International Journal of Pharmaceutics, 22 (1984) 31–43
Elsevier

IJP 00737

The influence of vehicles on the local bioavailability of betamethasone-17-benzoate from solution- and suspension-type ointments

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(Received February 1st, 1984)
(Modified version received June 5th, 1984)
(Accepted June 14th, 1984)

Summary

The relative bioavailability of betamethasone-17-benzoate from solution- and suspension-type ointments was evaluated on intact skin by the shift of the dose–response curves on their concentration axis. The penetration rate through the skin barrier (horny layer) after application of a solution-type ointment depends primarily on the affinity of the drug to the vehicle. A high solution capacity of the vehicle for the drug (i.e. a small partition coefficient between the skin barrier and the vehicle), leads to a low bioavailability. The penetration rate through the skin barrier from solution-type ointments with the same vehicle composition increases proportionally to the concentration of dissolved and diffusible drug, and reaches its maximum value when the concentration is equal to the solubility of the drug in the vehicle. The penetration rate from the suspension-type ointments is independent of the drug's solubility. Increasing the solubility by modifying the ointment base does not further increase the bioavailability. The amount of suspended drug also has no influence on the intensity of the action as long as the drug release is fast enough. However, the amount of drug needed for the same action differs according to the drug's solubility in the vehicle.

Introduction

The most important condition for the successful therapeutic application of a drug preparation is the bioavailability of the effective substance at its site of action. This

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also applies to topical preparations. To achieve a local or systemic effect the drug must be released from the vehicle and subsequently penetrate the horny layer which is the main barrier against transport through intact skin. Thereby the penetration generally is the rate-limiting step for percutaneous absorption.

Kinetic considerations of the transport process differentiate between solution- and suspension-type ointments (Poulsen, 1972; Lippold, 1981). The penetration rate in vivo after application of a solution-type ointment can be expressed as follows (sink conditions, steady state):

$$-\frac{dc_V}{dt} = \frac{D_B F f_B c_{sB}}{V_V d f_V c_{sV}} f_V c_V = k_p f_V c_V \qquad (1)$$

with

$$f_B c_B / f_V c_V = f_B c_{sB} / f_V c_{sV} = P$$

Accordingly, for a solution-type ointment (sink conditions, quasi-steady-state) holds:

$$-\frac{dc_V}{dt} = \frac{D_B F f_B c_{sB}}{V_V d f_V c_{sV}} f_V c_{sV} = k_p f_V c_{sV} = \text{const.} \qquad (2)$$

where $-dc_V/dt$ is the rate of decrease of drug concentration in the vehicle, D_B is the effective diffusion coefficient in the skin barrier, F is the application area, f_B and f_V are the fractions of drug unbound (free, diffusible) in the skin barrier and the vehicle, respectively, c_{sB} and c_{sV} are the solubilities of the drug in the skin barrier and the vehicle, respectively, c_B and c_V are the concentrations of drug dissolved in the

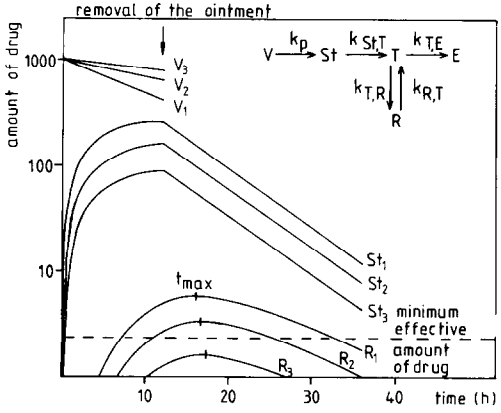

Fig. 1. Simulated levels of the amount of drug at the site of action (R), in the stratum corneum (St) (horny layer) and in the vehicle (V) as a function of time with different penetration rate constants k_p. The ointments are removed after temporary application. The applied dose is constant. All rate constants are first-order. Key: T = drug in the tissue compartment; E = drug in the elimination compartment; t_{max} = time of peak amount.

barrier and in the vehicle, k_p is the penetration rate constant, V_V is the volume of the applied vehicle, d is the thickness of the skin barrier and P is the partition coefficient of the drug between the skin barrier and the vehicle.

