carbamazepine and *N*-(2-hydroxyethyl) carbamazepine were isolated using column chromatography with

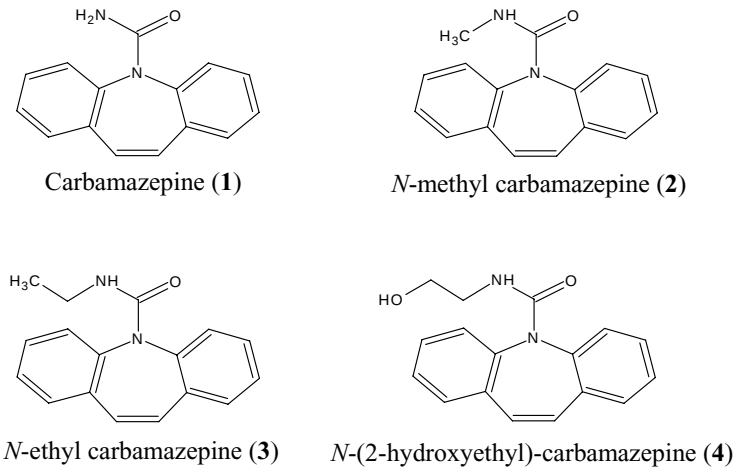

Fig. 1. Structures of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues.

ethyl acetate–petroleum ether 7:3 and 6:4, respectively, as eluent.

N-Ethyl carbamazepine (**3**) was synthesised whereby 0.002 mol ethyl iodide in 5 ml benzene was added drop wise to a stirred refluxing mixture of 0.002 mol carbamazepine, 20 ml 50% sodium hydroxide and 0.002 mol. tetrabutylammonium hydrogen sulphate in 25 ml benzene over a 1.5 h period. Once the addition had been completed, the mixture was refluxed for a further 2.5 h. The reaction was followed by TLC. The resultant mixture was cooled to 25 °C and diluted with water. The organic phase was separated and washed with 30 ml water, where after it was dried with magnesium sulphate. *N*-Ethyl carbamazepine was isolated using column chromatography with ethyl acetate–petroleum ether 7:3 as eluent.

2.2. Chromatographic procedure

Carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues were assayed by HPLC. The HPLC system used was a SpectraSYSTEM (Thermo Separation Products (TSP), California) and a SpectraSYSTEM UV variable wavelength UV-detector (TSP). The samples were injected automatically into the sample loop with a SpectraSYSTEM AS 3000 Autosampler (TSP). A Machery–Nagel Lichrospher 100-5 RP–18EC (4 mm × 250 mm) column was used (Machery–Nagel, Düren, Germany). The acquired data were processed by a SpectraSYSTEM SN 4000 coupled to a PC 1000 software integrator (TSP). The mobile phase for all the analyses consisted of 50% potassium phosphate buffer (0.01 M), 28% acetonitrile and 22% methanol. The flow rate was set at 1.5 ml/min, the spectra recorder at 254 nm and the injection volume was 200 μl.

2.3. Aqueous solubility determinations

The aqueous solubility of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues were determined whereby excess amounts of these solutes were equilibrated at 32 °C in phosphate buffer (pH, 7.4). After 24 h, the samples were filtered (PTFE filter media with polypropylene housing, 0.45 μm pore size, Whatman Inc., Haverhill, MA) and assayed by HPLC.

2.4. Melting point determination

The melting points of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues were determined by differential scanning calorimetry (DSC) using a Shimadzu DSC-50 instrument (Shimadzu). The heating rate was set at 10 °C/min. All tracings were repeated four times.

2.5. *N*-Octanol/water (K_{oct}) partition coefficient determinations

Equal volumes of *n*-octanol and phosphate buffer (pH, 7.4) were saturated for a period of 24 h. Solutions of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues (30 μg/ml) were prepared in the pre-saturated *n*-octanol phase, where after 5 ml of these solutions were transferred to test tubes containing 5 ml pre-saturated buffer. The tubes were stoppered and agitated for 1 h, followed by centrifugation. The *n*-octanol and buffer phases were separated and diluted 100 times with methanol and HPLC mobile phase respectively, prior to being assayed by HPLC. Partition coefficients were calculated as the ratio of drug concentration in the *n*-octanol phase to that in the buffer phase.

