ENHANCED FLURBIPROFEN PERMEATION THROUGH HUMAN SKIN: USE OF N-METHYL-2-PYRROLIDONE (NP), 2-PYRROLIDONE (2P) AND DIMETHYLISOSORBIDE (DS)

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NP enhances permeation of flurbiprofen (Akhter & Barry, 1985). Here we examine further the accelerant activity of NP, 2P and DS.

We simulated in vivo conditions using diffusion cells with donor chambers open to controlled conditions (22 ± 1°C; 60 ± 5% RH), while receptors contained physiological buffer (37 ± 0.5°C). In the first study radiolabelled flurbiprofen (approx 1 μCi cm^{-2}) was deposited as a film (4.8 mg cm^{-2}) by solvent evaporation (acetone solution, 50 μl) onto dermatomed skin in 4 diffusion cells. The cumulative penetration was monitored for 70h, representing absorption from acetone and then a drug film. NP (100 μl) was added to two cells and 2P to the remainder; permeation was monitored for 50h. Then 2P was added to the first two cells and NP to the second two; absorption was monitored up to 160h. In the second study flurbiprofen (0.4 mg cm^{-2}; 1.8 μCi cm^{-2}) was deposited as a film and monitored for 30h; DS (100 μl) was added and absorption studied to 180h. This experiment was repeated using NP instead of DS. Fig. 1 illustrates typical rate and cumulative penetration profiles of flurbiprofen from a film and the effect of 2P and NP. The initial acetone peak due is similar to that produced by 2P, but both are small compared to the NP peak. Table 1 summarises overall effects, using the acetone peaks as a control. Results indicate that 2P and DS are not marked penetration enhancers of flurbiprofen. However, NP does dramatically increase the flux. T_{max} (the time of maximum flux) is short for acetone and NP but long for DS, although the solubilities are similar. This is because acetone and NP evaporate or pass through the skin quickly (2 min for acetone; 2-4h for NP) but DS remains on the surface longer, providing a depot from which drug partitioning into skin is unfavourable until the DS eventually permeates. This observation suggests that to exert an accelerant effect NP alters the skin structure as it passes through - DS does not appear to do so. Hence DS may be used as a vehicle when an accelerant effect is unwanted, e.g. as a control when evaluating enhancers.

Table 1 Flurbiprofen penetration; data expressed as maximal rate (J, μg $cm^{-2}h^{-1}$), the rate ratio (J*) relative to acetone and T_{max} - the time (h) of J.

	Study 1		Study 2		
Treatment	J	J*	J	J*	T_{max}
Acetone	9.0	1.0	1.0	1.0	9.5
2P	6.6	0.73	-	-	-
DS	-	-	1.7	1.7	133
NP	41	4.5	17	17	13

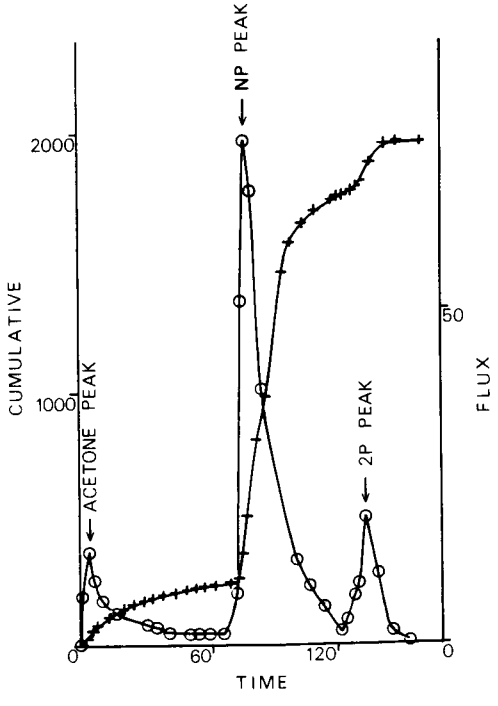

Fig. 1. Typical cumulative (+) and rate (O) profiles for flurbiprofen.

Akhter, S.A. & Barry, B.W. J. Pharm. Pharmacol. (1985) 37, 27-37.