It is therefore expected that the application of a solution-type ointment in contrast to a suspension-type ointment reveals a marked vehicle effect on the penetration rate. To study these vehicle effects on percutaneous absorption we used betamethasone-17-benzoate because of its measurable pharmacodynamic effect, causing a blanching response.

From analog-computer simulations, based on a pharmacokinetic model that takes into account the stratum corneum reservoir of the drug, one can expect that differences in the bioavailability caused by the vehicle result in a different action (see Fig. 1). Hereby the following compartments and relevant rate constants are used according to the biological model of Fig. 1: V = vehicle, St = stratum corneum, T = tissue (e.g. viable epidermis, corium), R = site of action (e.g. receptors), E = elimination compartment; $k_{St,T} = 0.126\ h^{-1}$, $k_{T,R} = 0.03\ h^{-1}$, $k_{R,T} = 0.107\ h^{-1}$, $k_{T,E} = 0.99\ h^{-1}$, $k_p = 0.071\ h^{-1}$, $0.035\ h^{-1}$ and $0.017\ h^{-1}$, respectively, for the curves with the subscript 1, 2 and 3, respectively.

As long as there is only an insignificant decrease of the drug concentration in the corticosteroid preparation during the application time and as a long as the percutaneous absorption can be regarded as approximately constant with time, the maximum drug amount at the site of action R_{max} changes practically proportional to k_p. But if the drug concentration in the ointment decreases considerably during the time of application as with low dosed preparations, the process of drug uptake must be taken as first-order (Eqn. 1). Then R_{max} does not increase proportionally with k_p but more slowly. With an unchanged penetration rate constant, R_{max} behaves proportionally to the applied concentration, too.

Materials and Methods

Materials

The materials for the preparation of the ointments were neutral oil (liquid triglycerides) [2], mineral oil [2], oleyl alcohol [3], high melting paraffin [4], white petrolatum [2], colloidal silicon dioxide [2], cetyl alcohol [5], polyethylene 10,000 [6] and betamethasone-17-benzoate [7]. Blenderm double-sided adhesive polyethylene tape [8] and Melinex film [9] were used for the occlusive dressings.

[2] DAB 8.
[3] Henkel-Dehydag, Duesseldorf, F.R.G.
[4] Lunacera M, H.B. Fuller GmbH, Lueneburg, F.R.G.
[5] DAC.
[6] BASF Ludwigshafen, F.R.G.
[7] Goedecke AG, Freiburg, F.R.G.
[8] 3M Deutschland, Neuss, F.R.G.
[9] ICI Plastics Division, Welwyn Garden City, U.K.

Preparation of the ointments

Table 1 shows the composition of the neutral oil/paraffin and oleyl alcohol/paraffin vehicles and Table 2 that of the paraffin vehicles. The vehicles in Table 1 were prepared by heating the fluid and solid phase until fusion (125 °C) followed by appropriate stirring [10] under reduced pressure and water cooling until the vehicle reached about 60 °C. Gel formation occurred at about 100 °C. After cooling to room temperature the relatively solid mass was homogenized and thereby made spreadable by a single pass through a roller mill.

The components of the paraffin vehicles were heated up to fusion and subsequently manually stirred until room temperature was reached. The micronized betamethasone-17-benzoate was incorporated into the vehicle at room temperature and the preparations were stored at 30 °C at least four weeks prior to use.

Solubility of the drug in the vehicles

The solubility of the betamethasone-17-benzoate in the vehicles (see Table 3) was determined by the partition coefficient of the drug between a thin layer of the vehicles as the acceptor and an ethylene glycol/water mixture as the donator phase (Lippold, 1981):

$$c_{sV} = \frac{Pf_D c_{sD}}{f_V} \tag{3}$$

TABLE 1

COMPOSITION OF THE NEUTRAL OIL/PARAFFIN VEHICLES AND THE OLEYL ALCOHOL/PARAFFIN VEHICLE

Vehicle	Portion fluid phase (w/w)		
	neutral oil	mineral oil	oleyl alcohol
V 10/90	10	90	–
V 20/80	20	80	–
V 40/60	40	60	–
V 60/40	60	40	–
V 85/15	85	15	–
V Oly	–	30	70