2.6. Skin preparation

The skin used in the transdermal permeation studies was obtained from the abdomen of female patients who underwent cosmetic surgery. The full-thickness skin was frozen at −20 °C within 24 h after removal. Prior to preparation, the skin was thawed to room temperature, where after the excess fat was carefully removed. The epidermal layers were separated by immersing the skin in water at 60 °C for 1 min. The epidermal tissue was gently peeled from the remaining tissue with forceps, floated on filter paper in distilled water and left to dry. The prepared samples were kept frozen at −20 °C until used. The epidermal tissue was thawed prior to experimental use and was carefully inspected for any defects.

2.7. Skin permeation

Vertical Franz diffusion cells with 2.3 ml receptor compartments and 1.075 cm^2 diffusion areas were

used during the permeation studies. The epidermal skin layer was mounted carefully on the lower half of the Franz cell with the stratum corneum (SC) facing upwards. The upper and lower parts of the Franz cell were fastened together by means of a clamp, with the SC acting as a seal between the donor and receptor compartments. The receptor compartments were filled with isotonic phosphate buffer (pH, 7.4). Special care was taken that there were no air bubbles between the buffer and the SC in the receptor compartment. The prepared Franz cells, containing the buffer, were equilibrated for 1 h in a water bath at 37 °C, prior to the addition of the saturated solutions to the donor compartments. Only the receptor compartment was in contact with the water at 37 °C and each Franz cell was equipped with a stirring magnet. After an hour, 700 μl of freshly prepared saturated solution of the studied compound was added to each donor compartment, which was immediately covered with Parafilm®, to avoid the evaporation of any of the constituents. Six replicates were conducted.

2.8. Preparation of donor solutions

Donor solutions of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues were prepared by equilibrating excess amounts of each with phosphate buffer (pH, 7.4) in stoppered vials. These solutions were stirred in a water bath at 37 °C over a period of 24 h in order for solvent saturation to occur. After 24 h, the samples were filtered through preconditioned filters (PTFE filter media, 0.45 μm). The initial portion of the filtrate was discarded to avoid any adsorption of the compounds on the film or filtering apparatus. At predetermined intervals (2, 4, 6, 8, 10, 12 and 24 h), the entire receptor volumes were withdrawn and replaced with 37 °C fresh buffer solution in order to maintain sink conditions. The withdrawn samples were assayed directly by HPLC to determine the concentrations of drugs that had permeated through the SC. The permeation data were plotted as the cumulative amount of drug penetrated through the skin as a function of time.

3. Results

N-Methyl carbamazepine presented with a melting point of 143 °C, an R_f value of 0.42 (ethyl acetate–petroleum ether, 7:3) and a yield of 64%. ^{1}H NMR ($CDCl_3$) δ, 2.7 (s, 3H, CH_3), 4.3 (s, 1H, NH), 6.9 (s, 2H, H-10, H11), 7.2–7.6 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$) δ, 27.1 (CH_3), 127.5 (CH), 129.1 (CH), 129.2 (CH), 129.5 (CH), 130.5 (CH), 135.3 (C), 140.1 (C), 156.9 (CO); ν_{max} (cm^{-1}): 1600, 1680, 3440; MS EI$^+$ *m*/*z* 250.1 (M^+, 22%), 193.1 (97%), 119.0 (17%), 107.1 (21%), 69.0 (62%).

N-Ethyl carbamazepine presented with a melting point of 115 °C, an R_f value of 0.51 (ethyl acetate–petroleum ether, 7:3) and a yield of 10%. ^{1}H NMR ($CDCl_3$) δ, 1.1 (t, 3H, CH_3), 3.7 (q, 2H, CH_2), 4.9 (s,1H, NH), 6.7 (s,2H, H-10, H-11), 6.9–7.3 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$) δ, 15.2 (CH_3), 35.3 (CH_2), 127.5 (CH), 129.2 (CH), 129.3 (CH), 129.6 (CH), 130.5 (CH), 135.3 (C), 140.3 (C), 156.2 (CO); ν_{max} (cm^{-1}): 1600, 1680, 3440; MS EI$^+$ *m*/*z* 264.0 (M^+, 22%), 193.0 (97%), 165.0 (16%), 69 (14%).

