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Optimization of bioavailability of topical steroids: non-occluded penetration enhancers under thermodynamic control

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The non-occluded vasoconstrictor test under thermodynamic control assessed the effect of penetration enhancers on the topical bioavailability of a model steroid betamethasone 17-benzoate, using aqueous dimethylisosorbide (DMI) as a standard solvent. The aqueous potential penetration enhancers used were at 10% steroid saturation i.e. ideally at identical steroid thermodynamic activity. In the vasoconstrictor test, 2-pyrrolidone, *N*-methyl-2-pyrrolidone, propylene glycol with oleic acid, propylene glycol with azone and dimethylformamide (DMF) increased the steroid bioavailability compared with that from DMI, while propylene glycol alone produced borderline improvement. Azone and oleic acid in combination with DMI or Betnovate cream did not increase the steroid bioavailability indicating the importance of the correct cosolvent. The pyrrolidones established superior stratum corneum reservoirs compared with DMI, the other vehicles being similar to DMI. It was concluded that excepting DMI, the solvents tested were penetration enhancers for the model steroid betamethasone 17-benzoate and are worthy of further study. However, irritant effects may make some of them unacceptable for clinical use.

We have previously investigated techniques for optimizing the bioavailability of topical drugs by employing a thermodynamic approach and by monitoring the effect of penetration enhancers under occlusion using a model steroid, betamethasone 17-benzoate (Woodford & Barry 1982; Barry et al 1984). The thermodynamic approach involves formulating the vehicle in such a way that the drug has maximum tendency to leave the base and partition into the skin; thus the vehicle design promotes drug release by optimizing the thermodynamic activity of the medicament. The alternative tactic is to incorporate penetration enhancers in the formulation, i.e. molecules which enter the stratum corneum and decrease its resistance to drug penetration in a dynamic and reversible fashion. This study extends the work and uses penetration enhancers under thermodynamic control, thus combining the previous two strategies. We also employ a non-occluded vasoconstrictor test instead of an occluded assay to prevent masking of any enhancement by skin hydration. The possible penetration enhancers selected were: two pyrrolidones (2-pyrrolidone and *N*-methyl-2-pyrrolidone); an aprotic solvent (dimethylformamide); propylene glycol (a widely used solvent in topical formulations); azone and oleic acid (two compounds recently investigated as penetration enhancers) (Stoughton 1982a, b; Stoughton & McClure 1983; Cooper 1984). Dimethylisosorbide, a solvent already shown not to be a penetration enhancer (Akhter et al 1982; Akhter & Barry 1984), was included as a baseline vehicle with which to compare the other solutions.

This study therefore investigates the changes in the vasoconstrictor activity and thus the bioavailability of an anti-inflammatory steroid, betamethasone 17-benzoate, when dissolved in aqueous solutions of possible penetration enhancers, using a non-occluded vasoconstrictor (v.c.) test (Barry & Woodford 1978; Barry 1976; Bennett & Barry 1984).

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MATERIALS AND METHODS

The test solutions contained betamethasone 17-benzoate (B17B) at 10% saturation in vehicles containing: 2-pyrrolidone, *N*-methyl-2-pyrrolidone, dimethylformamide (DMF), propylene glycol—source BDH Chemicals, dimethylisosorbide (DMI)—Atlas, oleic acid—Sigma Chemical Company, azone—Nelson Fine Chemicals. All the vehicles were thickened with Carbopol 940—BF Goodrich Chemical Company—at the concentrations listed in Table 1. Betnovate cream (betamethasone 17-valerate 0·1%, Glaxo) was used as a standard preparation to control the v.c. assay; additional Betnovate cream samples incorporated azone and oleic acid. A second sample of Betnovate

Table 1. Composition of aqueous test samples and creams.

