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International Journal of Pharmaceutics 155 (1997) 241–250

international journal of pharmaceutics

Transdermal and dermal enhancing activity of pyrrolidinones in hairless mouse skin

Donald A. Godwin [a,*], Bozena B. Michniak [b], Mark R. Player [c], J Walter Sowell Sr. [b]

[a] *Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of New Mexico, Albuquerque, NM 87131, USA*
[b] *Department of Basic Pharmaceutical Sciences, College of Pharmacy, University of South Carolina, Columbia, SC 29208, USA*
[c] *Section on Biomedical Chemistry, Laboratory of Medicinal Chemistry, National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, Bethesda, MD 20892, USA*

Received 14 February 1997; received in revised form 27 May 1997; accepted 28 May 1997

Abstract

The transdermal penetration-enhancing abilities of 16 pyrrolidinones were tested against the model drug hydrocortisone using a hairless mouse skin model in vitro. Skins were pretreated for 1 h with the enhancer in propylene glycol before application of the drug also in propylene glycol. Enhancement ratios (ER) were calculated for permeability coefficient (P), 24-h receptor concentration (Q_{24}), and skin content of drug (SC) and compared to control values (no enhancer present). *N*-Dodecyl-2-pyrrolidinone and 2-pyrrolidinone-1-acetic acid dodecyl ester were found to produce the greatest enhancement for all the parameters calculated with ER for Q_{24} of 23.11 and 11.68, respectively. These same enhancers also produced high ERs for P with 42.95 and 41.07, respectively. These values exceed Azone's enhancement ratios for the same parameters and hence these enhancers are candidates for further development as penetration enhancers. © 1997 Elsevier Science B.V.

Keywords: Transdermal drug delivery; Pyrrolidinones; Hairless mouse; Percutaneous penetration; Hydrocortisone; Skin retention

1. Introduction

Over the past decade a number of advances in transdermal drug delivery have been made which make it possible for a larger number of drugs to be added to the list of therapeutic agents which can be delivered through the skin. Much of the recent success in this field can be attributed to the increase in knowledge of the structure and function of the stratum corneum. The combination of the intercellular lipids along with the highly keratinized intracellular environment make the stratum corneum a very effective barrier to drug

* Corresponding author. Tel.: +1 505 2722939; fax: +1 505 2726749; e-mail: dgodwin@unm.edu.