N-(2-Hydroxyethyl) carbamazepine presented with a melting point of 137 °C, an R_f value of 0.40 (ethyl acetate–petroleum ether, 6:4) and a yield of 74%. ^{1}H NMR ($CDCl_3$) δ, 3.6 (t, 2H, CH_2), 3.9 (t, 2H, CH_2), 6.7 (s, 2H, H-10, H-11), 6.9–7.1 (m, 8H, Ar); ^{13}C NMR ($CDCl_3$) δ, 52.7 (CH_2), 58.5 (CH_2), 127.6 (CH), 129.2 (CH), 129.3 (CH), 129.6 (CH), 130.5 (CH), 135.3 (C), 140.3 (C), 148.5 (CO); MS EI$^+$ *m*/*z* 280.0 (M^+, 32%), 193 (97%), 109 (45%), 105 (34%), 147 (24%).

The NMR, IR and MS results above indicated that *N*-methyl (2), *N*-ethyl (3) and *N*-hydroxyethyl carbamazepine (4) were synthesised successfully.

The melting points, aqueous solubilities (μg/ml) and octanol/water partition coefficients (K_{oct}) of carbamazepine and its analogues are presented in Table 1. The steady state flux values (J), permeability coefficients (k_p), lag times (TL) and diffusion coefficients (D) of carbamazepine and its analogues are presented in Table 2. The steady state flux was calculated from the slope of the linear portion of the cumulative transdermal concentration versus time plot. The lag time (τ was calculated by the extrapolation of the linear portion of the curve to its intersection with the X-axis and D estimated using a diffusional path length (l) of 10 μm and the equation $D = l^2/6\tau$.

For all four compounds, steady state was reached within 1 h of the application of the saturated drug solutions. The transdermal permeation profiles of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues over a 24 h period are presented in Fig. 2.

Table 1
Selected physicochemical properties ($N = 3$, S.D.) of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues together with predicted log *K* using ACD software (Toronto, Canada)

Compound	Melting point (°C)	32 °C Aqueous solubility (pH 7.4) (μg/ml)	Log K_{oct}	Log *K* (ACD)
Carbamazepine	189 ± 0.71	440.6 ± 20.6	2.7 ± 0.3	2.67
N-methyl carbamazepine	143 ± 1.41	489.5 ± 16.7	3.5 ± 0.3	3.47
N-ethyl carbamazepine	115 ± 0.35	454.2 ± 12.5	4.0 ± 0.6	4.00
N-(2-hydroxyethyl) carbamazepine	137 ± 0.64	781.0 ± 17.3	2.8 ± 0.8	2.84

Table 2
Permeation parameters (±S.D.) of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues

Compound	J(μg/cm^2/h)	T_L (h)	k_p (cm/h)	D (cm^2/h)
Carbamazepine	3.29 ± 0.64	0.43 ± 0.68	0.0075	3.9×10^{-7}
N-methyl carbamazepine	12.68 ± 1.30	0.67 ± 0.50	0.0259	2.5×10^{-7}
N-ethyl carbamazepine	8.40 ± 0.70	0.74 ± 0.44	0.0185	2.2×10^{-7}
N-(2-hydroxyethyl) carbamazepine	13.05 ± 1.60	0.20 ± 0.21	0.0167	8.3×10^{-7}