Preparation	Solvent (% w/v)	C (% w/v)	A (% v/v)	OA (% v/v)	B17B (% w/v)
Solutions					
2P	70 2P	0·15	—	—	0·50
NMP	70 NMP	0·30	—	—	0·15
DMF	70 DMF	0·35	—	—	0·03
DMI	70 DMI	0·35	—	—	0·07
DMI + A	70 DMI	0·35	2·5	—	0·07
DMI + OA	70 DMI	0·35	—	1·5	0·07
PG	90 PG	0·25	—	—	0·08
PG + A	90 PG	0·25	2·0	—	0·08
PG + OA	90 PG	0·25	—	5·0	0·08
Creams					
BC	BC[a]	—	—	—	—
BC + A	BC[a]	—	2·0	—	—
BC + OA	BC[a]	—	—	5·0	—

[a] Commercial formulation.
2P = 2-Pyrrolidone; NMP = *N*-methyl-2-pyrrolidone; DMF = dimethyl formamide; A = azone; OA = oleic acid; BC = Betnovate cream; B17B = Betamethasone-17-benzoate; C = Carbopol 940; DMI = dimethylisosorbide; PG = propylene glycol.

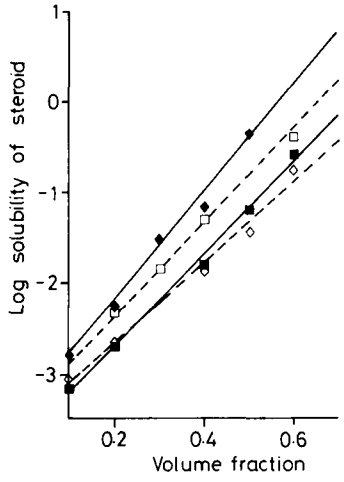

FIG. 1. Solubility of betamethasone 17-benzoate in aqueous solvent mixtures at 25 °C. Solvents: 2-pyrrolidone (◆, 2P); *N*-methyl-2-pyrrolidone (□, NMP); dimethylisosorbide (■, DMI); dimethylformamide (◇, DMF).

cream* was used to check the reproducibility of results.

Miscibility determinations

The miscibility of azone and oleic acid with 70% aqueous DMI and 90% aqueous propylene glycol was determined by titration and maximum values used so that both were at maximum thermodynamic activity (i.e. saturation) in the vehicles.

Solubility of betamethasone 17-benzoate

Aqueous vehicles containing 10–60% v/v 2-pyrrolidone, methyl pyrrolidone, DMF or DMI, thickened with Carbopol 940 were equilibrated at 25 °C; propylene glycol at 80% alone and at 90% plus 5% oleic acid were treated similarly. Excess B17B was added to the above solutions and also to pure oleic acid and azone. All solutions were equilibrated at 25 °C for 14 days in a Grant 3530 shaking water bath. Samples were centrifuged at 25 °C and B17B concentration in supernatant layer determined by HPLC (Pye Unicam LC-XPD), column: 250 × 4·6 mm Partisil 10 μm-ODS, mobile phase: 55% v/v acetonitrile: water, flow rate: 2 ml min^{-1}, detector: LC-UV at 234 nm, sample size 20 μl. The slight solubility of the steroid (0·05% w/v) in oleic acid and azone was neglected when preparing solutions containing them. The solubility of the steroid in 70% vehicle mixtures was then determined by extrapolation of a log linear plot of solubility against vehicle composition as shown in Fig. 1. Ten per cent saturated solutions were used in the v.c. test as shown in Table 1 and it was assumed that the steroid in these solutions would be at the same thermodynamic activity; for this to be valid, we must assume that the steroid activity coefficient in each solvent was the same and changed in the same way on dilution. Although this is unlikely to be strictly true, it provides an acceptable starting point for our test, bearing in mind that the composition of the solutions will change after application to the skin, as components penetrate the stratum corneum, evaporate and skin secretions enter the vehicle.

Stability of betamethasone 17-benzoate in vehicles

Test solutions were assayed before and after the v.c. study by thin layer chromatography (0·2 mm silica gel 60 F_{254}) using benzene–methanol–acetone, 75 : 4 : 25. Under shortwave uv light (254 nm), B17B was seen as a purple spot on a green background R_F 0·36 while betamethasone and betamethasone 21-benzoate were seen as grey spots R_F of 0·21 and 0·44 respectively. The presence of B17B in DMI could not be determined by this method because of an apparent interaction, so these samples were analysed by high performance liquid chromatography using ethylacetate–chloroform–methanol, 71 : 28 : 1, silica column, uv detector: 260 nm, flow rate 1 ml min^{-1}. There was no appreciable change in the composition of the solutions assayed after the study compared with freshly prepared solutions, so decomposition was assumed to be negligible.