PII S0378-5173(97)00163-4

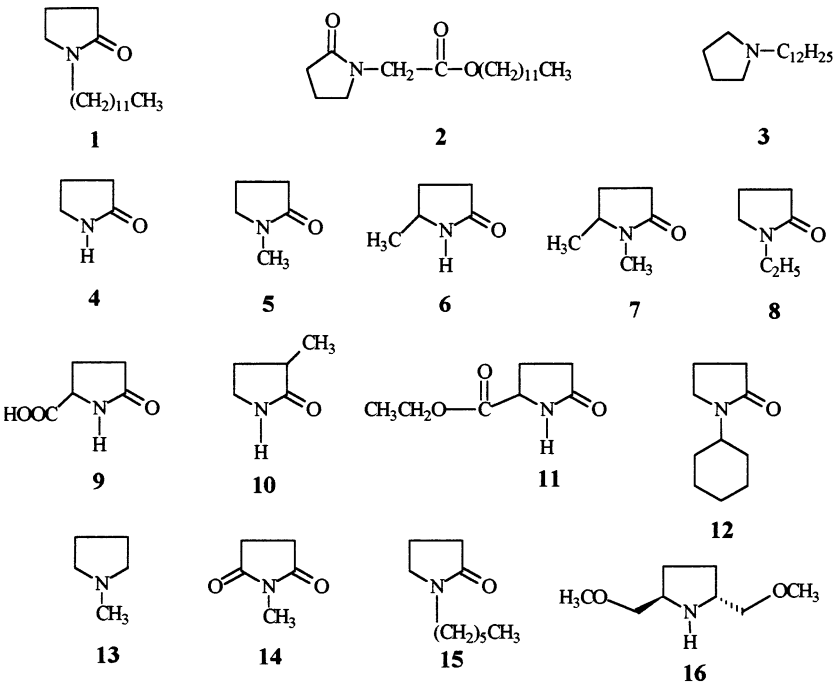

Fig. 1. Structures of pyrrolidinone enhancers tested: (**1**) *N*-dodecyl-2-pyrrolidinone; (**2**) 2-pyrrolidinone-1-acetic acid dodecyl ester; (**3**) *N*-dodecyl-pyrrolidine; (**4**) 2-pyrrolidinone; (**5**) 1-methyl-2-pyrrolidinone; (**6**) 5-methyl-2-pyrrolidinone; (**7**) 1,5-dimethyl-2-pyrrolidinone; (**8**) 1-ethyl-2-pyrrolidinone; (**9**) 2-pyrrolidinone-5-carboxylic acid; (**10**) (±)-3-methyl-2-pyrrolidinone; (**11**) ethyl (*R*)-(−)-2-pyrrolidinone-5-carboxylate; (**12**) 1-cyclohexyl-2-pyrrolidinone; (**13**) 1-methylpyrrolidine; (**14**) 1-methylsuccinimide; (**15**) 1-hexyl-2-pyrrolidinone; (**16**) (*R*,*R*)-(−)-2,5-bis(methoxymethyl)pyrrolidinone.

penetration. In order to overcome this barrier, transdermal penetration enhancers are used to *reversibly* diminish the barrier function of this layer of skin (Smith and Maibach, 1995). Pyrrolidinones (Fig. 1) have recently become of interest to the pharmaceutical industry as penetration enhancers. 2-Pyrrolidinone and *N*-methyl-2-pyrrolidinone are versatile solvents which are widely established in the petrochemical industry. In addition, another pyrrolidinone derivative, 2-pyrrolidinone-5-carboxylic acid, is a component of the natural moisturizing factors in the skin (Smith and Maibach, 1995). The development and characterization of various pyrrolidinone derivatives is reported by Sasaki et al. (1995).

The goal of this work is to examine the penetration-enhancing abilities of a wide range of pyrrolidinone compounds, including those with differing chain lengths and functional groups using an in vitro hairless mouse skin model. In order to achieve this goal hydrocortisone is selected as the model drug based on its molecular weight, moderate polarity, relevance to transdermal delivery, and its reported use in the literature (Wahlberg and Swanbeck, 1973; Feldman and Maibach, 1974; Michniak et al., 1994b, 1995b).

2. Materials and methods

All chemicals were purchased from Sigma Chemical Co. in the highest available purity. Baxter Diagnostics, Inc. (McGraw Park, IL, USA) supplied reagent grade solvents, except for methanol and acetonitrile which were HPLC grade. All enhancer compounds or other chemicals for the synthesis of novel enhancers were purchased from Aldrich Chemical Co. (Milwaukee, WS, USA) in the highest available purity. Elemental analyses were conducted by Atlantic

Microlabs (Atlanta, GA, USA) and were within $\pm 0.4\%$ of theoretical for all compounds. The syntheses for enhancers **1**, **2**, **3**, and **15** have been reported previously (Player, 1995).

2.1. In vitro permeability studies

Male hairless mice strain SKH1 (hr/hr), 8 weeks old, were obtained from Charles Rivers Laboratories, Inc. (Wilmington, MA, USA). Animals were sacrificed by CO_2 asphyxiation and full-thickness abdominal and dorsal skin was excised. Any extraneous subcutaneous fat was removed from the dorsal surface. The skins were stored at -80°C (Revco Scientific, Asheville, NC, USA) until utilized. Skins were then slowly thawed, cut into small pieces and mounted on modified Franz diffusion cells.

Each receptor cell (donor surface area, 3.14 cm^2; volume, 12 ml) contained isotonic phosphate buffer solution (pH 7.2), 0.1% v/v, 36% aqueous formaldehyde as a preservative (Sloan et al., 1991), and 0.5% w/v polyoxyethylene 20 cetyl ether as a solubilizer (Chien, 1982). The receptors were maintained at 37 ± 0.5°C through the use of a circulating water bath. The receptors were continuously stirred at 600 rpm using magnetic stirring bars. Skins were allowed to hydrate for 1 h prior to experimentation.

Control experiments consisted of no pretreatment of the skin with enhancer solution, while propylene glycol (PG) control consisted of pretreating the skin with 8 μl of PG. All enhancers were tested at 0.4 M in propylene glycol. Following hydration each skin was covered with 8 μl of enhancer solution. The enhancer solution was left on the skin for 1 h prior to drug application and was not washed off at the end of this period.