Gel matrix: 10% (w/w) polyethylene 10,000

TABLE 2

COMPOSITION OF THE PARAFFIN VEHICLES (w/w)

Vehicle	Mineral oil	High melting paraffin	White petrolatum	Cetyl-alcohol	Colloidal silicon dioxide
V TmK	68	10	16	3	3
V To2	68	10	16	3	–

[10] Homogenisator Multi-Homo, Brogli and Co., Allschwill, Switzerland.

TABLE 3

SOLUBILITY OF BETAMETHASONE-17-BENZOATE IN THE NEUTRAL OIL/PARAFFIN, THE OLEYL ALCOHOL/PARAFFIN AND THE PARAFFIN VEHICLES (30 ± 1°C)

Vehicles	Solubility (mg/100 g) (means ± range, n = 2)	
V 10/90	2.8 ± 0.7	
V 20/80	7.7 ± 0.3	
V 40/60	29.1 ± 2.8	
V 60/40	59 ± 1	
V 85/15 (extrapolated)	150	
V Oly	398 ± 2	
V To2	1.8	
V TmK	23.8	$f_V = 0.075$

where c_{sD} is the experimentally determined solubility of the drug in the donator phase and f_D, f_V are the fractions of drug unbound (free, diffusible) in the donor and acceptor phase, respectively. An additional dimethyl polysiloxan sheeting [11] for separating the two phases was only used for the paraffin vehicle V TmK. After adding a saturated betamethasone-17-benzoate solution with excess drug in this case, the drug concentration in the vehicle was determined at equilibrium. Starting from the assumption that the drug in all preparations except V TmK is present unbound ($f_V = 1$), the ratio c_{sVTo2}/c_{sVTmK} yields the factor f_V for V TmK with all sorption sites of the colloidal silicon dioxide in this preparation saturated.

In vivo testing

Twenty-three volunteers (12 female, 11 male, 19–31 years) were selected without reference to their steroid sensitivity. None had received corticosteroid treatment at least 6 weeks prior to the investigation. The volunteers were randomly divided into two groups. In the first group, with 18 volunteers, the neutral oil/paraffin ointments and V Oly (n = 10) were tested. In the second group with 7 volunteers the paraffin ointments and freshly produced preparations of the vehicle V 85/15 (= V 85/15, 2-trial) were investigated. 5.5 ± 0.5 mg of each preparation were applied on 7 × 7 mm squares of the forearm randomly and under double-blind conditions according to the standard vasoconstrictor test (Barry and Woodford, 1978), but with 12 h occlusion. The concentrations corresponding to the drug's solubility in the vehicle were applied 3–4 times on each volunteer. After removal of the ointments the blanching response was assessed visually by a single trained investigator on a 0–4 scale with half-point ratings (Barry and Woodford, 1978) under standard lighting conditions. Two light fittings (25 W tubes) on the left and right side of the arm and at a height of 55 cm were centered on an area corresponding to the forearms. The

[11] Silastic, Dow Corning, Medical Products Div., Midland, MI, U.S.A.

emitted light was defined by interference line filters [12] (λ_m [13] = 554 nm, T_{max} = 0.51, HW [14] = 12 nm). Under these lighting conditions unequal pigment formations were equalized and a more contrasted appearance of the blanching response was created, because of the skin showing a broad absorption peak at about 560 nm. Readings were taken 14, 16, 19 and 21 h after application. No placebo response was observed. The mean score of the preparation V 85/15, c_o = 150 mg/100 g at time of maximum blanching (= t_{max}) served as an internal standard (= B_{St}) and the scores of the test preparations (= B_T) were set in proportion to B_{St}.

Results and Discussion

Fig. 2 shows the mean blanching response as a function of time for various concentrations of betamethasone-17-benzoate in V 85/15. First reactions at the application sites are detectable immediately after removal of the occlusive dressings. Thereafter the intensity of blanching increases relatively steeply in the B_T/B_{St} versus time graph and reaches a peak response (= B_{max}) at about 21 h (= t_{max}) after application of the preparation.