Assessment of irritancy of vehicles

The ventral forearms of a panel of 5 male and 6 female volunteers (22–25 years) who were *not*

members of the v.c. panel were used to assess the irritancy of the vehicles. Ten μl of each vehicle was rubbed into an area 0·6 cm^2 (delineated with a template and silicone grease) using a glass rod.

Methylpyrrolidone, DMF, propylene glycol, DMI and the preparations containing azone and oleic acid produced erythema to varying degrees which generally subsided within 6 h. Two females with fair skins had more severe reactions which lasted longer than 6 h. 2-Pyrrolidone produced erythema in most volunteers which lasted longer than 6 h; the initial pallor associated with 2-pyrrolidone in the v.c. study may have been partially masked by this erythema and some erythema occurred with this solution during the actual v.c. assay. However, errors produced in the blanching results would be slight.

Non-occluded vasoconstrictor assay

The 10 caucasian volunteers (4 male and 6 female) had not received topical steroid application for at least 2 months. Five μl of each of the test solutions (which produced no placebo blanching), or 5 mg of each of the creams, was applied to a site on the washed flexor surface of each forearm. The application sites were 7 × 7 mm areas punched from Blenderm tape, to which formulations were applied using a random design. The tape was then removed and a perforated plastic screen, held in place by a self-adhesive bandage, was used to protect the sites for 6 h. The screen was removed and the areas washed with soap and water at body temperature and dried. Readings were taken double-blind after 10 min and after 1, 2, 3, 6, 18, 26, 42, 66, 74 and 90 h to provide data points for skin blanching at 6, 7, 8, 9, 12, 24, 32, 48, 72, 80 and 96 h after application.

Assessment was made according to a 0–4 scale with half-point ratings for intermediate readings: 0 = normal skin, 1 = slight vasoconstriction of indistinct outline, 2 = more intense vasoconstriction, 3 = general even vasoconstriction with a clear outline of the square and 4 = more marked vasoconstriction with very distinct blanching.

The 10 volunteers provided a total of 260 application sites: 13 sites per forearm for each volunteer. The total possible score for each preparation was 4 per site, i.e. 8 per volunteer (1 site on each forearm) if, at any single time, *all* the sites for a particular preparation scored 4 on the above scale, the maximum score would be 80 for the 10 volunteers. Results were expressed as 'percent of total possible score' achieved at each time so 80 is equal to 100%.

To assess the retention of steroid in the skin, the sites were occluded twice with type S12 μm Melinex film for 6 h in all 10 volunteers at 120 and 216 h after commencement of the experiment. Blanching was estimated at set times after occlusion finished: 2, 5, 7, 18, 24, 31, 42 and 54 h for the first occlusion and at 2, 5, 7 and 18 h for the second occlusion. In two volunteers the sites were occluded a third time 288 h after the commencement of the experiment and scored at 2, 5 and 7 h.

The data were submitted to an analysis of variance, which is used to compare more than 2 sample means (Goldstein 1964).

A computer program analysed the data without transformation or in 1 of 5 (x^{-1}, $x^{-\frac{1}{2}}$, log x, $x^{\frac{1}{2}}$ and x^2) transformations (Tukey 1957). Test for non-additivity (Harter & Lum 1962) indicated that all non-additivity T values were low, suggesting that selection of transformation is not important. The square root transformation was therefore used as this had been employed previously. The analysis of variance was calculated using these values.

Calculation of the minimum significance range by using the Studentized range test (Goldstein 1964) permitted comparison of the corticosteroid formulations. If the Tm/10 (square root transformation of sum of scores divided by number of volunteers) mean values of two preparations (see Table 3) differ by more than the minimum significance range value, k, there is a significant difference at the 5% level between these formulations.