At this time 80 μl of saturated suspension of hydrocortisone in propylene glycol was placed on each skin (Michniak et al., 1993). The saturation solubility of hydrocortisone in propylene glycol at 32 ± 0.5°C was 0.03 M. The donor compartment was then occluded with Parafilm®. Samples (300 μl) were withdrawn at specified time points over 24 h, with the withdrawn volume being immediately replaced with fresh buffer. Analysis of samples was corrected for all previous samples removed.

2.2. Skin homogenization

At 24 h, the skins were removed from the receptor cells and washed three times in 100 ml of methanol for a total of 15 s. Following room temperature drying, each skin was weighed, cut up, placed in 4 ml of methanol, and homogenized using a tissue homogenizer (Kinematica GmbH, Switzerland). The homogenate was then gravity filtered, passed through a Sep-pak C_{18} cartridge (Waters, Milford, MA, USA), and all samples were stored at -80°C until analysis (Michniak et al., 1993).

2.3. Sample analysis

Analysis of samples for drug content was performed using high-performance liquid chromatography. All solvents were HPLC grade. HPLC analysis were performed using a Perkin-Elmer system which consisted of an ISS 100 Automatic Sampling System, an SEC-4 Solvent Environment Control, a Series 410 LC pump, and an LC-235 diode array detector. The HPLC was controlled by an Epson III+ computer with Omega peak integration software (Perkin-Elmer, CT, USA).

All drug samples were analyzed using a reversed-phase C18 column (Rainin Microsorb MV, 4.6 mm I.D. $\times$ 25 cm, 5 μm) kept at room temperature. Hydrocortisone was detected at 242 nm with a retention time of approximately 4.5 min using a mobile phase of 40:60 acetonitrile:water at a flow rate of 1.0 ml min^{-1}. An external standard of hydrocortisone (5 mg/100 ml) was used. Testing the linearity of the validation plot from 1.0 to 100 μg ml^{-1} revealed a correlation coefficient of 0.9960. Intraday and interday variabilities were determined to be 10.1 and 14.0%, respectively.

2.4. Data analysis

Cumulative amounts of drug (μM) corrected for sample removal were plotted against time (h). Permeation profiles yielded the following: permeability coefficients (cm h^{-1}), calculated by taking the volume of the receptor in cm^3 multiplied by the slope of the linear portion of the graph (μm/h) divided by the area of the donor in cm^2 multi-

plied by the donor concentration in μM, and receptor concentration at 24 h (Q_{24}, μM). Skin content of drugs was expressed as μg of drug per g of hydrated full-thickness skin. Enhancement ratios (ER) were calculated as permeation parameters (permeability coefficients, Q_{24}, skin content) from enhancer-treated skin divided by the same parameter from control (no enhancer treatment):

$$\text{ER} = \frac{\text{permeation parameter after enhancer treatment}}{\text{permeation parameter from control}}$$

Statistical treatment of the data involved the use of analysis of variance (ANOVA) and two-tailed Student's t-test. The α value was set at 0.05 and the null hypothesis assumed the variances between enhancer and control to be equal. Therefore if $p < 0.05$, there is a significant difference between the enhancer and control.

3. Results and discussion

All results are expressed as mean $\pm$ standard deviation. Control experiments are run with only propylene glycol and hydrocortisone present with no enhancer. Control values for permeability coefficients are $0.72 \times 10^{-4} \pm 0.27 \times 10^{-4}$ cm h^{-1}; Q_{24}, 11.86 ± 3.36 μM; and skin content of drug 44.6 ± 18.54 μg g^{-1}.