Beyond 23 h the radial diffusion of the betamethasone-17-benzoate in the skin leads to an increasingly diffuse appearance of the blanching. About 40 h after the beginning of the experiment the blanching vanished. B_{max} of all preparations appears at the same time. Even among the preparations with low solubilities, from which the drug should be absorbed faster (Lippold, 1981), a theoretically expected shifting of t_{max} to shorter times is not detectable (see Fig. 1).

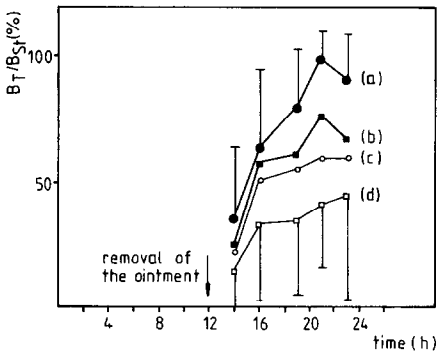

Fig. 2. Blanching–time relationship for various concentrations of betamethasone-17-benzoate in V 85/15. Key: (a) c_o = 150 mg/100 g (= internal standard); (b) c_o = 100 mg/100 g; (c) c_o = 60 mg/100 g; (d) c_o = 15 mg/100 g; (a) and (d) ± SDM as examples (n = 17–18 volunteers).

[12] Glaswerke Schott, Mainz, F.R.G.

[13] λ_m indicates the spectral position of the filter defined by the arithmetic mean of the wavelength measured by half-maximum transmission (= $T_{max}/2$).

[14] HW is the width of the transmission curve at $T_{max}/2$.

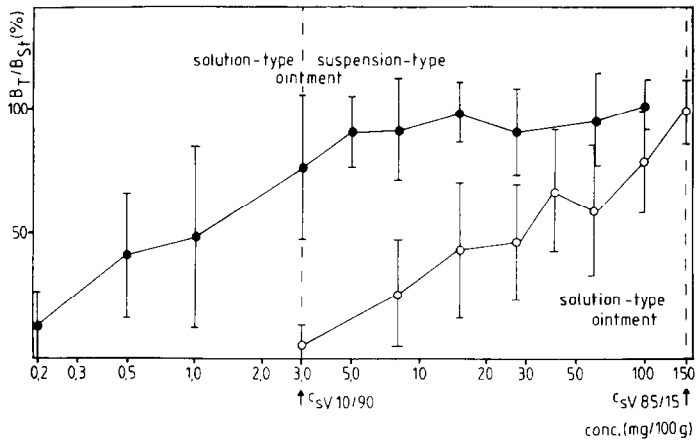

Fig. 3. Dose-response relationship of betamethasone-17-benzoate in V 85/15 (= internal standard) and V 10/90. Semi-logarithmic graph. Mean ± SDM (n = 17–18 volunteers). Key: ○, V 85/15, applied conc.: 3 (n = 9), 8, 15, 27, 40, 60, 100 and 150 mg/100 g; ●, V 10/90, applied conc.: 0.2 (n = 8), 0.5, 1, 3, 5, 8, 15, 27, 60 and 100 mg/100 g.

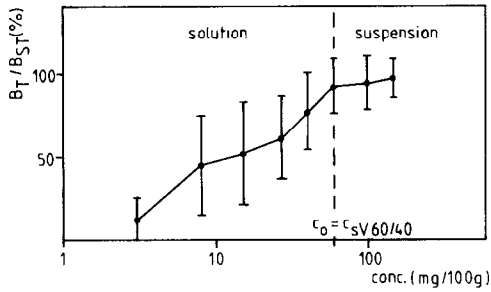

Fig. 4. Dose-response relationship of betamethasone-17-benzoate in V 60/40. Semi-logarithmic graph. Mean ± SDM (n = 17–18 volunteers). Applied conc.: 3, 8, 15, 27, 40, 60, 100 and 150 mg/100 g.

