REFERENCE

Barker, N. and Hadgraft, J. Facilitated percutaneous absorption : a model system. Int. J. Pharm. 8 (1981) : 193 - 202.

Behl, C.R., Kumar, S., Malick, A.W., Terzo, S.D., Higuchi, W.I. and Nash, R.A. Iontophoretic drug delivery : Effects of physicochemical Factors on the skin uptake of nonpeptide drugs. J. Pharm. Sci. 78 (May 1989) : 355 - 359.

Bellamy, L.J. An infrared spectra of complex molecules. vol. 1. 3rd ed. London : Chapman and Hall, 1975.

Bokesch, P.M., Post, C. and Strichartz, G. Structure-activity relationship of lidocaine homologs producing ionic and frequency-dependent inpulse blockade in nerve. J. Pharmacol. Exp. Ther. 237 (1986) : 773 - 781.

Broberg, F. and Evers, H. European patent no. 0002425 (1981).

Brodin, A., Nyqvist-Mayer, A., Wadsten, I., Forslund, B. and Broberg, F. Phase diagram and aqueous solubility of the lidocaine-prilocaine binary system. J. Pharm. Sci. 17 (1984) : 481 - 484.

Bronaugh, R.L. and Collier, S.W. **In vitro** methods for measuring skin permeation. Cosmetics & Toiletries. 105 (November 1990) : 86 - 93.

Budovari, S. The Merck index. 11th ed. U.S.A. : Merck & Co., 1989.

Cahalan, M.D. and Almers, W. Interactions between quaternary lidocaine, the sodium channel gates, and tetrodotoxin. Biophys. J. 27 (July 1979) : 39 - 56.

Catz, P. and Friend, D.R. Transdermal delivery of levonorgestrel. VIII. effect of enhancers on rat skin, hairless mouse skin, hairless guinea pig skin, and human skin. Int. J. Pharm. 58 (1990) : 93 - 102.

Chien, Y.W. and Bange, A.K. Iontophoretic(Transdermal) delivery of drugs : Overview of historical development. J. Pharm. Sci. 78 (May 1989) : 353 - 354.

Chien, Y.W., Siddiqui, O., Shi, W. - M., Lelawongs, P. and Liu, J. - C. Direct current iontophoretic transdermal delivery of peptide and protein drugs. J. Pharm. Sci. 78 (May 1989) : 376-383.

Clarke, S. and Radford, M. Topical anaesthesia for venepuncture. Arch. Dis. Child. 61 (1986) : 1132 - 1134.

Clarke, E.G.C. Clarke's isolation and identification of drugs. 2nd ed. London : The Pharmaceutical Press, 1986.

Concepcion, M. and Covino, B.G. Rational use of local anaesthetics. Drugs 27 (1984) : 256 - 270.

Connors, B.W. and Prince, D.A. Effects of local anesthetic QX-314 on the membrane properties of hippocampal pyramidal neurons. J. Pharmacol. Exp. Ther. 220 (1982) : 476 - 481.

Evers, H., Dardel, O.V., Juhlin, L., Ohlsen, L. and Vinnars, E. Dermal effects of compositions based on the eutectic mixture of lignocaine and prilocaine (EMLA). Br. J. Anaesth. 57 (1985) : 997 - 1005.

Fell, A.F. Analysis of coloring agents in pharmaceuticals by derivative ultraviolet visible spectroscopy. Proc. Anal. Div. Chem. Soc. 15 (1978) : 260 - 267.

Frazier, D.T., Narahashi, T. and Yamada, M. The site of action and active form of local anesthetics. II. experiments with quaternary compounds. J. Pharmacol. Exp. Ther. 171 (1970) : 45 - 51.

Green, P.G., Guy, R.H. and Hadgraft, J. **In vitro** and **in vivo** enhancement of skin permeation with oleic and lauric acids. Int. J. Pharm. 48 (1988) : 103 - 111.

Groningsson, K., Lindgren, J.E., Lundberg, E., Sandberg, R. and Wahlen, A. Lidocaine base and hydrochloride. Anal. Profiles. Drug. Sub. 14 (1984) : 209 -243.