Compound **1** generated the highest enhancement ratios of the pyrrolidinone enhancers tested for all parameters. Compound **1** has a permeability coefficient of $30.63 \times 10^{-4} \pm 6.16 \times 10^{-4}$ cm h^{-1} (ER 42.0), a Q_{24} of 274.44 ± 50.90 μM (ER 23.0), and a skin content of 226.4 ± 51.8 μg g^{-1} (ER 5.1) (Table 1, Fig. 2). The compound with the next highest enhancement ratios is compound **2**, the acetate analog of compound **1**, with a permeability coefficient of $29.28 \times 10^{-4} \pm 3.88 \times 10^{-4}$ cm h^{-1} (ER 41.0), a Q_{24} of 138.62 ± 8.67 μM (ER 11.9), and a skin content of 124.7 ± 30.1 μg g^{-1} (ER 2.8) (Table 1, Fig. 2). These compounds are the most effective in increasing both transdermal and dermal delivery (skin retention) of hydrocortisone. All parameters associated with these enhancers are significantly higher ($p < 0.05$) than control. A structure–activity relationship between ring size and enhancer ability has been previously reported (Fuhrman, 1995). There exists an inverse relationship between ring size and enhancement capabilities for cyclic enhancers containing a dodecyl side chain. One of the most well-known enhancers is Azone® which consists of a 7-membered lactam ring and a dodecyl chain. Using hydrocortisone and hairless mouse skin Azone® gives a permeability coefficient of 12.9×10^{-4} cm h^{-1} and a 24-h receptor concentration of 91.61 μM. Of the three cyclic enhancers tested Azone (7-membered ring) has the lowest enhancement ratios for permeability coefficients

Table 1
Percutaneous absorption parameters for hydrocortisone with pyrrolidinone enhancers

Enhancer in PG	$P \times 10^{-4}$ (cm h^{-1})	Q_{24} (μM)	SC (μg g^{-1})
Control ($n = 9$)	0.71 ± 0.27	11.86 ± 3.36	44.6 ± 18.4
PG control ($n = 14$)	0.79 ± 0.22	11.74 ± 3.86	32.8 ± 20.2
1 ($n = 5$)	30.63 ± 6.16*	274.44 ± 50.90*	226.4 ± 51.8*
2 ($n = 4$)	29.28 ± 3.88*	138.62 ± 8.67*	124.7 ± 30.1*
3 ($n = 5$)	3.90 ± 1.40*	61.16 ± 21.55*	50.1 ± 6.5
4 ($n = 5$)	0.41 ± 0.11	13.74 ± 5.70	67.1 ± 13.0
5 ($n = 5$)	0.63 ± 0.16	11.64 ± 2.10	85.2 ± 13.1*
6 ($n = 5$)	0.55 ± 0.14	15.92 ± 0.009	133.0 ± 37.6*
7 ($n = 4$)	0.99 ± 0.60	15.42 ± 3.63	100.4 ± 17.8*
8 ($n = 5$)	0.86 ± 0.42	12.77 ± 5.13	57.7 ± 9.0
9 ($n = 5$)	0.48 ± 0.32	13.38 ± 4.60	135.6 ± 65.9*
10 ($n = 5$)	0.31 ± 0.11	21.82 ± 5.86*	62.1 ± 11.2
11 ($n = 5$)	0.64 ± 0.16	12.66 ± 1.89	118.7 ± 27.3*
12 ($n = 5$)	0.73 ± 0.45	13.75 ± 3.20	53.5 ± 11.0
13 ($n = 6$)	0.99 ± 0.34	16.08 ± 5.53	33.5 ± 11.6
14 ($n = 5$)	2.77 ± 0.69*	16.59 ± 5.53	131.9 ± 92.8*
15 ($n = 5$)	0.60 ± 0.13	14.51 ± 5.31	29.1 ± 5.2
16 ($n = 5$)	1.34 ± 0.55*	23.25 ± 4.57*	33.2 ± 15.6

PG, propylene glycol; P, permeability coefficient; Q_{24}, receptor concentration after 24 h; SC, skin content of hydrocortisone.
* Significant difference from control ($p < 0.05$).

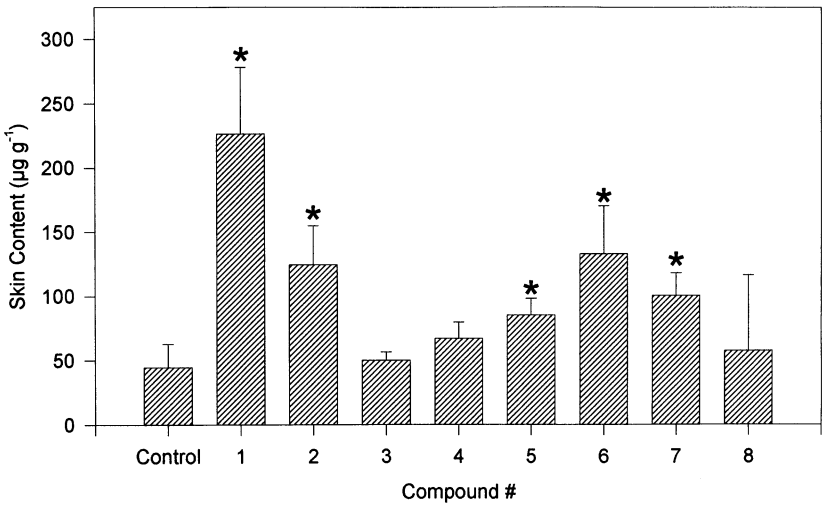

Fig. 2. Effect of pyrrolidinone enhancers on diffusion of hydrocortisone through hairless mouse skin.

