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Investigations into the Pharmacodynamic Effects of Dermally Administered Microemulsions Containing β-Blockers

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Abstract—Water uptake from the skin changes dermally applied near-saturated solutions of β-blockers in microemulsion-bases into supersaturated microemulsions. Due to an enhanced thermodynamic activity, high absorption rates are expected from these preparations. The pharmacodynamic effect after dermal administration of such preparations has been evaluated using rabbits as a suitable in-vivo model. The dose dependency, influence of lipophilicity and of the thermodynamic activity of the drug is described. Assessment of dermal doses which were therapeutically equivalent to i.v. doses as, for example, shown with carazolol is possible. Although not all observed pharmacodynamic effects were due to these influences but rather due to the numerous other skin-vehicle-drug interactions which could not be explained with this model, the presented in-vivo model is helpful in evaluation of β-blockers which were suitable candidates for transdermal administration.

Transdermal administration of drugs exhibits several advantages in therapy compared with oral or parenteral administration (Chien 1987). Absorption via the transdermal route is limited by the generally poor penetration of drugs through the stratum corneum (Blank 1971). Either reducing the barrier properties of the stratum corneum (by using absorption enhancers) or increasing the diffusion properties of the drug can be used to improve absorption. To optimize the vehicle, we have used microemulsions as the vehicles for dermal application in this work.

An important parameter of the vehicle is its thermodynamic activity (Higuchi 1960, 1982; Katz & Poulsen 1971). Generally the absorption rate of a drug increases as its thermodynamic activity in the vehicle increases. Thermodynamic activity can be approximately expressed as (current concentration in vehicle)/(concentration in saturated vehicle) (Coldman et al 1972). Hence, absorption rate should be very high from supersaturated vehicles. However, because of the physical instability of supersaturated systems there are no commercial dosage forms available. This problem might be overcome by application of systems which become supersaturated in-situ. Such systems are represented by the microemulsions tested in this work.

Microemulsions are characterized as thermodynamically stable, clear or slightly opalescent isotropic systems. They are self-emulsifying, possess low viscosity and consist of an aqueous compound, a lipophilic compound and a surfactant or a surfactant/cosurfactant mixture. The microemulsions examined here possess two characteristics making them suitable as candidates for vehicles for transdermal absorption: they show a decreasing solubility for apolar drugs with increasing water content (Kölln 1986; Kleinebudde 1987; Kemken et al 1989), and in-vitro, no crystallization of drugs occurs in supersaturated microemulsions over a 10–14 day period (Sveine 1986).

Application of a saturated, water-free microemulsion with an occlusive patch should lead to water uptake from the skin and should change the water-free microemulsion into a water-containing microemulsion; solubility of the incorporated drug decreases and a high absorption rate due to an enhanced thermodynamic activity will be expected.

The present paper examines a method for determination of the pharmacodynamic effects after dermal application of such saturated solutions of model drugs in water-free microemulsions. Different β-blockers were used as model drugs and the suppression of the tachycardia produced by a standard dose of isoprenaline was used as the pharmacodynamic parameter.

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Materials and Methods

Male New Zealand White rabbits, 3·0–5·2 kg, were clipped over an area (~40 cm^2) of the dorsal skin with an electric clipper. Heart rate was determined on an ECG. Two electrodes (stainless steel cannules, Sterijekt, TSK, Tochigi, Japan) were set subcutaneously (one in the left chest, the other in the right side of the thorax), and the animals were immobilized in a pyrogen-test-box (type P/1, Ruco Metaalindustrie b.v., Vokenswaard, Netherlands). A catheter (Venofix S 0·5 mm i.d., B. Braun, Melsungen, Germany) was placed in the ear-vein. Four to six i.v. bolus injections of a standard-dose isoprenaline (0·25 $\mu g\ kg^{-1}$) were given at intervals of 15–20 min. The catheter was rinsed with a heparin solution (1·0 mL, 500 int. units mL^{-1}) to keep the catheter patent and to overcome its dead volume. The ECG was recorded (Servomed SMS 308, Hellige GmbH, Freiburg, Germany) from two min before to approximately five min after the bolus injection. Heart rate was determined by counting the 'R-peaks' of the ECG. The differences in heart rate before and maximum heart rate after each injection were calculated. The mean of these differences was taken as an individual response to the standard dose of isoprenaline.