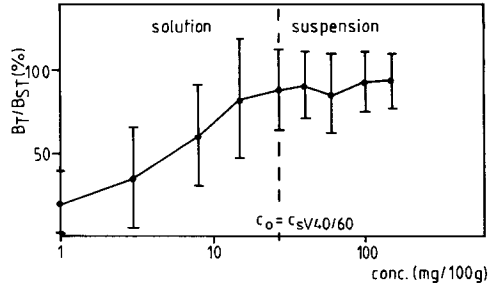

Fig. 5. Dose-response relationship of betamethasone-17-benzoate in V 40/60. Semi-logarithmic graph. Mean ± SDM (n = 17–18 volunteers). Applied conc.: 1, 3, 8, 27, 40, 60, 100 and 150 mg/100 g.

Determination of the relative, intensity-related bioavailability factor f_I

Figs. 3–6 show the dose–response relationships of the neutral oil/paraffin ointments and Fig. 7 those of the paraffin ointments and V 85/15, 2-trial. They are obtained with the ratio B_T/B_{St} at the time of peak response. Plotting B_T/B_{St} versus log concentration results in a practically linear relation for V 85/15 and V 85/15 2-trial. But these preparations include only solution-type ointments. The dose–response relationships of the other preparations can be divided into two segments: a segment with a nearly linear increase of action with increasing concentration for the solution-type ointments; and a segment with practically constant action for the suspension-type ointments.

With the knowledge of the dose–response relationships for the solution-type ointments, statements about the relative bioavailability of the betamethasone-17-benzoate from these preparations can be made. The horizontal distance log f_I of the dose–response relationships reflects the different penetration rates of the drug between the test and the standard in the case of the same extent of bioavailability

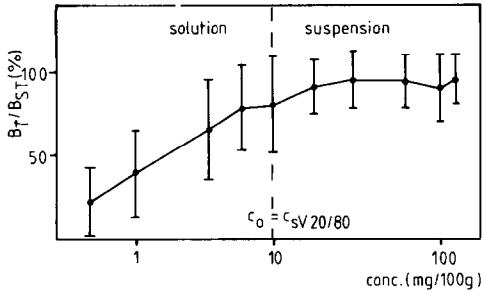

Fig. 6. Dose–response relationship of betamethasone-17-benzoate in V 20/80. Semi-logarithmic graph. Mean ± SDM (n = 17–18 volunteers). Applied conc.: 0.5, 1, 3, 5, 8, 15, 27, 60, 100 and 150 mg/100 g.

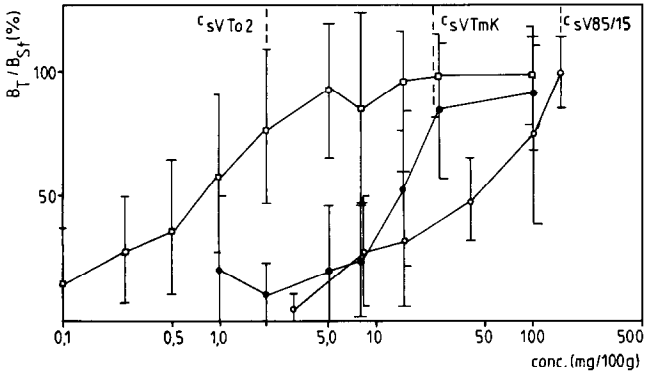

Fig. 7. Dose–response relationship of betamethasone-17-benzoate in V To2, V TmK and V 85/15 2-trial. Semi-logarithmic graph. Mean ± SDM (n = 6–7 volunteers) Key: □, V To2, applied conc.: 0.1, 0.25, 0.5, 1, 2, 5, 8, 15, 25 and 100 mg/100 g; ●, V TmK, applied conc.: 1, 2, 5, 8, 15, 25 and 100 mg/100 g; ○, V 85/15 2-trial, applied conc.: 3, 8, 15, 40, 100 and 150 mg/100 g.