(13.1) and receptor concentrations (12.8) with *N*-dodecyl-2-piperidinone (6-membered ring) having higher enhancement ratios (18.1 and 15.8, respectively), and compound **1** (*N*-dodecyl-2-pyrrolidinone) (5-membered ring) having the highest penetration enhancement ratios (20.7 and 18.5, respectively).

Previous studies have demonstrated that cyclic and acyclic amides are more effective in enhancing transdermal drug delivery than their reduced amine analog compounds (Michniak et al., 1995a). Compound **3** is the amine analog of compound **1**. This compound is not as effective of an enhancer as compound **1**. Although compound **1**'s permeability coefficient of $3.87 \times 10^{-4} \pm 1.40 \times 10^{-4}$ cm h^{-1} and its Q_{24} of 61.16 ± 21.55 μM (Table 1) are statistically higher ($p < 0.05$) than control, they are much lower than the other pyrrolidinone enhancers previously reported. Compound **3** skin content of 50.1 ± 6.5 μg g^{-1} is not significantly different from control.

Only two other pyrrolidinone enhancers tested out of this series of compounds showed significant activity as transdermal enhancers. Compound **14** has a significantly ($p < 0.05$) higher permeability coefficient of $2.77 \times 10^{-4} \pm 0.69 \times 10^{-4}$ cm h^{-1} (Table 2). Compound **16** has a significantly ($p < 0.05$) higher permeability coefficient and Q_{24} with $1.34 \times 10^{-4} \pm 0.54 \times 10^{-4}$ cm h^{-1} and 23.25 ± 4.57 μM, respectively (Table 2, Fig. 2). Compound **16** (Fig. 1) contains a methoxymethyl moiety within its structure. Michniak and coworkers reported that the methoxymethyl moiety

Table 2
Percutaneous absorption parameter enhancement ratios for hydrocortisone with pyrrolidinone enhancers

Enhancer in PG	ER_P	ER_{Q24}	ER_{SC}
Control ($n = 9$)	1.0	1.0	1.0
PG control ($n = 14$)	1.1	1.0	0.7
1 ($n = 5$)	42.0	23.0	5.1
2 ($n = 4$)	41.0	11.0	2.8
3 ($n = 5$)	5.4	5.2	1.1
4 ($n = 5$)	0.6	1.2	1.5
5 ($n = 5$)	0.9	1.0	1.9
6 ($n = 5$)	0.8	1.3	3.0
7 ($n = 4$)	1.4	1.3	2.3
8 ($n = 5$)	1.2	1.1	1.3
9 ($n = 5$)	0.7	1.1	3.0
10 ($n = 5$)	0.4	1.8	1.4
11 ($n = 5$)	0.9	1.1	2.7
12 ($n = 5$)	1.0	1.2	1.2
13 ($n = 6$)	1.4	1.4	0.8
14 ($n = 5$)	3.9	1.4	3.0
15 ($n = 5$)	0.8	1.2	0.7
16 ($n = 5$)	1.9	2.0	0.8

PG, propylene glycol; ER, enhancement ratio.

