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In-vitro Permeability of the Human Nail and of a Keratin Membrane from Bovine Hooves: Penetration of Chloramphenicol from Lipophilic Vehicles and a Nail Lacquer

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Abstract

Lipophilic vehicles and especially nail lacquers are more appropriate for topical application on the nail than aqueous systems because of their better adhesion. This work has, therefore, studied the penetration through the human nail plate of the model compound chloramphenicol from the lipophilic vehicles medium chain triglycerides and *n*-octanol and from a lacquer based on quaternary poly(methyl methacrylates) (Eudragit RL). The results were compared with data obtained with a keratin membrane from bovine hooves.

If the swelling of the nail plate or the hoof membrane is not altered by use of lipophilic vehicles, the maximum flux of the drug is independent of its solubility in the vehicle and is the same as that from a saturated aqueous solution. These vehicles are not able to enter the hydrophilic keratin membrane because of their non-polar character and so cannot change the solubility of the penetrating substance in the barrier. If the concentration of the drug in the nail lacquer is sufficiently high, the maximum flux through both barriers equals that from aqueous vehicles or even exceeds it because of the formation of a supersaturated system. Penetration through the nail plate follows first order kinetics after a lag-time of 400 h. The course of penetration through the hoof membrane is initially membrane-controlled and later becomes a matrix-controlled process because of the membrane's greater permeability. Chloramphenicol is dissolved in the lacquer up to a concentration of 31%. The relative release rates from these solution matrices are independent of the drug concentration but they decrease on changing to a suspension matrix.

These results show that drug flux is independent of the character of the vehicle and that penetration of the drug is initially membrane-controlled and changes to being matrix-controlled as the drug content of the lacquer decreases.

The nail plate and the bovine hoof membrane behave like hydrophilic gel membranes rather than lipophilic partition membranes (Mertin & Lippold 1997). The maximum flux of a drug through both barriers is primarily a function of its water-solubility. Because aqueous solutions are not important in the topical therapy of nail infections, due to their insufficient adhesion, lipophilic vehicles or nail lacquers were investigated to determine whether the flux from these reached the maximum obtained from aqueous vehicles.

Studies of the penetration of the antifungal agents ciclopirox (Hänel & Ritter 1990; Nolting & Seebacher 1993) and amorolfine (Polak & Zaug 1990; Franz 1992; Polak 1992) show that active drug concentrations are obtained in the whole nail plate after a few days. Little is, however, known about the relationship between flux and concentration in the lacquer. The influence of the release on the kinetics of nail penetration have, moreover, not yet been described.

According to Fick's law (eqn 1) the penetration rate from an aqueous solution at sink conditions is directly proportional to the drug concentration in the barrier on the donor side (C_{BD}) (Mertin & Lippold 1997):

$$dM/dt = D_B A C_{BD}/h_B \quad (1)$$

in which dM/dt is the amount penetrating per unit time, D_B the effective diffusion coefficient in the barrier, A the diffusion area, and h_B the thickness of the barrier. For a suspended substance in a given vehicle, the saturation concentration (C_{sBD}) forms on the donor side owing to partition. Then the maximum concentration gradient causes the maximum flux:

$$J_{max} = dM_{max}/dtA = D_B C_{sBD}/h_B \quad (2)$$

As long as the vehicle does not change the barrier (e.g. by deswelling), the maximum flux from a suspension is independent of the vehicle (Lippold 1984). The swelling of hydrophilic gel membranes should be unchanged in contact with lipophilic vehicles as long as they also stay in contact with an aqueous solution. Simulating the swelling of a living nail, which is ventrally supplied by the richly vasculated nail bed, by using an aqueous solution as acceptor and a lipophilic vehicle as donor, the flux from a saturated solution should equal the maximum flux from an aqueous suspension assuming an identical extent of swelling.