(Lippold and Teubner, 1981). To evaluate $\log f_I$ of betamethasone-17-benzoate (Eqn. 4) V 85/15 serves as a standard ($f_I = 1$).

$$\log f_I = \bar{x}_{St} - \bar{x}_T - \frac{\bar{B}_{St} - \bar{B}_T}{\bar{b}} \tag{4}$$

where $\bar{x}_{St}$, $\bar{x}_T$ are the mean of the log concentration of the standard and the test preparation respectively, $\bar{B}_{St}$, $\bar{B}_T$ are the corresponding responses, $\bar{b}$ is the mean regression coefficient. Testing the conditions for the validity of this parallel-line assay by an analysis of variance (Finney, 1964) showed no evidence of deviation from parallelism at a probability level of 0.1 and no significant deviation from linearity at the 0.01 level (Schneemann, 1983).

Table 4 shows the f_I-values and the corresponding confidence limits, calculated with the techniques for an unsymmetrical test design (Finney, 1964a). The relative bioavailability of the betamethasone-17-benzoate improves remarkably with increasing paraffin content of the vehicle. The vehicle V 60/40 and V 10/90 achieve the same blanching response as the standard with the use of only about one-half and one-twentyfourth the concentration, respectively. The paraffin ointment V To2 is 37-fold more active than the standard but the same preparation with colloidal silicon dioxide is only 2-fold more active.

From the penetration kinetics in Eqn. 1 it follows that the differences in blanching response between the solution-type ointments must be seen in connection with the partition coefficient of the drug between the skin barrier and the vehicle (Poulsen, 1972; Lippold, 1982). Together with the barrier-specific parameters, D_B and d, and with the constants F and V_V the partition coefficient P determines the penetration rate constant k_p. Because the relative bioavailability factor expresses the different penetration rates of the drug from the standard and the test preparation, f_I contains the ratio of the k_p-values for the standard and the test. If these k_p-values differ only because of their different partition coefficients (i.e. the different solubilities, c_{sV}, see Eqn. 1), then a plot of f_I versus $1/f_V c_{sV}$ of the test preparations should

TABLE 4

RELATIVE, INTENSITY-RELATED BIOAVAILABILITY FACTORS f_I WITH CORRESPONDING CONFIDENCE LIMITS ($P = 0.01$)

Vehicle	f_I	Confidence limits
V 85/15	1	–
V 60/40	1.98	1.5– 2.7
V 40/60	5.03	3.5– 7.3
V 20/80	12.5	8.4–18.7
V 10/90	24.1	15.1–38
V To2	37.5	18.2–74.6
V TmK	2.1	0.9– 3.9

result in a straight line with the slope $f_V c_{sV}$ of the standard preparation.

From this plot as seen in Fig. 8 follows that for the neutral oil/paraffin ointments V 60/40 and V 40/60 a small partition coefficient (i.e. high solubility of the drug in the vehicle) is equivalent to a low relative bioavailability. On the other hand, reduction of the solubility by a factor of 5 by increasing the paraffin content results in an increased bioavailability by exactly this factor. For these vehicles the partition coefficient alone seems to be decisive for the bioavailability differences. The preparations with low solubilities V 20/80, V 10/90, V To2 and V TmK are less bioavailable as may be expected from the reciprocal solubilities.

To interpret these deviations further factors have to be considered. As the increase of the partition coefficient is caused by a reduced solubility, this leads to an accelerated penetration. The latter can enlarge so much that the release rate from the vehicle is no longer sufficient to maintain that high penetration rate. Under these circumstances the release rate could influence the whole diffusion process. But it is not rate-determining because the bioavailability of V To2 (with the lowest solubility) is clearly improved in comparison to V 10/90 although the diffusion coefficient in V To2 ($D = 0.19 \times 10^{-8}$ cm^2/s) is about one-tenth smaller than for V 10/90 ($D = 3.8 \times 10^{-8}$ cm^2/s) (Schneemann, 1983).