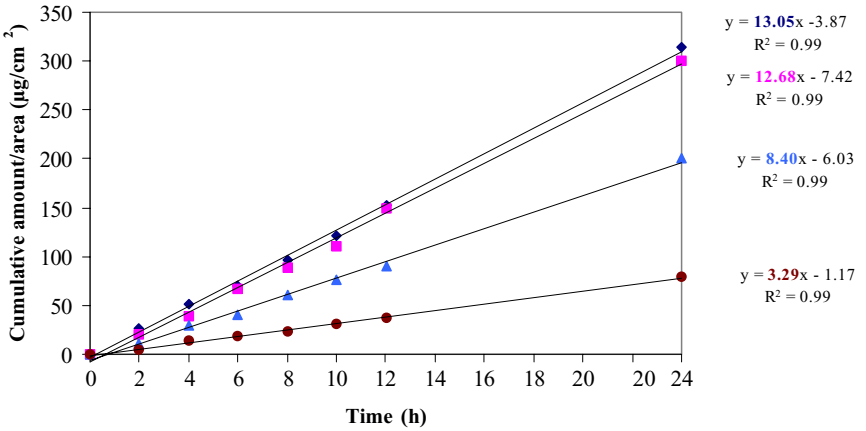

Fig. 2. Permeation profiles of carbamazepine and its *N*-alkyl and *N*-hydroxyalkyl analogues from saturated solutions. (●) carbamazepine; (■) *N*-methyl carbamazepine; (▲) *N*-ethyl carbamazepine; (◆) *N*-(2-hydroxyethyl) carbamazepine ($N = 6$).

4. Discussion

4.1. Structures of carbamazepine and its N-alkyl and N-hydroxyalkyl analogues

Carbamazepine is a derivative of iminostilbene with a carbamyl group at the five position. The iminostilbene group is symmetrical and as such provides one set of signals. In the ^{1}H NMR spectrum of carbamazepine, the multiplet at δ, 7.20–7.50 integrates for eight protons, representing the protons situated on C-1; C-2; C-3; C-4; C-6; C-7; C-8 and C-9 of the aromatic rings. The singlet at δ, 6.92 integrates for two protons and represents the protons situated on C-10 and C-11 of the iminostilbene group. The two amide protons resonate as a broad singlet at ca. δ, 5.13. In the ^{13}C NMR of carbamazepine, the signal at δ, 157.38 is attributed to the carbonyl carbon atom (C-12) and the signals at δ, 140.18 and δ, 135.02 represent the four quaternary carbons atoms, C-4a and C-5a; and C-9a and C-11a, respectively. The signals at δ, 129.49, δ, 129.33, δ, 128.74 and δ,

127.59 represent the tertiary carbons in the aromatic rings.

The ^{1}H and ^{13}C NMR spectra of *N*-methyl carbamazepine are identical to those of carbamazepine, except for the singlet at δ, 2.68 integrating for three hydrogen atoms (CH_3) in the ^{1}H NMR spectrum and the signal at δ, 27.10 in the ^{13}C NMR spectrum. The mass spectrum shows the molecular ion at *m*/*z* 250.

The ^{1}H and ^{13}C NMR spectra of *N*-ethyl carbamazepine are identical to those of carbamazepine, except for the triplet integrating for three hydrogen atoms at δ, 1.10 (CH_3) and the quartet integrating for two hydrogen atoms at δ, 3.70 (CH_2) in the ^{1}H NMR spectrum and corresponding signals at δ, 15.20 (CH_3) and δ, 35.30 (CH_2) in the ^{13}C NMR spectrum. The mass spectrum confirms the molecular ion at *m*/*z* 264.

The ^{1}H and ^{13}C NMR spectra of *N*-ethyl carbamazepine are identical to those of carbamazepine, except for the triplet signals integrating for two hydrogen atoms each at δ, 3.59 (CH_2) and δ, 3.92 (CH_2) in the ^{1}H NMR spectrum and corresponding signals at δ, 52.70 (CH_2) and δ, 58.50 (CH_2) in the ^{13}C NMR spectrum. The hydroxy group resonates as a broad singlet at ca. δ, 2.50 in the ^{1}H NMR spectrum. The mass spectrum confirms the molecular ion at *m*/*z* 280.

4.2. Physicochemical properties

The major physicochemical determinants in transdermal delivery are the partition characteristics and the solubility properties. Compounds which are either insoluble in water or have a very low lipid solubility are expected to diffuse across the stratum corneum at a very limited rate (Parikh et al., 1984; Naik et al., 2000). Carbamazepine has a $\log K_{oct}$ value of 2.7, which is close to the optimum value for transdermal permeation of 2.5 (Hadgraft and Wolff, 1993). As can be seen in Table 1, the *N*-alkyl and *N*-hydroxyalkyl analogues have $\log K_{oct}$ higher than that of carbamazepine. This is as expected from predicted values, these are shown in Fig. 1 for comparison and the correlation between the two is extremely good.