To test this hypothesis, the model compound chloramphenicol was used because it is relatively highly soluble in water, which causes sufficiently high fluxes, and it is analytically easy to determine, through both the nail plate and the hoof membrane. Its molecular size is, moreover, in the range of most antimycotics and the results can, therefore, be transferred to these drugs. Differences between the solubilities of chloramphenicol in pH 7·4 phosphate buffer on the one hand and in medium-chain triglycerides and *n*-octanol on the other

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Table 1. Solubility of chloramphenicol in pH 7·4 phosphate buffer, *n*-octanol and medium-chain triglycerides at 32°C.

Vehicle	Solubility ($mg\,L^{-1}$)
Phosphate buffer, pH 7·4	4520 ± 64
n-Octanol	23210 ± 767
Medium-chain triglycerides	2350 ± 13

N = 3, mean ± s.d.

(Table 1) seem to be large enough to indicate a possible influence of drug solubility in the vehicle on the maximum flux through the barrier.

Results obtained using lipophilic liquids should be transferable to nail lacquers, assuming that membrane diffusion, and not release from the polymer, is the rate-limiting step. For both barriers, however, it must be investigated whether the penetration rate is controlled by the permeability of the barrier as well as the release of drug from the lacquer. The liberation of a substance which is suspended or dissolved in a nail lacquer should follow kinetics typical of a matrix system. From Fick's first law Higuchi (1961) developed an equation for the release of a suspended drug from a matrix (sink conditions):

$$Q = A\sqrt{(D_{eff}C_S(2C_0 - C_S)t)} \quad (3)$$

Where Q is the amount of drug released at time t, A is the release area, D_{eff} is the effective diffusion coefficient in the matrix, C_S is the solubility of the drug in the matrix, and C_0 is the initial concentration of the drug in the matrix.

On the premise that $C_0 \gg C_S$ equation 3 can be reduced to:

$$Q = A\sqrt{(2D_{eff}C_SC_0t)} \quad (4)$$

Higuchi also deduced an equation describing the course of liberation of a drug which is completely dissolved in the matrix (up to 30% release, sink conditions):

$$Q = 2AC_0\sqrt{(D_{eff}t/\pi)} \quad (5)$$

Transformation of this equation leads to:

$$Q/Q_0 = (2A/V_L)\sqrt{(D_{eff}t/\pi)} \quad (6)$$

in which Q_0 is the initial amount of drug in the matrix and V_L the matrix volume. Equation 6 shows that the relative release rate (Q/Q_0) is, in contrast with equation 4, independent of the amount of drug incorporated and so enables distinction between solution and suspension matrix.

The release rate can deviate from the ideal $\sqrt{t}$ kinetic, especially at the beginning of the process, if the drug has to penetrate an adherent membrane or aqueous layer after leaving the matrix. Roseman & Higuchi (1970) described the course of penetration from such systems by combining equations 1 and 4.

This work has investigated the penetration of chloramphenicol from lacquers based on quaternary poly(methyl methacrylates) with dibutyl sebacate as a plasticizer through the nail plate and the hoof membrane. Eudragit RL was used because of its ten-fold higher permeability in comparison with Eudragit RS (Lehmann 1989). Because previous results have shown the permeability characteristics of both barriers to be similar (Mertin & Lippold 1997), most of the investigation was performed with the hoof membrane.

Studies with different drug concentrations in the polymer (from 2·2 to 47·6%) should show whether penetration from the lacquer is matrix- or membrane-controlled.

Materials and Methods

Chemicals

A phosphate buffered saline solution, pH 7·4, was used as acceptor. Chloramphenicol was obtained from Caesar & Lorentz (Hilden, Germany), medium-chain triglycerides (Miglyol 812) from Hüls AG (Witten, Germany), *n*-octanol and methanol from J. T. Baker (Deventer, Netherlands), Eudragit RL PO from Röhm GmbH (Darmstadt, Germany) and dibutyl sebacate (Rilanit DBS) from Henkel KGaA (Düsseldorf, Germany). HPLC-grade methanol (chromasolv methanol) is a product of Riedel-de-Haën (Seelze, Germany).