RESULTS AND DISCUSSION

Fig. 1 shows a linear relation between log solubility of steroid and volume fraction of solvent in water, thus allowing extrapolation of the line to give a solubility value for 70% cosolvent. Plots of log solubility vs cosolvent composition have been found by several workers to be linear for many systems (e.g. Poulsen et al 1968; Yalkowsky et al 1976). Martin et al (1982) concluded that the log-linear solubility relation gives a good linear fit for semi-polar drugs in a number of water-cosolvent mixtures. As B17B is polar, but with substantial hydrophobic areas, it would be expected to comply with this relation. This was confirmed. The equations of the lines in Fig. 1 and correlation coefficients are shown in Table 2 illustrating that good correlation exists for all solvents. Yalkowsky & Roseman (1981) have shown that by defining the solubilizing power of the cosolvent for the solute as σ, the log solubility (log Sm) may be related to the volume fraction of solvent (fc) by:

$$\log Sm = \log Sw + \sigma fc$$

Table 2. Equations for lines of log solubility (log Sm) of betamethasone 17-benzoate vs. volume fraction of co-solvent (fc) in water.

Cosolvent*	Equation of line	Correlation coefficient
2P	log Sm = 5·75 fc − 3·33	0·992
NMP	log Sm = 5·18 fc − 3·44	0·996
DMF	log Sm = 4·39 fc − 3·54	0·994
DMI	log Sm = 5·04 fc − 3·71	0·995

* See Table 1 for definitions.

where Sw is the aqueous solubility of the solute. Personal communication with Warner Lambert has shown that the aqueous solubility of B17B is about 5 μg ml^{-1} (0·0005% w/v) at 22 °C although problems were experienced in determining it due to the low solubility. Using the above equation the aqueous solubility can be calculated from the intercept on the linear axis and was found to be $3·29 \times 10^{-4} \pm 1·16 \times 10^{-4}$% w/v. Bearing in mind the problems in determining the solubility at this solubility level, the agreement is good.

Fig. 2 shows example blanching curves for the steroid solutions; data are plotted as percent total possible score vs time. The experimental points are mean values of 10 volunteers with error bars showing the standard error of the mean. Fig. 2A illustrates the initial blanching curve and Fig. 2B the first two occlusion periods. No further blanching was seen with any preparation after the third occlusion. As with other studies (Barry & Woodford 1978; Woodford & Barry 1982; Barry et al 1984) 3 parameters were used to compare the bioavailability of the steroid from various vehicles: the area under the blanching curve (AUC) as measured by a planimeter; the summed percent total possible score (S% TPS); and the square root transformation of the sum of scores divided by the number of volunteers (Tm/10). The results are shown in Table 3.

From Table 3 it can be seen that the values obtained for the coded Betnovate cream and that incorporated in the study as a control were similar, indicating the reproducibility of the visual method of assessment, as has also been illustrated by Barry & Woodford (1978) using the occluded v.c. test.

The ranking of the solutions and creams, in this study, was similarly based on either AUC or S% TPS values. The comparative bioavailability assessments were approximately the same by either of the two methods used (Table 4). DMI, a solvent promoted for use in topical formulations was chosen as the standard solution vehicle as it is relatively poorly absorbed and does not appear to be a penetration