A near-saturated solution of a β-blocker in a water-free microemulsion was applied with an occlusive patch (3M Medica, Borken/Westfalia, Germany). Solubility and com-

Table 1. Composition of the microemulsion bases (amount of the components % w/w) and solubility of β-blockers in these preparations (% w/w).

β-Blocker	P85	P101	IPP	Solubility
Alprenolol	35	30	35	>10
Atenolol	30	45	25	0·63
Bupranolol	35	25	40	8·05
Carazolol	35	20	45	4·16
Metipranolol	35	30	35	2·05
Metoprolol	35	15	40	>10
Penbutolol	40	25	35	8·75
Propranolol	35	35	30	6·49
Timolol	35	20	45	>10

P85 = Polysorbat 85, P101 = Poloxamer 101, IPP = Isopropylpalmitate.

position of the preparations are given in Table 1. The composition of the systems vary because of the interactions between the different drugs and the components of the vehicle. To avoid crystallization, the drugs were prepared up to only 95% of their solubility. Interaction of several β-blockers (alprenolol, metoprolol, timolol) with the system was very intensive so that a near-saturated microemulsion could not be prepared; in these cases drug concentrations were reduced to 5% in order to reduce the influence of the β-blockers on the systems and to obtain microemulsions according to the given definition. These "unsaturated" preparations are marked * in this paper.

The patch (Fig. 1, 50 × 60 mm, about 2 mm in thickness) contains an application-chamber (30 mm in diameter). A piece of viscose fleece (about 0·5 cm^2/100 mg preparation) soaked with the drug preparation, corresponding to the required dose, was placed in the chamber.

Further isoprenaline effects were determined at intervals over 10 h after application of the patches. The effect of the β-blocker was quantified by comparing the response to isoprenaline with that under control conditions. The effects are given in relative figures where 100% corresponds to a complete suppression of the pharmacological response. Three runs of each preparation were made with different rabbits. For plotting the β-blocker effect vs time the mean values of the three runs were fitted to equation 1 (Hartmann et al 1983):

$$E = E_{max} \times \left(1 + \frac{1}{k_1 - k_2}(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})\right) \quad \text{(eqn 1)}$$

where, E = effect at time t, E_{max} = maximum effect, k_1, k_2 = first order time constants, describing changes of effects with time in different compartments (fictive constants, here used as an aid for determination of the parameters named below), t = time after application of the preparation.

Fits were computed with a non-linear-regression program according to the algorithm of Ebert & Ederer (1983). The algorithm was programmed in GFA-BASIC (GFA Systemtechnik, Düsseldorf, Germany) and run on an Atari Mega ST4. The following parameters were calculated from the fitted function: E_{max} = maximum effect, t_{max} = time to reach 98% of the maximum effect, t50 = time to reach 50% isoprenaline-inhibition, S = slope of the curve when 50% of the maximum effect was reached.

If 50% inhibition or steady-state was not reached, no value is given in the table.

Drugs and preparations

Isoprenaline solution (2·5 μg mL^{-1} free base) was prepared from Aludrin (Boehringer GmbH, Ingelheim, Germany) by dilution with 0·9% sterile NaCl solution (saline). Heparin solution (500 int. units mL^{-1}) was prepared from Lipo-Hepin 25000 (3M Medica, Borken/Westfalia, Germany) by dilution with saline.

The microemulsions were prepared by mixing their components and adding the necessary amount of the drug. The mixture was heated to 40°C for 3 h and well shaken to accelerate solution of the β-blocker.

Components of the microemulsion-bases were Polysorbat 85 (Tween 85, Atlas Chemicals AG, Essen, Germany), Poloxamer 101 (Pluronic L31, C.H. Erbslöh, Düsseldorf, Germany), isopropylpalmitate (Rilanit, Henkel KGaA, Düsseldorf, Germany). β-Blockers were alprenolol hydrochloride (Ciba Geigy, Wehr, Germany), atenolol (ICI Pharma, Plankstadt, Germany), bupranolol (Schwarz GmbH, Monheim, Germany), carazolol and metipranolol (Boehringer GmbH, Mannheim, Germany), metoprolol tartrate (Ciba Geigy, Germany), penbutolol sulphate (Hoechst AG, Frankfurt, Germany), propranolol hydrochloride (Stada AG, Bad Vilbel, Germany), timolol maleate