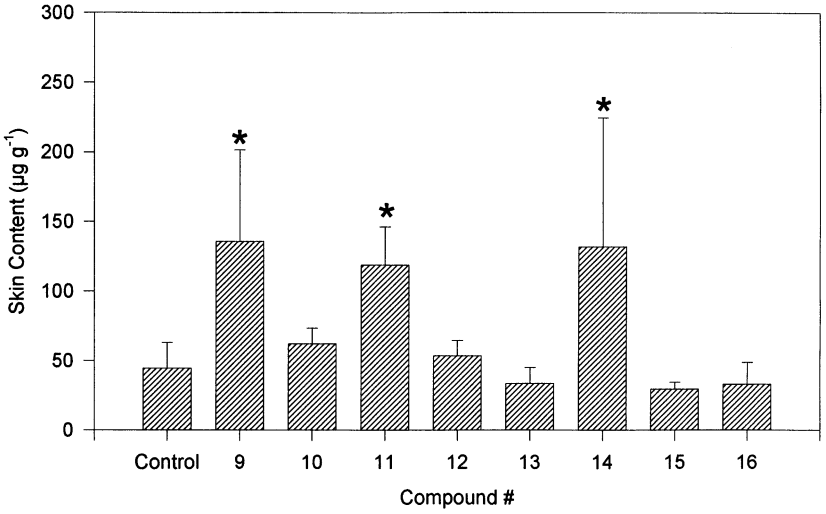

Fig. 3. Effect of pyrrolidinone enhancers on skin content of hydrocortisone in hairless mouse. *Denotes statistically significant difference from control ($p < 0.05$)

was important for both amine and amide penetration enhancers when examining structure–activity relationships (Michniak et al., 1995a, 1994a).

There was an interesting observation concerning pyrrolidinone structure and skin content of hydrocortisone. While only three enhancers produced significant increases in P or Q_{24}, eight compounds produced steroid skin contents which are significantly higher than control (Table 1; Figs. 3 and 4). Compound 1 displays the highest enhancement ratio for skin content in addition to P and Q_{24}. This compound is easily the most effective enhancer tested in this series for all parameters. However, the other compounds which had significant increases in skin content of drug had a different chemical structure. Compounds **5**, **6**, **7**, **9**, and **14** were all much less lipophilic than compound **1**. This hydrophilicity seems to contribute to the compound's ability to enhance the dermal delivery of hydrocortisone. Further study is needed to examine this relationship.

Pyrrolidinone derivatives have a wide range in their hydrophilic/lipophilic nature depending on their substituted functional groups. The lipophilicity of these enhancers affects both their behavior and localization within the stratum corneum. Sasaki and co-workers conducted a series of studies with full-thickness rat skin and various pyrrolidinone compounds. One study found that increasing the length of the alkyl chain from methyl to lauryl increased both the penetration and skin retention of the hydrophilic drug phenol red (Sasaki et al., 1988, 1990a). In another study Sasaki et al. (1991) found that the same increase in chain length increases the drug penetration of a number of both hydrophilic and lipophilic model drugs such as 5-fluorouracil, triamcinolone acetonide, and flurbiprofen. The enhancers tested include 1-methyl, 1-hexyl, and 1-lauryl-2-pyrrolidinone. It was shown that the pyrrolidinone derivatives enhance the penetration of all drugs tested. The penetration of triamcinolone acetonide and flurbiprofen are enhanced by pyrrolidinone derivatives although the increase is smaller than that for 5-fluorouracil. In addition, the lag time decreases with increasing chain length of the derivatives (Sasaki et al., 1991). Combining data from the study done by Sasaki et al. and data from the present project shows an interesting trend. Comparing $\log P$ values (5-FU $= -2.0$, hydrocortisone $= 1.5$, triamcinolone acetonide $=$ 2.4, and flurbiprofen $= 3.3$) of model drugs vs.

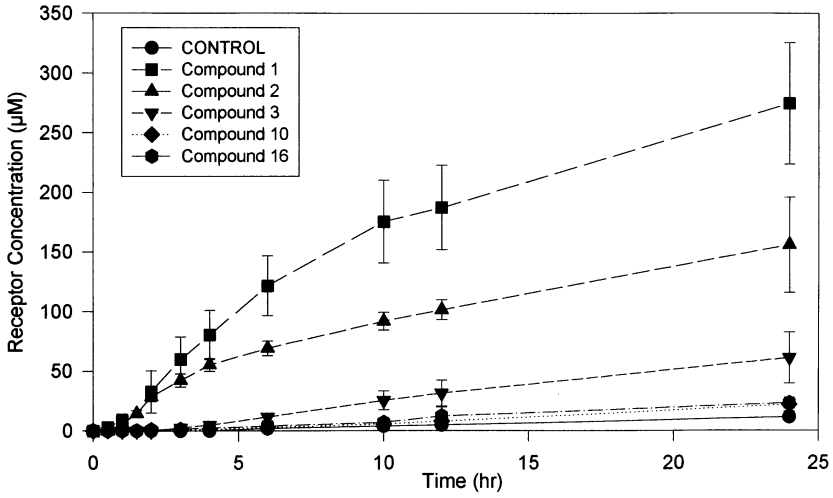

Fig. 4. Effect of pyrrolidinone enhancers on skin content of hydrocortisone in hairless mouse. *Denotes statistically significant difference from control ($p < 0.05$)