Furthermore the increased penetration rate especially in the low-dosed preparations may cause such a decline of drug concentration during the application time that the percutaneous absorption can no longer be regarded as zero-order but must

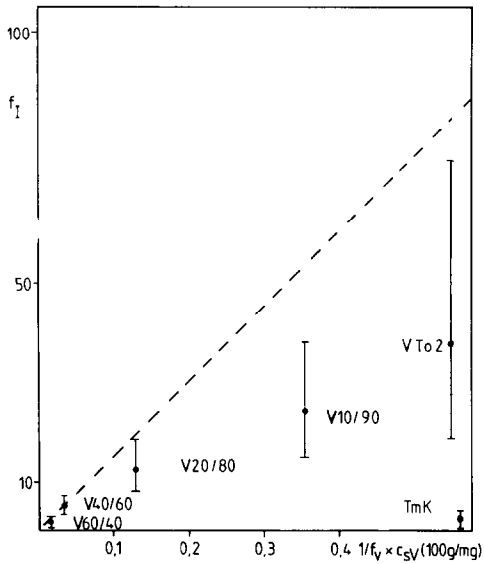

Fig. 8. Relative, intensity-related bioavailability factors f_I (incl. confidence limits, $p = 0.01$) versus the reciprocal value of the solubility $f_V c_{sV}$ of betamethasone-17-benzoate in the vehicles. $f_V = 1$ for the neutral oil/paraffin ointments and $f_V = 0.075$ for V TmK. Key: - - - - - - theoretical straight line with the slope $f_V c_{sV} = 150$ mg/100 g corresponding to the solubility of the drug in the standard preparation V 85/15.

be taken as first-order. Thus R_{max} (i.e. the maximum blanching response), is no longer proportional to k_p (see Fig. 1) and the relative bioavailability turns out to be lower than expected from the low solubilities.

Among the paraffin ointments, the binding of drug on colloidal silicon dioxide takes an additional effect on the relative bioavailability (see Fig. 8). It is reduced from V To2 to V TmK by about that factor that corresponds to the fraction of drug unbound in V TmK (see Table 3).

Potency estimation of the suspension-type ointments

The dose–response relationships in Figs. 3–7 reached a plateau when changed from a solution- to a suspension-type ointment. Increasing the drug concentration 20-fold for instance in V 10/90 leads to no further improved action. In Figs. 9 and 10 the blanching responses of all suspension-type ointments of the neutral oil/paraffin and paraffin ointments as well as of the internal standard and V Oly are plotted

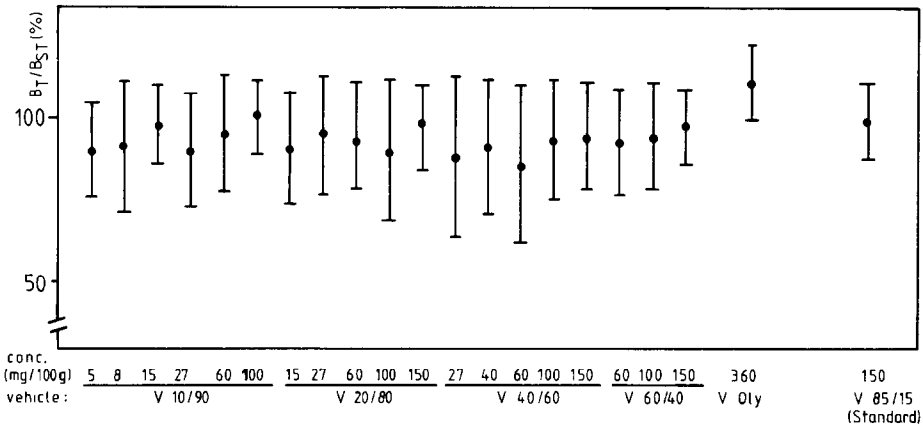

Fig. 9. Blanching responses B_T/B_{St} of the suspension-type ointments made with the neutral oil/paraffin vehicles and of V Oly and the internal standard V 85/15. Mean ± SDM (n = 17–18 volunteers, except V Oly, n = 10).

