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Branched-chain alkanols as skin permeation enhancers: quantitative structure-activity relationships

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One long-standing approach for improving transdermal drug delivery is using penetration enhancers which reversibly decrease the skin barrier resistance. Though the skin permeation enhancement effect of chemical penetration enhancers has been studied extensively, their quantitative structure-activity relationships have not been adequately investigated. In this paper, we established the correlation equations between enhancement potencies and the physico-chemical parameters relevant to lipophilicity and position of hydroxyl group for 16 alkanols using the stepwise multiple linear regression analysis. These equations reveal that the enhancement potencies of alkanols are excellently correlated with their lipophilicity and position of the hydroxyl group. The enhancement potency of an alkanol will increase when it has greater lipophilicity but will decrease as the hydroxyl group moves from the end of the alkyl chain towards the center.

1. Introduction

Transdermal drug delivery receives increasing attention as an attractive alternative to traditional drug delivery because it has the following advantages: (1) it avoids first-pass metabolism; (2) it reduces side effects due to reduction of the peaks in plasma levels; (3) it improves therapy due to maintenance of plasma levels; (4) it is easy to discontinue the administration; (5) it can be used for drugs with a short half-life; (6) it avoids side effects in the gastrointestinal tract, etc (Cho et al. 1998). However, only a limited number of drugs are able to reach the system due to the highly organized structure of the stratum corneum forms an effective barrier to the permeation of a diverse range of substances. Different methods have been implemented to overcome the barrier property of the stratum corneum (Sloan et al. 1984; Mezel 1985; Morimoto et al. 1992; Chang and Banga 1998). Chemical penetration enhancers which can reversibly decrease skin barrier resistance are widely used (Smith and Maibach 1995). The use of chemical penetration enhancers would significantly increase the number of candidates suitable for transdermal delivery. Alkanols, amides, surfactants, terpenes, organic acids, and sulfoxides may serve as penetration enhancers (Kim et al. 1999). Alkanols are commonly used in transdermal formulations and are often the solvent of choice for use in patches. They are also commonly employed as cosolvents with water for ensuring sink conditions during *in vitro* permeation experiments. The skin penetration enhancement effect of alkanols has been demonstrated in many *in vitro* studies (Aungst et al. 1986; Kanikkannan et al. 2000, 2002), but very few studies have been performed to analyze their quantitative structure-activity relationships. A series of alkanols are selected as model skin permeation enhancers to establish mathematical correlations between their skin permeation enhancement and their physico-chemical parameters including the octanol-PBS (pH 7.4 phosphate-buffered saline) partition coefficients (log K), the first-order valence connectivity index ($^1x^v$), and the relative position of the hydroxyl group in the alkanols (R_p, defined as the ratio of the hydroxyl group position in the enhancer alkyl chain to the carbon number of alkyl chain). The effort to obtain more information about the quantitative structure-activity relationships of permeation enhancers could bring more rational and convenient approaches designing potential enhancers for transdermal formulations.

2. Investigations, results and discussion

The alkanols analyzed are listed in the Table. $C_{E=10}$, which is defined as the aqueous solution concentration of an enhancer that could yield 10-fold permeant transport enhancement to the control (no enhancer present), is the measure of the enhancer potency. The $C_{E=10}$ values of these alkanols to enhance the permeability of corticosterone across hairless mouse skin in PBS and their octanol-PBS partition coefficients are taken from Chantasart et al. (2004).

The following correlation equation between $\log(C_{E=10})$ and log K is obtained from the stepwise regression analyses:

$$\log(C_{E=10}) = 3.5400(\pm 0.1664) - 1.0031(\pm 0.0582)\log K \quad (1)$$

$$n = 16 \qquad r = 0.9772 \qquad s = 0.1360 \qquad F = 296.6$$

Table: $C_{E=10}$ values of 16 alkanols and their physico-chemical parameters

Enhancers	log K	$^1x^v$	R_P	log ($C_{E=10}$)			
				Exp.[a]	Calc.[b]	Calc.[c]	Calc.[d]
1-Hexanol	2.08	3.023	1/6	1.342	1.454	1.222	1.370
2-Hexanol	1.83	2.951	2/6	1.681	1.704	1.585	1.633
3-Hexanol	1.81	2.989	3/6	1.756	1.724	1.724	1.783
1-Heptanol	2.54	3.523	1/7	0.845	0.992	0.757	0.832
2-Heptanol	2.43	3.451	2/7	1.114	1.102	0.967	1.068
3-Heptanol	2.42	3.489	3/7	1.230	1.112	1.079	1.191
4-Heptanol	2.32	3.489	4/7	1.255	1.213	1.279	1.353
1-Octanol	3.13	4.023	1/8	0.230	0.400	0.170	0.301
2-Octanol	3.03	3.951	2/8	0.544	0.501	0.357	0.516
3-Octanol	2.94	3.989	3/8	0.699	0.591	0.533	0.619
4-Octanol	2.88	3.989	4/8	0.724	0.651	0.682	0.761
1-Nonanol	3.52	4.523	1/9	−0.260	0.009	−0.220	−0.225
2-Nonanol	3.48	4.451	2/9	−0.100	0.049	−0.102	−0.026
3-Nonanol	3.47	4.489	3/9	0.146	0.059	−0.012	0.061
4-Nonanol	3.46	4.489	4/9	0.243	0.069	0.077	0.187
5-Nonanol	3.42	4.489	5/9	0.279	0.109	0.196	0.313

log K, logarithm of the octanol-PBS partition coefficient; $^1x^v$, the first-order valence connectivity index; R_P, the ratio of polar group position in alkanols to the carbon number of alkyl chain (e.g. 1-Hexanol, whose polar group position is 1, carbon number of alkyl chain is 6, ratio is 1/6); a, from Chantasart et al. (2004); b , from Eq. (1); c, from Eq. (2); d, from Eq. (5)

where n is the number of compounds, r is the correlation coefficient, s is the standard deviation, F is the significance test (F-test), and the figures in brackets are the standard errors of the regression coefficients. Eq. (1) indicates good linear relationships between $\log(C_{E=10})$ and log K, and the enhancer with higher lipophilicity has greater enhancement potency. The calculated $\log(C_{E=10})$ values from Eq. (1) for the 16 enhancers are listed in the Table.

The calculated $\log(C_{E=10})$ values of four normal alkanols positively deviate from the corresponding experimental ones, while the calculated $\log(C_{E=10})$ values of four branched alkanols with the hydroxyl groups farthest from the terminal negatively deviate from the corresponding experimental ones. The enhancer potencies may be affected by the position of the hydroxyl group in the alkanols in addition to their lipophilicity. When added with a new parameter, R_p, which is defined as the ratio of polar group position in alkanols to the carbon number of alkyl chain, the following regression equation is obtained:

$$\log(C_{E=10}) = 3.1285(\pm 0.1106) - 0.9740(\pm 0.0334)\log K + 0.7170(\pm 0.1293)\,Rp \quad (2)$$

$$n = 16 \qquad r = 0.9933 \qquad s = 0.0770 \qquad F = 478.6$$

Eq. (2) is statistically more significant than Eq. (1). The calculated $\log(C_{E=10})$ values are in good accordance with the corresponding experimental ones. Eq. (2) shows that the enhancement potency of an alkanol decreases as the hydroxyl group moves from the end of the chain towards the center of the enhancer alkyl chain. Branching of the alkyl chain reduces the ability of the enhancer to effect lipid fluidization in the stratum corneum lipid lamellae at the target site (Chantasart et al. 2004).

Determination of the Molecular connectivity index is a method for the quantitation of a molecular structure that encodes information about size, branching, cyclization, unsaturation, and heteroatom content (Kier and Hall 1976). Wallace (1975) demonstrated that the molecular connectivity index was linearly related to the octanol-water partition coefficient in a variety of monofunctional chemical classes. We verified the good linear correlation between the partition coefficients of these alkanols and their first valence molecular connectivity indexes ($^1x^v$).

$$\log K = 1.2227(\pm 0.0.1423) + 1.0492(\pm 0.0368)\,{}^1x^v \quad (3)$$

$$n = 16 \qquad r = 0.9915 \qquad s = 0.0812 \qquad F = 814.4$$

So, $^1x^v$ can replace log K in Eqs. (1) and (2), then Eqs. (4) and (5) are obtained:

$$\log(C_{E=10}) = 4.7052(\pm 0.3358) - 1.0366(\pm 0.0868)\,{}^1x^v \quad (4)$$

$$n = 16 \qquad r = 0.9543 \qquad s = 0.1915 \qquad F = 142.8$$

$$\log(C_{E=10}) = 4.2703(\pm 0.1139) - 1.0218(\pm 0.0277)\,{}^1x^v + 1.1328(\pm 0.1014)\,R_p \quad (5)$$

$$n = 16 \qquad r = 0.9958 \qquad s = 0.0610 \qquad F = 765.2$$

Eqs. (4) and (5) show the similar linear relationships as Eqs. (1) and (2). The calculated $\log(C_{E=10})$ values from Eq. (5) are listed in the Table and the calculated and ex-