permeability coefficient enhancement ratios for the different chain lengths gives high regression coefficients (Fig. 5). 1-Methyl-2-pyrrolidinone produces r^2 of 0.75, while 1-hexyl-2-pyrrolidinone and 1-lauryl-2-pyrrolidinone produce r^2 values of 0.99 and 0.90, respectively. This suggests that pyrrolidinone compounds may have similar enhancing capabilities depending on the log *P* of the model drug. Each of the compounds exhibit higher enhancement ratios for hydrophilic than for lipophilic drugs. The lipophilic enhancers, 1-hexyl- and 1-lauryl-pyrrolidinone showed the greatest enhancing effect on the penetration of 5-fluorouracil and hydrocortisone. These enhancers also greatly increase the solubility of these drugs in the vehicle isopropyl myristate. These results suggest that enhancers may increase the flux of these model drugs by increasing their solubility within the stratum corneum (Sasaki et al., 1991).

A trend is also noticed when comparing carbon chain length to enhancement of both permeability coefficient and 24-h receptor drug concentration. Pyrrolidinone compounds with various carbon chains (0, 1, 2, 6, and 12 carbons) were examined for their enhancement of hydrocortisone penetration. Although compound **5** (methyl chain) does not show any enhancement ($ER_P < 1$) of penetration of hydrocortisone when compared to control, there is an increase in penetration enhancement with increasing chain length. Compound **5** (methyl chain), **15** (hexyl chain), **1** (lauryl chain) exhibit $ER_{Q_{24}}$ values of 1.0, 1.2 and 23.0, respectively. A regression analysis finds regression coefficients of 0.79 for *both* permeability coefficient and 24-h receptor concentration when relating these parameters to carbon chain length. The results of the present study are in agreement with the studies done by Sasaki and co-workers which show that longer (hexyl and lauryl) chain pyrrolidinone enhancers produce better enhancement than shorter chain (methyl) enhancer for a variety of penetrants including 5-FU, flurbiprofen, and the unabsorbable drug phenol red (Sasaki et al., 1988, 1990b). Additional evidence of dependence on chain length of enhancing ability is shown in a study by Aoyagi et al. (1991). In an in vivo study examining the effect of increasing alkyl chain length on a pyrrolidinone derivative containing a dodecyl chain at the 3-position and the short (methyl, ethyl, propyl, or butyl) variable length chain at the 1-position on transdermal penetration of indomethacin was investigated. It was found that propyl and butyl chains have an enhancing effect on penetration, while there was little or no effect with the shorter chains (Aoyagi et al.,

1991). Finally, in a study examining the effect of alkyl chain length on penetration enhancement, Yoneto et al. (1995) showed that, as alkyl chain length increases, there is a proportional increase in transport for β-estradiol, corticosterone, and hydrocortisone. A nearly semilogarithmic relationship was found between enhancement potency and the carbon number of the alkyl chain. There is an approximately 3.5-fold increase in the enhancement potency per 1-alkyl-2-pyrrolidone methylene group (Yoneto et al., 1995).

