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The synergistic effect of laurocapram pretreatment and iontophoresis on the percutaneous permeation of non-steroidal anti-inflammatory drugs *in vitro*

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Oral administration is currently the principal route of administration for non-steroidal anti-inflammatory drugs. The clinical use of these drugs, however, is often limited because of their potential adverse reactions such as irritation and ulceration of the gastrointestinal mucosa, particularly at high dose levels [1]. To minimize the side effects and the health hazard for patients, transdermal drug delivery is a good way, and iontophoresis was used in conjunction with chemical penetration enhancers to boost transdermal drug delivery even further. In this study, four non-steroidal anti-inflammatory drugs, piroxicam, naproxen, indomethacin and diclofenac sodium were employed to reseach the effects of constant current iontophoresis and laurocapram pretreatment on the percutaneous fluxes. The synergistic effect is also discussed.

The results suggest that iontophoresis is an effective method to enhance the delivery of negatively charged drugs into and through the skin, the fluxes of the drugs investigated were significantly greater than the passive fluxes. The degrees of enhance rate (ER) were different, the most obvious enhance effect occured with piroxicam, ER was as large as 37.2. Laurocapram pretreatment could also increase the fluxes. ERs were between 1.4 and 5.7, but the results showed that the enhance effect of iontophoresis was greater than that of laurocapram pretreatment.

The combination of iontophoresis and enhancer pretreatment is a promising way to enhance the subcutaneous permeation of drugs. The ERs of piroxicam, indomethacin, naproxen and diclofenac sodium were 97.2, 20.0, 17.0 and 12.1, respectively. The degrees of drug delivery were significantly greater than the sum of those delived by pretreatment alone and iontophoresis alone, but diclofenac sodium was different from the other drugs. The results obviously verified that the percutaneous permeation of a charged drug was greatly enhanced by iontophoresis combined with laurocapram pretreatment, and the permeation coefficient of an uncharged drug was also increased, but to a lower extent.

Table 1: Percutaneous fluxes of four non-steroidal anti-inflammatory drugs with various treatments

Drugs	Passive diffusion	Flux (μg/h cm^2)		Iontophoresis and laurocapram pretreatment
		Iontophoresis	Laurocapram pretreatment	
Piroxicam	1.00 ± 0.27	37.2 ± 3.55	3.62 ± 0.39	97.2 ± 4.57
ER*	1	37.2	3.62	97.2
Indomethacin	5.06 ± 0.82	48.9 ± 14.1	7.19 ± 2.04	101 ± 4.02
ER	1	9.7	1.4	20.0
Naproxen	8.05 ± 1.64	51.5 ± 401	39.3 ± 13.3	137 ± 24.1
ER	1	6.4	4.9	17.0
Diclofenac sodium	24.4 ± 0.25	183 ± 40.5	139 ± 34.0	296 ± 17.62
ER	1	7.5	5.7	12.1

$$ER = \frac{\text{Flux of drugs with various treatments}}{\text{Passive diffusion flux of drugs}}$$

Table 2: Permeability coefficients of piroxicam with various treatments

Permeability coefficient	Passive diffusion*	Treatments		Laurocapram pretreatment and iontophoresis
		Iontophoresis	Laurocapram pretreatment	
P^a_{HA}	0.04387	0.08740	0.1181	0.1433
ER	1	2.0	2.7	3.3
$P^b_{A^-}$	0.001162	0.02369	0.01902	0.07797
ER	1	20.4	16.4	67.1

*: the results were obtained from our other experiment
[a]: permeability coefficient of uncharged drug
[b]: permeability coefficient of charged drug

The results imply that iontophoresis and the chemical enhancer show a synergistic effect on percutaneous drug permeation. This method might be a promising way to enhance transdermal drug delivery.

Experimental

1. Skin sampling

Rat skin specimen was prepared following the method of Singh [2].

2. Measurements

Skin specimen were mounted between Valia-Chien half-cells of each permeation system with the stratum corneum facing the donor half-cell. At least three skin specimen were used for every experimental condition studied. The donor and receptor solution was maintained at 32 ± 0.5 °C by a circulating water bath. Ag/AgCl electrodes were used as nonpolarizable and reversible electrodes with the cathode in the donor cell and the anode in the receptor cell. A constant current of 0.50 mA/cm^2 was applied with the power supply used in the iontophoresis transdermal permeation studies. The constant source had facile checking of voltage and resistance throughout the experiments. A saturated drug solution was employed as donar solution. Phosphate buffer (pH 7.4) was used as the receptor solution.

3. Analytical procedure and data analysis

The analytical procedure and data analysis followed the method of Gao [3].

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References

1 Zhao, W. Z.: Chin. Pharmacol. Bull. **1**, 79 (1993)
2 Singh, J.: Pharmazie **45**, 634 (1990)
3 Gao, J. Q.; Liang, W. Q.: Chin J. Pharm. **29**, 169 (1998)

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