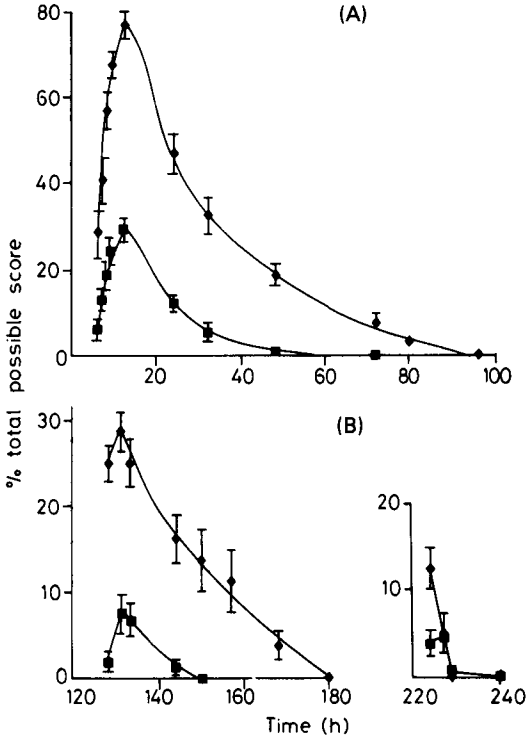

FIG. 2. Examples of blanching curves (percent total possible score vs time) for betamethasone 17-benzoate in 70% aqueous 2-pyrrolidone (◆, 2P) and 70% aqueous dimethyl-isosorbide (■, DMI). The curves are drawn from the mean responses for duplicate application to the arms of 10 volunteers with the standard error of the mean being shown by the error bars. A, Initial application at 0 h; B, Reocclusion, to demonstrate reservoir effect, at 120 and 216 h.

enhancer in in-vitro experiments. Using this standard it can be seen that in the initial assessment 2-pyrrolidone, methylpyrrolidone, propylene glycol with oleic acid or azone and DMF produced more active solutions than DMI ($P = 0·05$), while propylene glycol was on the borderline of improvement. Incorporation of oleic acid or azone in DMI produced no increase in the activity of the solution as is illustrated in Fig. 3A. Although the addition of azone or oleic acid to DMI or Betnovate cream produced no significant improvement in the bioavailability of the steroid ($P = 0·05$), the addition of either to propylene glycol produced a more active preparation compared with incorporating the same amount of steroid in propylene glycol alone. This suggests that there is a synergistic action between azone or oleic acid and propylene glycol and that the correct choice of cosolvent to be used with either azone or oleic acid is important. The cosolvent may

Table 3. Blanching responses to betamethasone 17-benzoate solutions and betamethasone 17-valerate creams in rank order of area under curve values.[a]

	Initial			First occlusion			Second occlusion
Preparations[b]	AUC[c] (S% TPS × h)	S% TPS[d]	Tm/10[e]	AUC[c] (S% TPS × h)	S% TPS[d]	Tm/10[e]	S% TPS[d]
2P	2170	379	5·49	636	124	3·08	17·5
NMP	1790	363	5·37	339	80·0	2·45	24·4
PG + OA	1140	228	4·21	108	23·1	1·11	6·3
BC + OA	1090	221	4·18	53·0	17·5	0·93	0·0
PG + A	1090	216	4·12	57·0	20·6	1·19	8·1
BC*[f]	1040	204	4·01	20·0	7·5	0·52	2·5
DMF	1030	215	4·10	90·5	31·3	1·53	5·0
BC[f]	1030	199	3·96	19·5	5·6	0·40	5·6
BC + A	973	216	4·13	79·5	20·0	1·14	5·0
PG	788	158	3·46	115	28·8	1·40	0·0
DMI + OA	505	102	2·79	110	25·0	1·33	3·8
DMI	493	111	2·92	64·5	16·3	0·93	6·9
DMI + A	445	92·5	2·63	36·3	11·3	0·71	1·9

[a] Data quoted to three significant figures.
[b] For exact compositions see Table 1.
[c] Area under the curve obtained by planimetry of the blanching profile.
[d] The percentage of the total possible scores summed for all volunteers over all reading times.
[e] The square root transformation of the sum of scores (Tm) divided by the number of volunteers (10). The minimum significance range value is k ($P = 0·05$) i.e. if the Tm/10 values of 2 preparations differ by more than k there is a significant difference between the preparations. Initial blanching k = 0·55, first occlusion blanching k = 0·73.
[f] BC*, Betnovate cream, control preparation. BC, Betnovate cream, coded in the study.

have a role to play in ensuring that enhancer molecules reach their site of action in the stratum corneum.