Penetration studies

The modified Franz diffusion cells, the preparation of the nails and the hoof membranes and the performance of the penetration studies have been described in an earlier publication (Mertin & Lippold 1997). For experiments with lipophilic liquid vehicles, chloramphenicol was used in a suspended form with its maximum thermodynamic activity. The formation of a saturated solution was guaranteed by stirring at 32°C for 48 h. Despite occasional very long penetration times no visual degradation of the nails was observed.

Analytical conditions

The HPLC method differs from that described earlier (Mertin & Lippold 1997) in one aspect: the mobile phase acetonitrile-water (3 : 1) was pumped at flow rates ranging from 1·0 to $1{\cdot}25\,mL\,min^{-1}$.

Composition and application of the lacquer solution

The effect of concentration was examined by varying the amount of chloramphenicol between 0·5 and 20% of the lacquer solution-equivalent to between 2·2 and 47·6% of the dry lacquer. The formulations were: Eudragit RL PO, 20·0%; dibutyl sebacate, 2·0%; chloramphenicol, 0·5, 5·0, 10·0 and 20·0%; and methanol to 100%.

The swollen membrane was fixed in the empty diffusion cell and dried under ambient conditions for 2 h. A 200-μm film resulted after application of the lacquer solution (500 μL on to about $2{\cdot}5\,cm^2$ hoof membrane and 120 μL on to $0{\cdot}64\,cm^2$ nail plate), initial drying with warm air for a period of 30 min and final drying at room temperature for 24 h. The filling of the acceptor compartment started the experiment.

Results and Discussion

Penetration from lipophilic liquids

Phosphate buffer pH 7·4, *n*-octanol and medium-chain triglycerides were used as donors (medium-chain triglycerides only in experiments with hoof membrane). Table 2 shows maximum fluxes (J_{max} (1000 μm)) from the different vehicles, standardized to a barrier thickness of 1000 μm corresponding to the average thickness of the big-toe nail.

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Table 2. Maximum flux of chloramphenicol, standardized to a barrier thickness of 1000 μm (J_{max}(1000 μm)), from different vehicles through hoof membrane and nail plate at 32°C.

Vehicle	Maximum flux of chloramphenicol ($mg\,cm^{-2}\,s^{-1}$)	
	Hoof membrane	Nail plate
Phosphate buffer, pH 7·4	$4{\cdot}07 \pm 1{\cdot}18 \times 10^{-6}$	$8{\cdot}21 \pm 2{\cdot}11 \times 10^{-7}$
n-Octanol	$3{\cdot}40 \pm 0{\cdot}68 \times 10^{-6}$	$9{\cdot}13 \pm 0{\cdot}63 \times 10^{-7}$
Medium-chain triglycerides	$4{\cdot}06 \pm 1{\cdot}00 \times 10^{-6}$	n.d.*

*Not determined. N = 3 or 4, mean ± s.d.

Fluxes through the hoof membrane are forty-fold those through the nail plate, confirming the different permeability of the barriers (Mertin & Lippold 1997). It is, however, more interesting that the vehicle has no influence on the maximum flux. There is no significant difference (P=0·05) between the fluxes from the various vehicles through both barriers. Because the fluxes from lipophilic vehicles are equal to those from aqueous saturated solutions, the assumption that the flux is independent of the character of the vehicle is completely confirmed. Obviously, a saturated solution and, therefore, the maximum concentration gradient forms on the donor side of the water-swollen membrane owing to distribution. Neither medium-chain triglycerides nor *n*-octanol have significant influence on keratin swelling or the solubility of chloramphenicol in the membrane. It is of practical significance that the therapeutically desired maximum flux is reached as soon as the drug is present at its maximum thermodynamic activity, i.e. the saturated state. Although low solubility can be used to save drugs, very low solubilities lead to emptying effects, i.e. the flux cannot be maintained over the whole period of application. This result is of great importance in respect of drug penetration from nail lacquers.