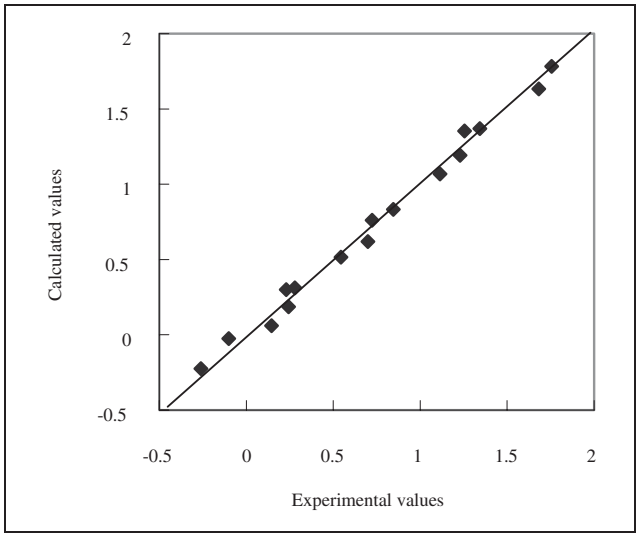

Fig.: Relationships between experimental and calculated $\log(C_{E=10})$ values of alkanols

perimental $\log(C_{E=10})$ values are plotted in the Fig. The calculated $\log(C_{E=10})$ values are in quite a good agreement with the corresponding experimental ones. As $^{1}x^{v}$ can be easily calculated, Eq. (5) is convenient and useful in predicting the enhancement potencies of alkanols.

References

Aungst B, Rogers N, Shefter E (1986) Enhancement of naloxone penetration through human skin *in vitro* using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. Int J Pharm 33: 225–234.

Chang SL, Banga AK (1998) Transdermal iontophoretic delivery of hydrocortisone from cyclodextrin solutions. J Pharm Pharmacol 50: 635–640.

Chantasart D, Li SK, He N, Warner KS, Prakongpan S, Higuchi WI (2004) Mechanistic studies of branched-chain alkanols as skin permeation enhancers. J Pharm Sci 93: 762–779.

Cho YJ, Choi HK (1998) Enhancement of percutaneous absorption of ketoprofen: effect of vehicles and adhesive matrix. Int J Pharm 169: 95–104.

Kim N, El-Khalili M, Henary MM, Strekowski L, Michniak BB (1999) Percutaneous penetration enhancement activity of aromatic *S*,*S*-dimethyliminosulfuranes. Int J Pharm 187: 219–229.

Kier LB, Hall LH (1976) Molecular Connectivity in Chemistry and Drug Research. Academic, New York, N.Y.

Kanikkannan N, Kandimalla K, Lamba SS, Singh M (2000) Structure-activity relationship of chemical penetration enhancers in transdermal drug delivery. Curr Med Chem 7: 593–608.

Kanikkannan N, Singh M (2002) Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. Int J Pharm 248: 219–228.

Morimoto K, Iwakura Y, Nakatani E, Miyazaki M, Tojima H (1992) Effects of proteolytic enzyme inhibitors as absorption enhancers on the transdermal iontophoretic delivery of calcitonin in rats. J Pharm Pharmacol 44: 216–218.

Mezel M (1985) Liposomes as a skin drug delivery system. In: Breimer DD, Speiser P (Eds.), Topics in Pharmaceutical Sciences. Elsevier, Amsterdam, pp. 345–358.

Smith EW, Maibach HI (1995) Percutaneous penetration enhancers: the fundamentals. In: Smith EW, Maibach HI (Eds.), Percutaneous Penetration Enhancers. CRC Press, Boca Raton, FL, pp. 1–4.

Sloan KB, Selk S, Haslam J, Caldwell L, Shaffer R (1984) Acyloxyamines as prodrugs of anti-inflammatory carboxylic acids for improved delivery through skin. J Pharm Sci 73: 1734–1737.

Wallace JM, Lowell HH, Lemont BK (1975) Molecular connectivity III: relationship to partition coefficients. J Pharm Sci 64: 1978–1981.