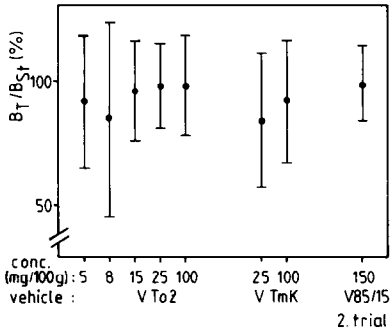

Fig. 10. Blanching responses B_T/B_{St} of the suspension-type ointments made with the paraffin vehicles and of the internal standard V 85/15 2-trial. Mean ± SDM (n = 7 volunteers).

side by side using the same scale. The diagrams show that there is also no significant ($P = 0.05$) difference in the level of the plateaus, except V Oly. Hence for the suspension-type preparations of the neutral oil/paraffin and paraffin ointments the vehicle has in contrast to the solution-type ointments no influence on the action of the drug (see Eqn. 2). However, with regard to the beginning of the plateau, differences are found. The preparations with high solubility—V 60/40 and V 40/60—approach the plateau of 100% action with a drug concentration corresponding to the solubility. In order to obtain the same response for the preparations with low solubility—V 20/80, V 10/90, V To2—requires a drug concentration that is significantly ($P = 0.05$) higher than the solubility ($c_o \approx 2\ c_{sV}$). The ratio of the drug concentration of the standard to the test preparation which is necessary to achieve this maximum action again corresponds to f_I.

This finding, moreover, indicates that the dissolution rate of the drug has no additional effect on the blanching response (Schneemann, 1983). Interactions between the vehicle and the stratum corneum that change the permeability of the horny layer and manifest an intensified blanching are not detectable while using neutral oil, mineral oil and their mixtures. However, oleyl alcohol as a vehicle component seems to enhance the permeability of the skin barrier significantly ($P = 0.01$) (see Fig. 9).

Conclusions

The intensity of action of a topical ointment preparation can be controlled over a wide extent by using the solubility of the drug in the vehicle (i.e. the partition coefficient stratum corneum/vehicle) and the drug concentration. The penetration rate across the skin barrier achieves its maximum value and is at the same time independent of the vehicle when the drug is applied in the form of a suspension-type ointment. The application of a solution-type ointment which additionally has a high solution capacity induces the drug to remain on the skin. One can use less drug substance to cause the same pharmacodynamic action by the choice of a vehicle with a high partition coefficient (= low solubility) and by adapting the dosage to the solubility of the drug or slightly above it. Conversely, an unfavourable partition coefficient for penetration can be compensated by an appropriate high drug concentration. The desired solubilities are easily adjustable by the use of binary solvents as liquid components. Mixture components that alter the permeability of the skin barrier can favour the penetration rate.

Because the drugs used in dermatology are frequently neither extremely hydrophilic nor extremely lipophilic but rather ambiphilic, mineral oil or white petrolatum, respectively, may serve as a lipophilic vehicle component to reduce the drug solubility. Less lipophilic solvents such as neutral oil are capable of guaranteeing the necessary minimum solubility.

References

Barry, B.W. and Woodford, R., Activity and bioavailbility of topical steroids. In-vitro/in-vitro correlations for the vasoconstrictor test. J. Clin. Pharm., 3 (1978) 43–65.

Finney, B.J., Statistical Methods in Biological Assay, Charles Griffin, London, 1964, p. 79.

Finney, B.J., Statistical Methods in Biological Assay, Charles Griffin, London, 1964a, p. 114.

Lippold, B.C., Kutane Resorption-Moeglichkeiten, Modelle, Beeinflussung. Acta Pharm. Technol., 27 (1981) 1–9.

Lippold, B.C. and Teubner, A., Biopharmazeutische Qualitaet von Arzneiformen, insbesondere fuer lokale Anwendung, abgeleitet aus Wirkungsmessungen. Pharm. Ind., 43 (1981) 71–73.

Lippold, B.C., In-vitro methods for simulating the absorption of drugs. In Brandau, R. and Lippold, B.H. (Eds.), Dermal and Transdermal Absorption, Wissenschaftliche Verlagsgesellschaft, Stuttgart, 1982, pp. 101–115.

Poulsen, B., Diffusion of drugs from topical vehicles: an analysis of vehicle effects. Adv. Biol. Skin, 12 (1972) 495–509.

Schneemann, H., Einfluss von Vehikeln auf die Bioverfuegbarkeit von Betamethason-17-benzoat aus Loesungs- und Suspensionssalben, Dissertation, Duesseldorf, 1983.