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Technical Note

The Effect of Vehicle Additives on the Transdermal Delivery of Nitroglycerin

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INTRODUCTION

Topical application of nitroglycerin is an effective method to bypass the first-pass inactivation in the liver, and for this reason nitroglycerin ointments have been used for over 30 years to treat angina pectoris (1). Their usage has never gained much enthusiasm since they have to be applied several times a day and covered with occlusive dressings to ensure steady delivery of nitroglycerin. For the past few years, transdermal delivery systems involving diffusion of nitroglycerin through gel, polymer matrices, or semipermeable membranes (2,3) have been used successfully. They are intended to deliver a sustained and controlled amount of the drug for at least 24 hr and the delivery rate is supposed to be controlled by the semipermeable membrane or polymer matrix. There are, however, indications that skin impermeability has a significant effect on the transdermal delivery of nitroglycerin from such devices (4,5). This will cause individual and unpredictable variations in the drug delivery. One way to overcome this obstacle is to add penetration enhancers to the delivery system to improve the permeability of nitroglycerine through the skin. Here we report our results on the effect of vehicle additives on the penetration of nitroglycerin through hairless mouse skin.

MATERIALS AND METHODS

Female hairless mice (SKH1-HR-1 strain, Temple University) were sacrificed by cervical dislocation and the whole dorsal skin was removed. Each skin was placed over a circular Teflon holder, providing a 7.07-cm^2 skin surface which could be suspended over a Plexiglas reservoir (diffusion cells from Kercso Engineering, Palo Alto, Calif.). Isotonic pH 7.40 phosphate buffer, filtered under vacuum to remove dissolved air, was used as the receptor phase. A stirring bar and 39 ml of buffer were added to each reservoir. A measured amount of a solution of 10% nitroglycerin in propylene glycol (ICI, lot SDM No. 27) was mixed with the desired vehicle additive. One milliliter of the resulting nitroglycerin solution was spread over each skin and the cells were stirred in a 35°C incubator for 6 hr. For analysis, 0.5-ml samples were removed from the receptor phase and replaced with fresh buffer (7). The samples were analyzed by a high-performance liquid chromatographic (HPLC) method using a Beckman Model 160 detector with a Zn lamp and 214-nm filter, a C-18 reverse-phase column (Waters Associates), and a mobile phase consisting of 55% acetonitrile in distilled water. The retention time was 10 min at flow rate of 1.00 ml/min.

RESULTS AND DISCUSSION

Small lipophilic molecules such as nitroglycerin generally show a good permeability through skin. Thus, the permeability coefficient of nitroglycerin from saturated aqueous solutions has been determined to be about 2 times larger than that for estradiol and over 1000 times larger than that for atropine (8). Classical penetration enhancers such as dimethyl sulfoxide (DMSO) result in an almost three times greater permeability (Table I). Water had an even more significant effect, but this was probably due to the decreased solubility of nitroglycerin in the vehicle and, consequently, the higher activity. Actually, the 20% water addition caused the appearance of small nitroglycerin droplets on the skin surface: maximal thermodynamic activity by saturation was achieved and the fivefold increase indicates this effect in addition to the flux corresponding to neat nitroglycerin. Two new potential penetration enhancers were also tested, the insect repellent 2-ethyl-1,3-hexanediol (EHD) and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidone (DPT). Both were also more effective than dimethyl sulfoxide.

Of all vehicle additives tested, oleic acid (9) showed the most dramatic effect on the permeability coefficient of nitroglycerin through hairless mouse skin. About a 30-fold increase in the permeability coefficient was observed when only 5% oleic acid was added to the propylene glycol vehicle, which is more than 10 times the increase that was observed when dimethyl sulfoxide was added to the vehicle. No further increase was observed upon further addition of oleic acid to the vehicle.

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Table I. The Effect of Vehicle Composition on Nitroglycerin Permeability Across Hairless Mouse Skin *in Vitro*

Vehicle composition (%, v/v)[a]						Cd	$P \pm SE \times 10^3$		
PG	Water	DPT	DMSO	EHD	OA	(M)[b]	(cm/hr)[c]	P/P_{PG}[d]	N[e]
100						0.22	0.22 ± 0.03	1.00	4
80	20					0.11	1.10 ± 0.15	5.00	4
90		10				0.22	0.78 ± 0.06	3.55	3
90			10			0.22	0.64 ± 0.15	2.91	3
40	20			40		0.11	0.75 ± 0.25	3.41	6
95					5	0.22	7.20 ± 1.78	32.7	6
90					10	0.22	6.12 ± 1.68	27.8	8
85					15	0.22	7.02 ± 0.68	31.9	3

[a] PG, propylene glycol; DPT, 1,3-dimethyl-3,4,5,6-tetrahydro-2 (1H)-pyrimidone; DMSO, dimethyl sulfoxide; EHD, 2-ethyl-1,3-hexanediol; OA, oleic acid.
[b] Initial concentration of nitroglycerin in the vehicle.
[c] Permeability coefficient (see Ref. 5).
[d] Permeability coefficient from the vehicle/permeability coefficient from propylene glycol.
[e] Number of experiments.

The irritation of oleic acid to human skin was also studied on six volunteers. No irritation could be detected when pure oleic acid or pure propylene glycol was applied to the skin under occlusion for 6 hr, only minor irritation was observed when 5% oleic acid in propylene glycol was applied, and severe irritation occurred when the concentration of oleic acid was increased to 20%. Oleic acid showed no irritation when mixed with 1-ethyl-1,3-hexanediol. Thus, the oleic acid irritation was dependent on the other vehicle additives used. The oleic acid did not seem to affect the excised hairless mouse skin, as after an initial lag time, linear plots were obtained in all cases, but with different slopes, corresponding to the increased flux.

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