Hadgraft, J. Formulation of anti-inflammatory agents. nonsteroidal anti-inflammatory drugs. 2(1989) : 21 - 43.

Kushla, G.P. and Zatz, J.L. Lidocaine penetration through human and hairless mouse skin **in vitro**. J. Soc. Cosmet. Chem. 40(January/ February 1989) : 41 - 50.

Kydonieus, A.F. and Berner, B. Transdermal delivery of drugs. vol. I, II, III. Floida : CRC Press, Inc., 1987.

Larsen, J.D., Bundgaard, H. and Lee, V.H.L. Prodrug forms for the sulfonamide group. II. water-soluble amino acid derivatives of N-methylsulfonamides as possible prodrug. Int. J. Pharm. 47 (1988) : 103 - 110.

Loftsson, T., Matsuo, M., Caldwell, R.W., Gildersleeve, N. and Bodor, N. Synthesis and evaluation of novel lidocaine sulfur analogs. Int. J. Pharm. 22 (1984) : 345 - 355.

Lubens, H.M., Ausdenmoore, R.W., Shafer, A.D. and Reece, R.M. Anaesthetic patch for painful procedures such as minor operations. Am. J. Dis. Child. 128 (August 1974) : 192 - 194.

Milton, J.S. and Tsokos, J.O. Staistical methods in the biological and health sciences. U.S.A. : McGraw-Hill, Inc, 1983.

Monash, S. Topical anaesthesia of the unbroken skin. A.M.A. Arch. Dermatol. 76 (1957) : 752 - 756.

O'Haver, T.C. and Green, G.L. Numerical error analysis of derivative spectrophotometry for the quantitative analysis of mixtures. Anal. Chem. 48 (1976) : 312 - 318.

Padmanabhan, R.V., Phipps, J.B., Lattin, G.A. and Sawchuk, R.J. **In vitro** and **in vivo** evaluation of transdermal iontophoretic delivery of hydromorphone. J. Controlled Release. 11 (1990) : 123 - 135.

Phipps, J.B., Padmanabhan, R.V. and Lattin, G.A. Iontophoretic delivery of model inorganic and drug ions. J. Pharm. Sci. 78 (May 1989) : 365 - 369.

Pouchert, C.J. The Aldrich library of infrared spectra. 2nd ed. Wisconsin :Aldrich Chemical Company, 1975.

Pouchert, C.J. The Aldrich library of NMR spectra vol.1,2, 2nd ed. Wisconsin :Aldrich Chemical Company, 1983.

Powell, M.F. Lidocaine and lidocaine hydrochloride. Anal. Profiles. Drug Sub. 15 (1986) : 761-779.

Pretsch, E., Clerc, T., Seibel, J., Simon, W. Chemical laboratory practice. Translated by Biemamm, K. Heidelberg : Beltz Offsetdruck, Hemsbach, 1983.

Reynolds, J.E.F. Martindale : The extra pharmacopaeia. 29th ed. London : The Pharmaceutical Press, 1989.

Sanderson, J.E., de Riel, S., Dixon, R. Iontophoretic delivery of nonpeptide drugs : Formulation optimization for maximum skin permeability. J. Pharm. Sci. 78 (May 1989) : 361 - 364.

Sarpotdar, P.P. and Zatz, J.L. Evaluation of penetration enhancement of lidocaine by nonionic surfactants through hairless mouse skin **in vitro**. J. Pharm. Sci. 75 (February 1986) : 176 - 181.

Sasaki, H., Takahashi, T., Mori, Y., Nakamura, J. and Shibbasaki, J. Transdermal delivery of 5-fluorouracil and its alkylcarbamoyl derivatives. Int. J. Pharm. 60 (1990) : 1 - 9.

Scheinmann, F. An introduction to spectroscopic methods for the identification of organic compounds : Nuclear magnetic resonance and infrared spectroscopy. vol. 1. Oxford : Pergamon Press, 1970.