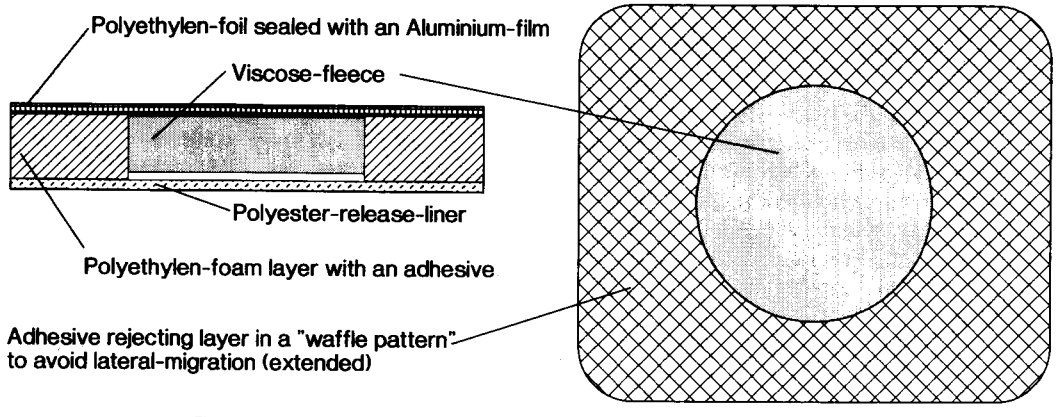

FIG. 1. Cross section of the patch and top view from the application side.

Table 2. Requirements of application and calculated parameters of the in-vivo experiments.

β-Blocker	D	C	E_{max}	t_{max}	t50	S
Alprenolol	2·0	5·00*	69·6	193	70	0·634
Atenolol	2·0	0·63	14·8	24	—	0·658
Bupranolol	2·0	2·00*	67·4	444	217	0·256
Bupranolol	2·0	5·00*	73·6	161	69	0·785
Bupranolol	2·0	7·65	86·4	97	28	1·696
Bupranolol	1·0	7·65	71·0	249	112	0·484
Bupranolol	0·5	7·65	41·4	184	—	0·334
Carazolol	2·0	3·95	95·3	143	44	1·210
Carazolol	1·0	3·95	84·1	288	103	0·514
Carazolol	0·5	3·95	76·8	—	276	0·128
Metipranolol	2·0	1·95	72·9	268	87	0·485
Metoprolol	2·0	5·00*	26·4	186	—	0·181
Penbutolol	2·0	8·17	88·9	152	50	1·048
Propranolol	2·0	6·17	36·6	—	—	0·072
Timolol	2·0	5·00*	89·1	116	38	1·386

D = applied dose (mg kg^{-1}). C = β-blocker-concentration of the applied microemulsion-base (% w/w, *unsaturated preparations), E_{max} = maximum effect (% of isoprenaline inhibition). t_{max} = time to reach 98% of the maximum effect (min), t50 = time to reach 50% isoprenaline inhibition (min), S = slope of the curve when 50% of the maximum effect was reached (Mean values, n = 3).

(Helm AG, Hamburg, Germany). β-Blockers were used as free bases. Where free bases were not commercially available they were extracted by diethylether from alkaline aqueous solutions of their salts.

Results

Doses and concentrations of the applied preparations and parameters calculated are summarized in Table 2. The placebo preparation did not show any statistically significant effect.

Dose dependency

Effects of different doses with time were evaluated with preparations containing bupranolol and carazolol, respectively (Figs 2, 3). Influence of dose on the extent of the effect and steepness of the curves is evident. To obtain the dose-effect curve, maximum effects were plotted vs log dose (Fig. 4). Compared with i.v. data (Bartsch et al 1980) the necessary dose of carazolol to produce the same inhibition of isoprenaline-induced tachycardia after dermal administration was nearly one hundred times greater, such that dermally applied carazolol is therapeutically equivalent to about 1% of the dose given intravenously.

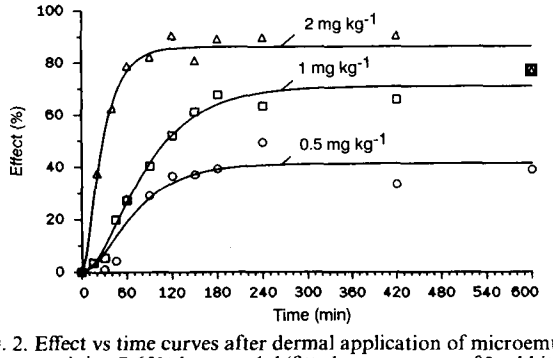

FIG. 2. Effect vs time curves after dermal application of microemulsions containing 7·65% bupranolol (fitted curves, mean of 3 rabbits).