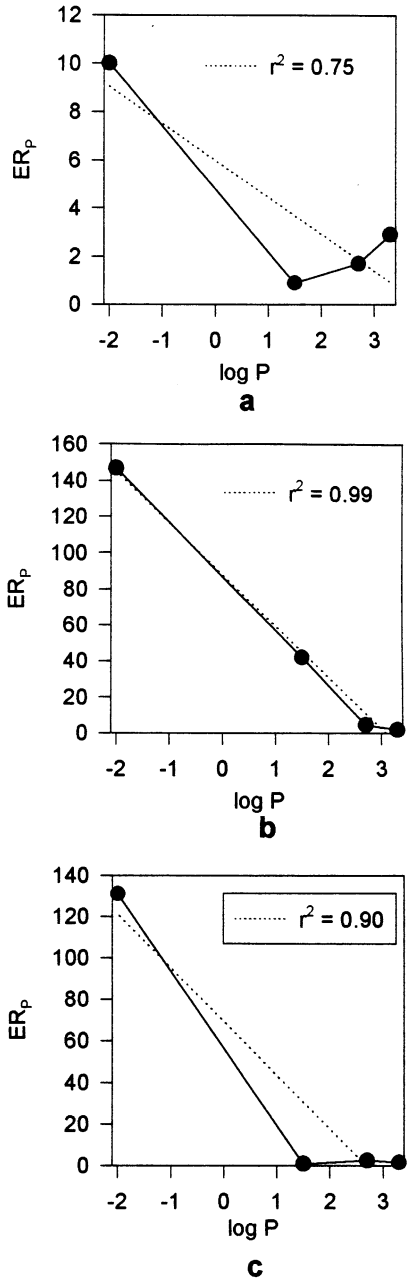

Fig. 5. Regression analysis of pyrrolidinone enhancers permeability coefficient enhancement ratio vs. log P of model drugs. (a) 1-Methyl-2-pyrrolidinone; (b) 1-hexyl-2-pyrrolidinone; (c) 1-lauryl-2-pyrrolidinone.

Due to the fact that one of the major obstacles to the use of penetration enhancers is their potential for localized toxicity, a study was done to find a 'soft' compound for use as an enhancer. A 'soft' compound is a compound which is active and then is metabolized to a non-toxic compound. This approach would be very useful with transdermal penetration enhancers. Enhancers exert their effect on the stratum corneum which is known to be a metabolically inactive tissue (Barry and Bennett, 1987). After lowering the barrier function of the stratum corneum, the enhancers would then be transformed to an inactive compound in the metabolically active epidermis. A study was performed using a pyrrolidinone derivative as a 'soft' enhancer and it was shown that *N*-(-2-hydroxyethyl)-2-pyrrolidinone is an effective compound for the enhancement of hydrocortisone penetration through hairless mouse skin. This compound increases the permeability coefficient of hydrocortisone by two orders of magnitude, while causing less irritation than traditional enhancers such as Azone (Lambert et al., 1993).

The mechanism of action of pyrrolidinone enhancers depends in part on the lipophilicity of the enhancer. Using differential scanning calorimetry, it has been suggested by Barry and Bennett (1987) that lipophilic pyrrolidinone enhancers exert their effects by entering the lipophilic domains of the stratum corneum and disrupting their structure, thereby increasing drug permeability. In another study, Southwell and Barry (1983) reports that the hydrophilic 2-pyrrolidinone enhances permeation through the polar route of the skin by increasing diffusivity. Thus it may follow that the longer carbon chain a pyrrolidinone enhancer possesses, the more transdermal penetration enhancement the compound is able to achieve. Results from

this study agree with this, as the more lipophilic enhancers (compounds **1**, **2**, **3**) have the highest degree of penetration enhancement. Finally, a study was conducted examining the mechanism of action of pyrrolidinones using both hairless mouse skin and stratum corneum lipid liposomes (SCLLs). A correlation is observed between enhancement effects induced by 1-alkyl-2-pyrrolidinones in the SCLL bilayer and those found in the lipophilic pathway in hairless mouse stratum corneum. In both systems it is found that the pyrrolidinone derivatives enhance the transport of percutaneous absorption mainly by fluidizing the lipids along the intercellular lipid domains in the stratum corneum (Yoneto et al., 1996).

In summary, the present study examines a series of pyrrolidinone penetration enhancers. *N*-Dodecyl-2-pyrrolidinone (**1**) produced the highest enhancement ratios for all parameters tested with permeability coefficient, 24-h receptor cell concentration, and skin content of $30.63 \times 10^{-4} \pm 6.16$ cm h^{-1} (ER 42.0), 274.44 ± 50.90 μM (ER 23.0), and 226.4 ± 51.7 μg g^{-1} (ER 5.1), respectively. Additionally, compound **2** (acetate analog of compound **1**) is also very active with a permeability coefficient of $29.28 \times 10^{-4} \pm 3.88 \times 10^{-4}$ cm h^{-1} (ER 41.0), a Q_{24} of 138.62 ± 8.67 μM (ER 12.0), and a skin content of 124.7 ± 30.1 μg g^{-1} (ER 2.8). These compounds which have demonstrated activity have the potential for further development as transdermal penetration enhancers.

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