The addition of azone or oleic acid to Betnovate cream may change the characteristics of the complex formulation. However, Stoughton (1981) has shown that incorporating azone in Topsyn gel or Lidex cream produced increased vasoconstriction for fluocinonide although no enhancement effect was seen with fluocinolone in Synalar cream. Therefore azone and oleic acid were incorporated in Betnovate cream; no enhancement was seen in the initial assessment and only a non-significant increase in vasoconstriction following the first occlusion ($P = 0·05$).

The rank order of the solutions changed slightly on occlusion. This effect may have been because of the low v.c. values recorded and therefore the larger errors, especially if all the material had not been removed from the skin during the washing process. The first occlusion data show that 2-pyrrolidone and methylpyrrolidone established superior reservoirs compared with the other solutions used in this study ($P = 0·05$).

For the second occlusion period (9 days after the start of the experiment), although all volunteers showed some blanching with both pyrrolidone solutions, responses to the remaining preparations were so variable that statistical analysis was inappropriate (although S% TPS values are listed in Table 3). Although AUC values provided a similar ranking they are not reported as they were derived from curves with only 2 or 3 data points. For these reasons we did not assess the comparative bioavailability, but the trend was still apparent whereby both pyrrolidone solutions were particularly potent.

In Fig. 3 the comparative bioavailability derived for the solvents used in this investigation are compared with those obtained in a previous *occluded* study (Barry et al 1984) in which all preparations contained 0·1% B17B in 100% potential penetration enhancer. No attempt was made then to correct for the differing thermodynamic activity of the various solutions and only methylpyrrolidone increased the steroid bioavailability. As the solubility of B17B is much lower in DMI than in methyl- and especially 2-pyrrolidone (Table 1), the DMI solution used in the previous occlusion study was of much higher thermodynamic activity than either pyrrolidone solution. This difference in thermodynamic activity may explain why in the earlier occluded study the enhancement effect seen with methylpyrrolidone was only moderate and the effect was negligible with 2-pyrrolidone. It was surprising that no significant enhancement was seen with DMF in the previous study, as according to the present solubility data that solution should have been more active than, or at least of a similar activity to, the standard DMI

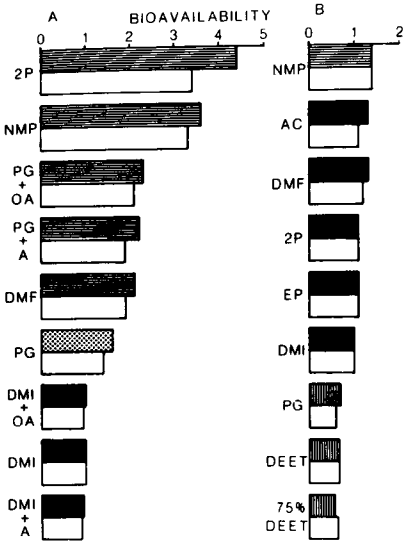

FIG. 3. Initial comparative bioavailability assessments for various solvents used in the vasoconstrictor study. Top, shaded, bar in each pair determined by area under the curve and lower, unshaded, bar by summed percent total possible score, see Table III. Shading: horizontal lines—better than standard (DMI); dots—borderline improvement; block—same as standard; vertical lines—poorer than standard (P = 0·05). A, Present non-occluded study. B, Previous occluded study (Barry et al 1984). Solvents: A, see materials and methods. B, 100% solvent: NMP = *N*-methyl-2-pyrrolidone; AC = Acetone; DMF = dimethylformamide; 2P = 2-pyrrolidone; EP = 1-ethyl-2-pyrrolidone; DMI = dimethylisosorbide; PG = propylene glycol; DEET = diethyl-*m*-toluamide; 75% DEET = 75% diethyl-*m*-toluamide in ethanol.

solution. As DMF is a known penetration enhancer and DMI has been shown not to be a penetration enhancer in in-vitro experiments, we would have expected to have seen much greater steroid penetration with DMF. In the present trial, enhancement was seen with a solution containing DMF. It was concluded previously that possible penetration enhancement effects may have been obscured by the marked effect of occlusive hydration, a view supported by Stoughton (1972). Therefore in the current study, as well as controlling the thermodynamic activity of the solutions (thus making release characteristics of all vehicles the same) the non-occluded v.c. test was used, so that any increase in blanching was not masked by hydration effects.