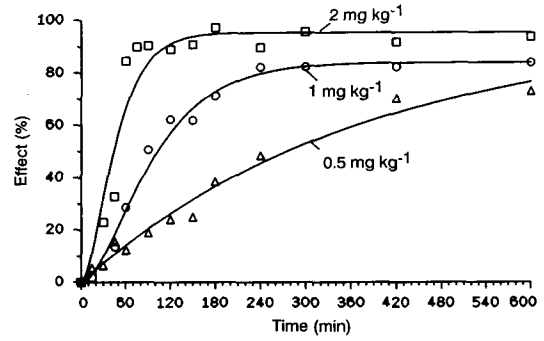

FIG. 3. Effect vs time curves after dermal application of microemulsions containing 3·95% carazolol (fitted curves, mean of 3 rabbits).

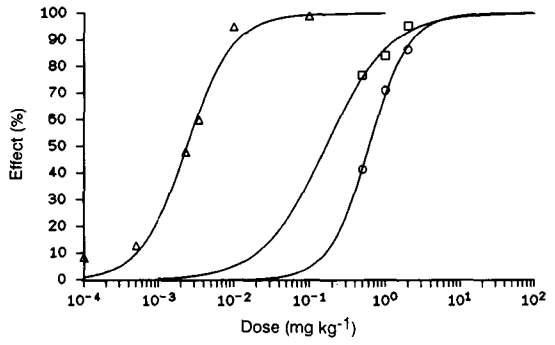

FIG. 4. Dose-effect curve of intravenous carazolol △ and curves after dermal application of microemulsions containing bupranolol ○ and carazolol □. Effect is given in % inhibition of the isoprenaline-induced tachycardia. Isoprenaline doses were: 1 μg kg^{-1} in the i.v. experiments (Bartsch et al 1980) and 0·25 μg kg^{-1} in experiments with dermal application (fitted curves, mean of 3 rabbits).

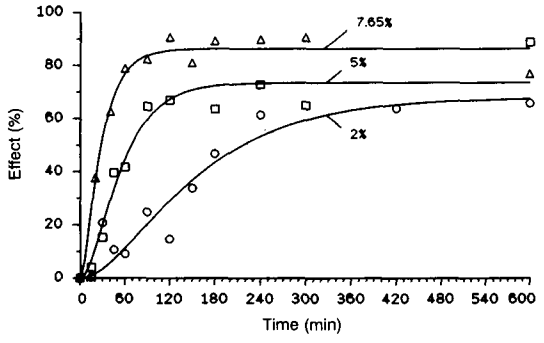

FIG. 5. Effect vs time curves after dermal application of microemulsions containing bupranolol (dose: 2 mg kg^{-1}, fitted curves, mean of 3 rabbits).

Influence of drug concentration

Influence of drug concentration on transdermal absorption was determined with preparations containing bupranolol (Fig. 5). The near-saturated preparation (7·65%) leads to the highest effects and shows the steepest increase of effect with time. Maximum effects (t > 420 min) of the 2 and 5% preparation do not differ significantly (Wilcoxon U-test, $P = 0·95$) but a difference in time to reach maximum effect is evident. For comparison the effect-time curve after application of alprenolol-containing microemulsion (5%) is

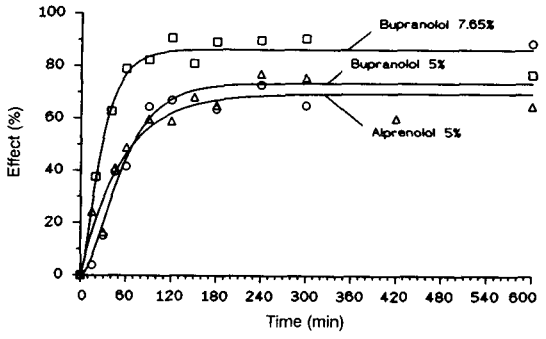

FIG. 6. Effect vs time curves after dermal application of microemulsions containing 5% of bupranolol or 5% alprenolol. For comparison the curve of the near-saturated (7·65%) bupranolol preparation is also plotted. (Dose: 2 mg kg^{-1}, fitted, and mean of 3 rabbits.)