Shah, V.P., Elkins, J., Lam, S.Y. and Skelly, J.P. Determination of **in vitro** drug release from hydrocortisone cream. Int. J. Pharm. 53 (1989) : 53 - 59.

Siddiqui, O., Roberts, M.S. and Polack, A.E. The effect of iontophoresis and vehicle pH on the **in vitro** permeation of lignocaine through human stratum corneum. J. Pharm. Pharmacol. 37 (1985) : 732 - 735.

Silverstein, R.M., Bassler, G.C. and Morrill, T.C. Spectrometric identification of organic compounds. 4nd ed. U.S.A. : John Wiley & Sons, 1981.

Siver, K.G. and Sloan, K.B. Alkylation of 6-mercaptopurine (6-MP) with N-alkyl-N-alkoxy-carbonylaminomethyl) chloride : S^6-(N-alkyl-N-alkoxycarbbonyl) aminomethyl-6-MP prodrug structure effect on the dermal delivery of 6-MP. J. Pharm. Sci. 79 (January 1990) 66-73.

Sokoloski, T.D. Solutions and phase equilibria. In A. Osol (ed.) Remington's pharmaceutical sciences, pp. 229 - 254. Pennsylvania : Mack Publishing Company, 1975.

Srinivasan, V., Higuchi, W.I., Sims, S.M., Ghanem, A.H. and Behl, C.R. Transdermal iontophoretic drug delivery : Mechanistic analysis and application to polypeptide delivery. J. Pharm. Sci. 78 (May 1989) : 370 - 375.

Thai Pharmacopoeia. vol. I. Thailand : Department of Medical Sciences, Ministry of Public Health, 1987.

The National Formulary XIV. 14th ed. Washington : The American Pharmaceutical Association, 1975.

The United States Pharmacopoeia XXII, 22 th. revision, The National Formulary, 17 th ed., Rockville, Md : United States Pharmacopeial Convential, Inc., 1988.

Traveset, V.S., Gonzalo, R. and Gelpi, E. Derivative and graphical procedures for correction of irrelevant UV spectrophotometric absorption in changeable matrices. J. Pharm. Sci. 69 (1980) : 692 - 633.

Tregear, R.T. Molecular movement. The permeability of skin. In R.T. Tregear (ed.), Physical functions of skin, pp. 1 - 52. New York : Academic Pess Inc., 1966.

Tu, Y. and Allen, L.V. Jr. **In vitro** Iontophoretic studies using a synthetic membrane. J. Pharm. Sci. 78 (March 1989) : 211 - 213.

Weast, R.C. Handbook of chemistry and physics. Ohio : CRC Press, Inc., 1974.

Wells, J.I. Pharmaceutical preformulation : The physiochemical propertites of drug substances. Series in Pharmaceutical Technology. Chichester : Ellis Harwood Limited, 1988.

Wildsmith, J.A.W., Gissen, A.J., Takman, B. and Covino, B.G. Differential nerve blockade : esters v. amides and the influence of pK_a. Br. J. Anaesth. 59 (1987) : 379 - 384.

APPENDIX

STATISTICS

1. Mean ($\bar{X}$)

$$\bar{X} = \frac{\Sigma X}{N}$$

2. Standard deviation (S.D.)

$$S.D. = \sqrt{\frac{(X - \bar{X})^2}{N - 1}}$$

3. Standard error of the mean (SEM)

$$SEM = \frac{S.D.}{\sqrt{N}}$$

4. Coefficient of Variation

$$C.V. = \frac{S.D.}{\bar{X}} \times 100$$

5. Analysis of variance (ANOVA)

ANOVA Table

Source of Variation	Sum of Squares(SS*)	d.f.	Mean Square (MS)	Variation (F)
Between treatments	$\sum_{i=1}^{k} \frac{T_{i}.^2}{n_i} - C$	k-1	$\frac{SS(between)}{(k-1)}$	$\frac{MS(between)}{MS(within)}$
Within(Err) treatments	SS(Total)-SS(between)	N-k	$\frac{SS(within)}{(N-k)}$	
Total	$\sum_{i=1}^{k} \sum_{j=1}^{n^i} (X_{ij})^2 - C$	N-1		