The aqueous solubility of carbamazepine was enhanced (11%) by its *N*-methylation. The increased aqueous solubility of *N*-methyl carbamazepine may be attributed to a lower melting point and thus a lowering of crystallinity. A reduction in the crystal lattice energy will result in a lower melting point, often resulting in increased aqueous solubility (Amidon, 1981). An increase in alkyl chain length from methyl to ethyl resulted in a further decrease in melting point and a lower aqueous solubility. This could be attributed to an increase in lipophilicity due to the addition of the ethyl substituent. The addition of the hydroxyalkyl functional group resulted in a decreased melting point and a noticeable increase in the aqueous solubility (almost double that of carbamazepine), which may be anticipated from the addition of the hydrophilic –OH fragment.

The *N*-alkylation and *N*-hydroxyalkylation of the carboxamide group in the carbamazepine molecule resulted in melting points at least 40 °C lower than that of carbamazepine. *N*-Ethyl carbamazepine presented with a melting point of 115 °C, which is 74 °C lower than that of carbamazepine. The lower melting points of the *N*-alkyl and *N*-hydroxyalkyl analogues of carbamazepine may be attributed to decreased crystallinity in comparison to carbamazepine.

Table 2 also shows the lag times for permeation. As in all in vitro skin permeation studies there will be considerable error associated with these and it is not possible to make definitive statements about their relative values. The lag times are comparatively short and correspond to a diffusion coefficient of the order of 4×10^{-7} cm^2/h (assuming a stratum corneum thickness of 10 μm). These are not unreasonable values in this type of study.

4.3. Transdermal permeation

The transdermal fluxes presented in Table 2 indicate an increase in flux of all three the analogues in comparison to that of carbamazepine itself. *N*-(2-Hydroxyethyl) carbamazepine presented with the greatest transdermal flux, being almost four times greater than that of carbamazepine. *N*-Methyl carbamazepine also had a greater transdermal permeability than that of carbamazepine, but it was slightly lower than that of *N*-(2-hydroxyethyl) carbamazepine. The greater flux values of *N*-methyl- and *N*-(2-hydroxyethyl) carbamazepine may be attributed to their decreased crystallinity and increased aqueous solubilities. *N*-Ethyl carbamazepine presented with a greater flux than that of carbamazepine, but somewhat lower than those of the *N*-methyl- and *N*-(2-hydroxyethyl) analogues.

The following rank and order of transdermal penetration may be established for the compounds studied here: *N*-(2-hydroxyethyl) carbamazepine > *N*-methyl carbamazepine > *N*-ethyl carbamazepine > carbamazepine. The analogue that presented with the highest transdermal flux indicated the highest aqueous solubility together with a favourable $\log K_{oct}$ value. This correlates well with previous studies, which indicated that the methyl analogue of nicotinate had the highest flux, smallest $\log K_{oct}$ and highest aqueous solubility (Le and Lippold, 1995).

The results from the research presented here correspond well with the theory reported by Sloan (Sloan, 1989) and accepted by other authors (Guy and Hadgraft, 1992) that in a homologous series of compounds with increasing lipophilicity, the highest flux through the skin is achieved by the derivative which shows the greatest aqueous solubility.

5. Conclusion

Since the stratum corneum is a lipophilic barrier, drug lipophilicity is regarded as being one of the primary factors influencing transdermal permeation. The greater the lipophilicity of the drug, the greater the partitioning and solubility thereof in the SC. However, the lipid bilayer structure of the intercellular lipids means that the permeant will also experience polar hydrophilic domains during its diffusion across the SC. It is of paramount importance that a drug intended for transdermal application should present with both hydrophilic and lipophilic properties. Ideally there should be a balanced solubility profile in both lipids and water. This work has shown that *N*-methyl-, *N*-ethyl- and *N*-(2-hydroxyethyl) carbamazepine permeate the skin to a greater extent than carbamazepine. The aqueous solubilities of *N*-methyl- and *N*-(2-hydroxyethyl) carbamazepine are significantly greater than those of carbamazepine. The aqueous solubility of *N*-ethyl carbamazepine was only slightly greater than that of carbamazepine. The relationship between the transdermal fluxes and aqueous solubility clearly demonstrates that the hydrophilicity of a compound intended for transdermal permeation also plays an important role in rate of transdermal permeation.

It may be concluded that not only do lipophilicity and crystallinity play important roles in transdermal permeability, but other factors, such as aqueous solubility should also be considered during the selection of drugs as suitable transdermal candidates.

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