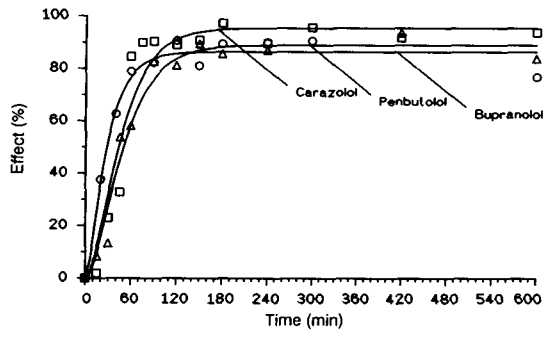

FIG. 7. Effect vs time curves after dermal application of saturated microemulsions containing 7·65% bupranolol, 3·95% carazolol or 8·17% penbutolol. (Dose: 2 mg kg^{-1}, fitted curves and mean of 3 rabbits.)

shown in Fig. 6. Alprenolol shows a curve very similar to the preparation containing 5% bupranolol.

Influence of drug-lipophilicity

The n-octanol/buffer pH 7·0 partition coefficient serves as a parameter of the lipophilicity (Table 3). Influence of lipophilicity on the effect-time curves after application of near-saturated preparations is presented in Figs 7 and 8 with respect to the bupranolol effect as a standard, and Fig. 9 demonstrates observed effects with time after application of unsaturated (5%) preparations.

In most cases the maximum effects increase and the rise of the effect with time is steeper with increasing lipophilicity (partition coefficient). However, there are some noticeable exceptions: propranolol shows little effect and reaches no steady-state in the observation period, atenolol shows an expected small effect but time to reach this level is very short, and application of timolol leads to unexpectedly high and rapid effects.

Discussion

The data were fitted to equation 1 developed for reaction-kinetics (Hartmann et al 1983) but also useful in the phenomenological description of these in-vivo data. Other mathematical models for plotting the possible course of the effect vs time curves were also investigated but were less successful due to the greater number of unknown variables (Kemken 1990).

For the reasons given below there are no values of variation given in the plots. Intra-individual and inter-individual variations in isoprenaline-induced tachycardia are very similar in the range 5–20 beats min^{-1}. This variation is not affected by β-blocker medication. Calculating the

Table 3. Physicochemical and pharmacological data of selected β-blockers.

β-Blocker	$PC_{7·0}$	$PC_{7·4}$	pK_a	pA_2	V
Alprenolol	3·3	9·5	9·5–9·7	8·6	1·0–3·5
Atenolol	0·0033	0·01–0·03	9·6	7·3–7·6	0·7–1·1
Bupranolol	3·8		9·6	8·7	
Carazolol	13·7			9·9	10·9
Metipranolol	0·7			7·5	3·5
Metoprolol	0·18	0·98–1·13	9·7	7·5	3·2–5·6
Penbutolol	19·9††	50	9·3	8·6	0·3
Propranolol	5·4	13·4–20·2	9·5	8·4	2·8–5·5
Timolol	0·28	1·16–1·27	8·8	8·7	1·4–2·5

Data from: Hellenbrecht et al (1973), Johnsson & Regardh (1976), McDevitt (1978), Palm (1980), Scriabine (1980), Dinnendahl & Fricke (1982), Reynolds (1982), Borchard (1983), Nieder et al (1987), Ridell et al (1987). ††Calculated from pK_a and $PC_{7·4}$, $PC_{7·0}$. $PC_{7·4}$ = partition coefficient in n-octanol/buffer at pH 7·0 and 7·4, respectively, pA_2 = negative common logarithm of the concentration necessary for a 50% occupation of the β_1-receptors, V = apparent volume of distribution (L kg^{-1}).

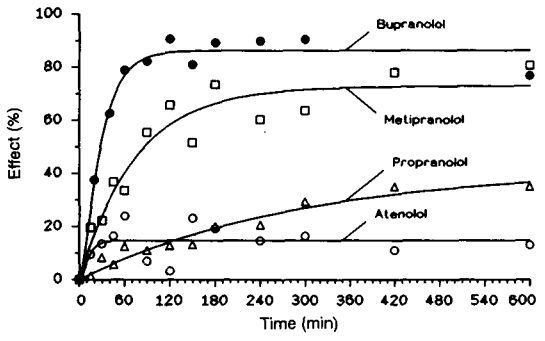

FIG. 8. Effect vs time curves after dermal application of saturated microemulsions containing 0·63% atenolol, 7·65% bupranolol, 1·95% metipranolol, or 6·17% propranolol. (Dose: 2 mg kg^{-1} fitted curves, mean of 3 rabbits.)

