The influence of a binary solvent system on the dermal delivery of lidocaine hydrochloride in human skin

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Objectives

The binary combination composed of polar and non-polar vehicles has been demonstrated as one of the approaches to enhance the permeation of drugs. In this study the effect of binary vehicles of Transcutol® (TC) as a polar solvent and isopropyl myristate (IPM) as a non-polar solvent on the enhancement of permeation of Lidocaine hydrochloride (LID-HCL) through human skin was determined.

Materials and Methods

In vitro infinite dose studies with female abdominal human skin were performed using Franz diffusion cells containing PBS pH 7.4 with 0.1 % sodium azide as the receptor solution. Saturated LID-HCL solutions of neat vehicles and the various combinations were used to maintain an equal (and unit) thermodynamic activity of LID-HCL.

Data analysis

Scientist Version. 3.0 (Micromath, Inc., United States) was used to fit the data to a Laplace model of Fick's second law (equation 1).

$$\partial C / \partial t = D \times \partial^2 C / \partial x^2 \qquad (1)$$

where C is the concentration, x is the position and t is the time. P_1 and P_2 were calculated from equations 2 and 3.

$$P_1 = K \times h \qquad (2)$$

$$P_2 = D / h^2 \qquad (3)$$

where K is partition coefficient, D is diffusion coefficient and h is the diffusional pathlength. The permeability coefficient (k_p) was obtained by the product of $P_1 \times P_2$.

Results and Discussion

Permeation profiles of LID-HCL through human skin with various binary combinations of TC and IPM are shown in Fig.1.

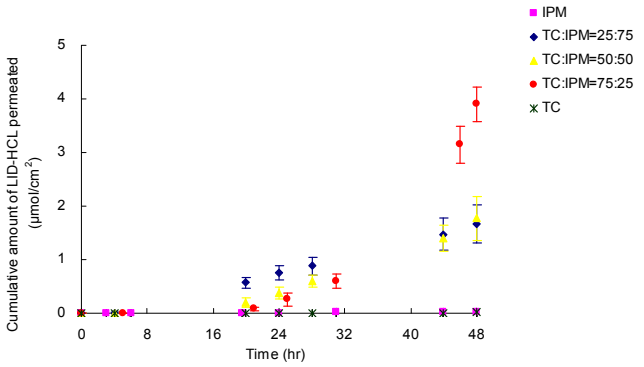

Fig. 1 Permeation profile of LID-HCL with Transcutol - IPM mixtures. Each data points represents the mean ± S.D. (n = 5)

Steady state fluxes of saturated TC and IPM mixtures are shown in Fig. 2. A strong synergistic enhancement effect was clearly demonstrated by the binary solvent system compared with the neat solvent systems.

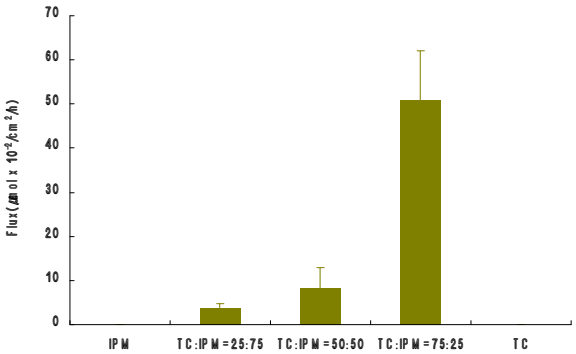

Fig. 2 Steady state fluxes of LID-HCL through human skin from the saturated Transcutol-IPM mixtures. Each data points represents the mean ± S.D. (n = 5)

The maximum enhancement for TC:IPM=75:25 showed a 1000-fold increase compared with neat solvents.

Table 1 Relative composition of TC-IPM binary solvents, mole fractions of LID-HCL and solvents; LID-HCL solubility at 32ºC; LID-HCL steady state flux, apparent partition coefficient, apparent diffusion coefficient, permeability coefficient. Each data point represents the mean ± S.D. (n = 5)

Formulation				LID-HCL properties				
	Mole fraction			Solubility	J	P_1	P_2	k_p
	Transcutol	IPM	LID-HCL	(μmol/mL)	(μmol x 10^{-2}/cm^2/h)	(cm x 10^{-3})	($x10^{-2}$/h)	($x10^{-4}$cm/h)
IPM	0.000	1.000	0.000	0.7 ± 0.03	0.04 ± 0.01	3.1 ± 1.0	14 ± 5	4 ± 2
TC:IPM=25:75	0.400	0.595	0.006	27 ± 0.7	4 ± 0.9	45 ± 25	4 ± 1	14 ± 3
TC:IPM=50:50	0.659	0.327	0.014	80 ± 2	8 ± 5	189 ± 178	0.8 ± 0.3	10 ± 6
TC:IPM=75:25	0.788	0.130	0.082	581 ± 68	51 ± 11	312 ± 105	0.3 ± 0.0	9 ± 2
TC	0.872	0.000	0.128	1096 ± 12	0.04 ± 0.02	0.04 ± 0.01	0.8 ± 0.2	0.003 ± 0.001

The solubility of LID-HCL in the formulations increased significantly as the concentration of TC increased.

Since the thermodynamic activity of the LID-HCL was the same for all formulations, the penetration of solvents and subsequent alteration of skin integrity appears to play an important role in drug partitioning.

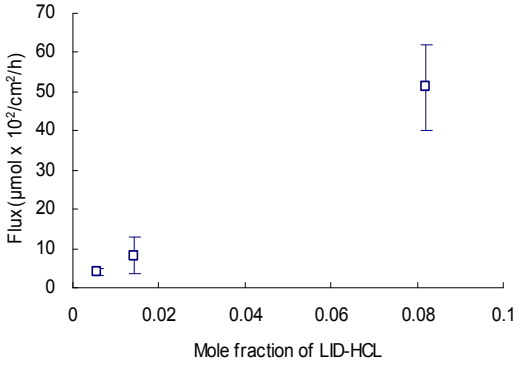

Fig. 3 Plot of mole fraction of LID-HCL in binary mixtures and flux. Each data points represents the mean ± S.D. (n = 5)

The plot of mole fraction of LID-HCL in the different binary mixtures and flux is shown in Fig.3. The flux of LID-HCL increases linearly with mole fraction of LID-HCL. For TC and IPM the increase in both flux and P_1 is evident with increasing TC concentration. However, pure TC itself did not increase the flux and P_1. These data suggest that TC and IPM interact, synergistically, to promote the penetration of LID-HCL by enhancement of drug partition coefficient. IPM is known to fluidize intercellular lipids and it is possible that IPM may facilitate the uptake of TC in the skin as reflected by an increase of P_1 because LID-HCL was predominantly dissolved in TC.

Conclusions

- The thermodynamic activity of TC and/or IPM may be altered with different concentrations of LID-HCL in binary mixtures.

– Binary solvents systems composed of TC and IPM have a synergistic effect on the permeation of LID-HCL across the skin.

– The results confirm the importance of determining the optimum balance between the activity of LID-HCL and the activity of the solvents in the binary system to obtain the maximum flux.

Reference

Twist JN, Zatz JL. J. Pharm. Sci. 1988;77:536-540.

Acknowledgments

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