where X_{ij} = Observed value i at treatment j
i = 1, 2,..., n
j = 1, 2,..., k

$$^*C = \frac{\left(\sum_{i=1}^{k} \sum_{j=1}^{n_i} X_{ij}\right)^2}{N}$$

$$T_i. = \sum_{i=1}^{n_j} X_{ij}$$

$$X_i. = \frac{T_i.}{n_j}$$

$$T.. = \sum_{j=1}^{k} T_i.$$

$$X.. = \frac{T..}{N}$$

$$N = \sum_{j=1}^{k} n_j$$

The F value is compared with the critical value, F, which is obtained from the table at degree of freedom (k-1) and (N-k).

If F > F(tab), the null hypothesis (H_o) that $u_1 = u_2 = \ldots = u_k$ is rejected and the alternative hypothesis is accepted. If F is not significant, the null hypothesis stands.

6. Duncan's multiple range test.

In multiple comparisons, we have been able to reject H_o and therefore conclude that there are some differences among the k population means. In this case, the analysis of the data has just begun, since it is natural to continue the investigation to try to pinpoint where the differences lie.

Duncan's multiple range test is designed to detect differences in population means by comparing sample means. This is done by dividing the k sample means, and therefore the k population means, into subgroups so that means within subgroups are not considered to be significantly different. The test is performed as follows :

1. Linearly order the k sample means.

2. Consider any subset of p sample means $2 \leq p \leq k$. For the means of any of the corresponding populations to be considered different, the range of the means in the subgroup (largest to smallest) must exceed a specific value, called the shortest significant range SSR_p.

3. The shortest significant range is calculated by means of Table A and the following formula :

$$SSR_p = r_p\sqrt{\frac{MS_E}{n}}$$

where r_p = least significant studentized range obtained from Table A.

MS_E = error mean square from ANOVA

n = common sample size

Υ = degrees of freedom for MS_E

4. Results are summarized by underlining any subset of adjacent means that are not considered to be significantly different at the α level selected.

The differences in population means are detected by comparing the largest sample mean with the smallest, the largest with the next smallest, and so forth. Thus potentially we need to consider pairs of the sample means in the order.

However, once a group of means has been found to be not significantly different, no further test will declare them to differ. Thus, in practice, it may not be necessary to perform all the comparisons indicated. No further comparisons need to be made at the point if no differences have been detected among the mean.

If = 0.05 is selected. The value α = 0.05 is the probability that at least one of these conclusions is incorrected.

The procedure is illustrated by continuing the analysis of the data of Example 1.

Example 1 Flux of compounds at 24 hours after application.

	Compound					
	X1	X2	X3	X4	X5	X6
	7.835	4.813	7.640	5.357	6.885	5.357
	15.861	4.851	10.016	5.613	5.922	5.500
	10.685	4.235	7.527	5.162	4.400	4.526
	13.045	4.273	7.046	3.299	5.514	4.118
$\bar{X}$	11.857	4.543	8.057	4.858	5.680	4.875

ANALYSIS OF VARIANCE

Source of Variation	Sum of Squares	d.f.	Mean Square	Variation (F)	P
Between treatments	163.318	5	32.664	12.128	.000
Within(Err) treatments	48.480	18	2.693		

Duncan's multiple range tests

Ordered means differ at alpha = .050 if they exceed following gaps

Gap order	Difference
2	2.440
3	2.559
4	2.634
5	2.687
6	2.725

This test assumes the counts per group are equal

In linear order, these are

X2	X4	X6	X5	X3	X1
4.543	4.858	4.875	5.680	8.057	11.857

P	2	3	4	5	6
r_p	2.971	3.118	3.210	3.274	3.321
SSRp	2.440	2.559	2.634	2.687	2.725

Difference d	Number in Subgroup p	SSRp	is d > SSrp?
X4-X2 = 0.315	2	2.440	no
X6-X4 = 0.017	2	2.443	no
X5-X6 = 0.805	2	2.440	no
X3-X5 = 2.377	2	2.440	no
X1-X3 = 3.800	2	2.440	yes
X6-X2 = 0.332	3	2.559	no
X5-X4 = 0.822	3	2.559	no
X3-X6 = 3.182	3	2.559	yes
X1-X5 = 6.117	3	2.559	yes
X5-X2 = 1.137	4	2.634	no
X3-X4 = 3.199	4	2.634	yes
X1-X6 = 6.982	4	2.634	yes
X3-X2 = 3.514	5	2.687	yes
X1-X4 = 6.999	5	2.687	yes
X1-X2 = 7.314	6	2.725	yes