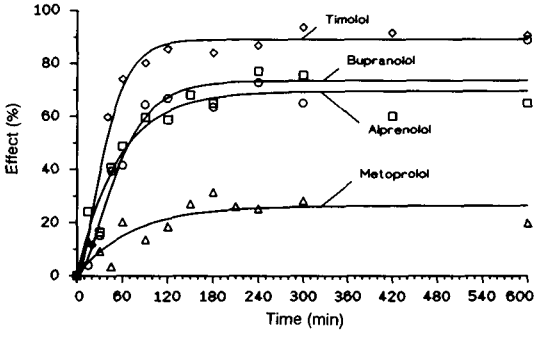

FIG. 9. Effect vs time curves after dermal application of unsaturated microemulsions containing 5% alprenolol, bupranolol, metoprolol or 5% timolol. (Dose: 2 mg kg^{-1}, fitted curves, mean of 3 rabbits.)

coefficient of variation from these absolute values with reference to the β-blocker effect leads to very high variations (typical coefficient of variation 30–50%, up to 80% for atenolol) when the β-blocker effect is small (e.g. metoprolol, propranolol, low doses of bupranolol and carazolol). On the other hand coefficients of variation are small (5–20%) for large effects (bupranolol 2 mg kg^{-1}, carazolol 2 mg kg^{-1}, penbutolol, timolol). Additionally the β-blockers may have sedating side effects so that the sensibility of the rabbits to external stimuli which could affect the heart rate is reduced. Possibly for this reason the more effective β-blockers lead to smaller variations.

Removing the bupranolol-microemulsion patches after an application of 22 h and cleaning the area with water, acetone and n-hexane did not show a decrease of the effects over 5 h. Therefore the observation period was set to 10 h and elimination is not documented.

In spite of these difficulties the model is applicable, as the experiments indicate. Dose-dependency as a requirement for a valid model is fulfilled. The investigations with carazolol showed that assessment of therapeutic equivalence is possible (Fig. 4).

Influence of concentration

High concentrations of drug in the vehicle lead to high steady-state effects and particularly steep increasing effects due to an enhanced diffusion as described by the concept of thermodynamic activity (Higuchi 1960, 1982). In this concept thermodynamic activity is the driving force for diffusion, so that saturated solutions as represented by the saturated water-free microemulsions possess high thermodynamic activity. Because of the decreasing solubility of the drug with increasing water content of the system, water uptake from the skin would immediately lead to supersaturated solutions with an increased diffusion pressure due to further rising thermodynamic activity (Kemken et al 1991). Water uptake by the unsaturated preparations increases the thermodynamic activity but systems would not become supersaturated, or supersaturation would occur later. This would explain why the blocking effect of the 2 and 5% bupranolol-microemulsion occurs slowly and why the maximum effects late in the application period are similar. The similar course of the alprenolol (5%) curve and the bupranolol (5%) curve is due to their similar physicochemical and pharmacological properties (Table 3).

Influence of lipophilicity

Increasing lipophilicity (partition coefficient) leads to higher maximum effects and steeper rising effects with time. This is due to the reduced barrier properties of the skin to lipophilic compounds (Scheuplein 1976; Barry 1983).

Partition coefficients greater than that of bupranolol (3·8) seemed to enhance the pharmacodynamic effects only slightly (Fig. 7) so that the similar curves of the higher lipophilic drugs (bupranolol, carazolol, penbutolol) could not be discriminated with this model. Perhaps reduction of dose can differentiate effects, whereas in the lower range of partition coefficients (atenolol, metipranolol, bupranolol) influence of lipophilicity is apparent (Fig. 8). This trend is continued by the effects resulting from application of unsaturated systems (Fig. 9).

Because of many interactions between drug, vehicle and skin the effects of dermally applied β-blockers could not simply be described by dose, concentration and lipophilicity. However, there are also some irregularities which make in-vivo investigations necessary. In spite of some difficulties we think the model presented is a valid model for carrying out such in-vivo tests. Measurement of the pharmacodynamic effects may be helpful in choosing β-blockers which are possible candidates for transdermal administration and for optimizing their vehicles. The in-vivo experiments indicate that water-free microemulsions can be advantageous vehicles in transdermal administration. The particularly high pharmacodynamic effects observed after dermal application of β-blockers in water-free microemulsions are due to an enhanced thermodynamic activity which is a result of the in-situ formation of supersaturated systems.

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