Looking at the specific solvents used in this study, it would appear that both pyrrolidones and DMF and the cosolvent combinations propylene glycol with azone or oleic acid are all penetration enhancers. Propylene glycol alone has borderline enhancement properties which may explain the conflicting views which exist on whether or not it is a penetration enhancer (e.g. Barrett et al 1965; Feldmann & Maibach 1966; Busse et al 1969). 2-Pyrrolidone and methylpyrrolidone have been reported as penetration enhancers (Stoughton 1976b, 1977; Resh & Stoughton 1976; Southwell & Barry 1983) and showed marked effects in this study, increasing the bioavailability of the steroid 3 or 4 fold. They also provided a high degree of steroid epidermal retention which confirms the observations of Stoughton (1976b, 1977; Resh & Stoughton 1976) with griseofulvin. The penetration enhancement effect of DMF is established (Munro & Stoughton 1965; Baker 1968; Southwell & Barry 1983) and was observed in this study, although the enhancement was to a lesser degree than with the pyrrolidones. The effects of azone and oleic acid, two new penetration enhancers (Cooper 1984; Stoughton 1982a, b; Stoughton & McClure 1983) were interesting as they were only effective in combination with propylene glycol and not with DMI or Betnovate cream. The importance of the correct choice of vehicle with azone or oleic acid has been observed by others (Stoughton & McClure 1983; Cooper 1984).

Table 4. Blanching responses to (a) betamethasone 17-benzoate solutions and (b) betamethasone 17-valerate creams in rank order of area under curve values expressed in terms of bioavailability.

	Initial bioavailability[a]		First occlusion bioavailability[a]	
Preparations	(i)	(ii)	(i)	(ii)
Solutions				
2P	4·4	3·4	9·9	7·6
NMP	3·6	3·3	5·3	4·9
PG + OA	2·3	2·1	1·7	1·4
PG + A	2·2	1·9	0·88	1·3
DMF	2·1	1·9	1·4	1·9
PG	1·6	1·4	1·8	1·8
DMI + OA	1·0	0·92	1·7	1·5
DMI	1·0	1·0	1·0	1·0
DMI + A	0·90	0·83	0·56	0·69
Creams				
BC + OA	1·0	1·1	2·7	2·3
BC*[b]	1·0	1·0	1·0	1·0
BC[b]	0·99	0·98	0·98	0·75
BC + A	0·94	1·1	4·0	2·7

[a] For steroid solutions, defined by relations:

(i) $\frac{\text{area under the curve for steroid solution}}{\text{area under the curve for steroid in DMI.}}$

(ii) $\frac{\text{summed \% total possible score for steroid solution}}{\text{summed \% total possible score for steroid in DMI.}}$

For betamethasone 17-valerate creams, similar relations apply but with the denominator being the control Betnovate cream.

[b] BC*, Betnovate cream, control preparation. BC, Betnovate cream, coded in the study.

This study has illustrated that more solvents than previously reported 2- and *N*-methyl-2-pyrrolidone, propylene glycol with azone or oleic acid and DMF, show penetration enhancement effects under optimum conditions as indicated by the v.c. test. As to the possible clinical benefits, Stoughton (1976a) reported five investigations in which two steroid preparations were compared for vasoconstriction and clinical performance in psoriasis and showed close correlation in all studies. Although it is difficult to prove conclusively that a correlation exists between the clinical efficacy of a topical steroid and its v.c. activity, it is widely accepted that a well-controlled v.c. test gives a good guideline as to how active a preparation will be in dermatological use (Place & Burdick 1970; Poulsen & Rorsman 1980; Schaefer et al 1982; Barry 1983).

This study therefore indicates that 2- and *N*-methyl-2-pyrrolidone, propylene glycol with azone or oleic acid and DMF are all penetration enhancers for the model steroid B17B and are worthy of further study. However, irritant effects may make some of them unacceptable for clinical use.

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