Table A : Duncan's table.[a]

least significant studentized ranges r_p $\alpha = 0.05$ *P*						least significant studentized ranges r_p $\alpha = 0.01$ *P*					
r	2	3	4	5	6	*r*	2	3	4	5	6
1	17.97	17.97	17.97	17.97	17.97	1	90.03	90.03	90.03	90.03	90.03
2	6.085	6.085	6.085	6.085	6.085	2	14.04	14.04	14.04	14.04	14.04
3	4.501	4.516	4.516	4.516	4.516	3	8.261	8.321	8.321	8.321	8.321
4	3.927	4.013	4.033	4.033	4.033	4	6.512	6.677	6.740	6.756	6.756
5	3.635	3.749	3.797	3.814	3.814	5	5.702	5.893	5.898	6.040	6.065
6	3.461	3.587	3.649	3.680	3.694	6	5.243	5.439	5.549	5.614	5.655
7	3.344	3.477	3.548	3.588	3.611	7	4.949	5.145	5.260	5.334	5.383
8	3.261	3.399	3.475	3.521	3.549	8	4.746	4.939	5.057	5.135	5.189
9	3.199	3.339	3.420	3.470	3.502	9	4.596	4.787	4.906	4.986	5.043
10	3.151	3.293	3.376	3.430	3.465	10	4.482	4.671	4.790	4.871	4.931
11	3.113	3.256	3.342	3.397	3.435	11	4.392	4.579	4.697	4.780	4.841
12	3.082	3.225	3.313	3.370	3.410	12	4.320	4.504	4.622	4.706	4.767
13	3.055	3.200	3.289	3.348	3.389	13	4.260	4.442	4.560	4.644	4.706
14	3.033	3.178	3.268	3.329	3.372	14	4.210	4.391	4.508	4.591	4.654
15	3.014	3.160	3.250	3.312	3.356	15	4.168	4.347	4.463	4.547	4.610
16	2.998	3.144	3.235	3.298	3.343	16	4.131	4.309	4.425	4.509	4.572
17	2.984	3.130	3.222	3.285	3.331	17	4.099	4.275	4.391	4.475	4.539
18	2.971	3.118	3.210	3.274	3.321	18	4.071	4.246	4.362	4.445	4.509
19	2.960	3.107	3.199	3.264	3.311	19	4.046	4.220	4.335	4.419	4.483
20	2.950	3.097	3.190	3.255	3.303	20	4.024	4.197	4.312	4.395	4.459
24	2.919	3.066	3.160	3.226	3.276	24	3.956	4.126	4.239	4.322	4.386
30	2.888	3.035	3.131	3.199	3.250	30	3.889	4.506	4.168	4.250	4.314
40	2.858	3.006	3.102	3.171	3.224	40	3.825	3.988	4.098	4.180	4.244
60	2.829	2.976	3.073	3.143	3.198	60	3.762	3.922	4.031	4.111	4.174
120	2.800	2.947	3.045	3.116	3.172	120	3.702	3.858	3.965	4.044	4.107
∞	2.772	2.918	3.017	3.089	3.146	∞	3.643	3.796	3.900	3.978	4.040

[a]Milton and Tsoko, 1983

VITA

Miss Supreeya La-ong was born on March 20, 1959 in Lopburi, Thailand. She graduated with Bachelor Degree of Science in Pharmacy with the second class honors in 1982 from Faculty of Pharmacy, Mahidol University. She has worked as a quality control pharmacist at B.J.(Benja-osoth) Ltd. in Bangkok.