Penetration from nail lacquers

Kinetics of penetration. Figs 1 and 2 illustrate the concentration-dependence of the diffusion of chloramphenicol from Eudragit RL lacquers through the hoof membrane. Plotting the amount penetrated against t gives linear relationships after a lag-time of a few hours; this is typical of matrix control (Fig. 1). As expected for a solution matrix, the rate of penetration of chloramphenicol increases with the concentration of the drug in the matrix between 2·2 and 18·5% and so the relative release rates (i.e. the amount penetrated relative to the total amount in the lacquer) remain constant. Increasing the concentration in the lacquer to 47·6% has no effect on the penetration rate, however, and so the relative rates decrease. This proves that, except for the lacquer containing 47·6% chloramphenicol, all systems are solution matrices as the relative release rates are independent of the amount of drug incorporated, in accordance with equation 6. Because the relative release rate decreases by half for the 47·6% lacquer, this, therefore, can be characterized as a suspension matrix. Fig. 1 does not enable distinction between matrix- and membrane-controlled processes. For membrane-controlled release from a solution matrix, first-order kinetics are expected. The plot of the amount of drug remaining in the lacquer (logarithmic scale) against time (Fig. 2) shows, because all curves are flattening, that membrane control does not occur over the whole period.

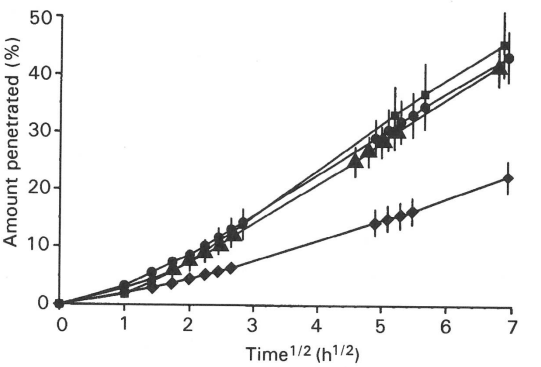

FIG. 1. Percentage penetration of chloramphenicol from Eudragit RL lacquers containing different concentrations, C_L, of drug through the hoof membrane at 32°C (n = 4, mean ± s.d.). Chloramphenicol concentration: ● 2.2%, ■ 18.5%, ▲ 31.3%, ◆ 47.6%.

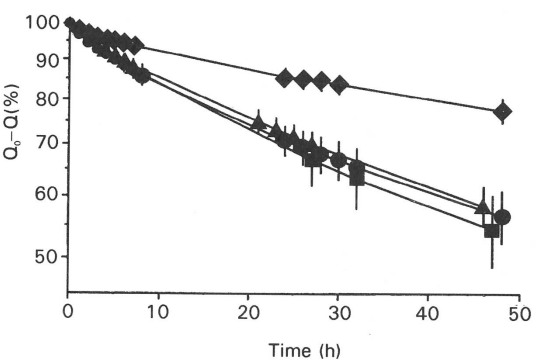

FIG. 2. Penetration of chloramphenicol from Eudragit RL lacquers containing different concentrations, C_L, of drug, through the hoof membrane at 32°C, plotted as the amount of drug remaining in the lacquer ($Q_0 - Q$; n = 4, mean ± s.d.). Chloramphenicol concentration: ● 2.2%, ■ 18.5%, ▲ 31.3%, ◆ 47.6%.

The ideal $\sqrt{t}$ kinetics follow after the expiry of the lag-time because of the initially predominant membrane control. Delayed drug release from silicone matrices through aqueous adherent layers results in similar penetration profiles (Haleblian et al 1971; Roseman 1972).

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Table 3. Release exponent, n, for the penetration kinetics of chloramphenicol from Eudragit RL lacquers through the hoof membrane at different drug concentrations.

C_L (%)	Calculated according to equation 7*		Calculated according to equation 8†		
	Exponent (n)	r‡	Exponent (n)	t_{lag} (h)	r
2·2	0·67 ± 0·04	0·9990	0·56 ± 0·03	1·55 ± 0·27	0·9999
18·5	0·73 ± 0·05	0·9917	0·50 ± 0·05	3·28 ± 0·19	0·9985
31·3	0·70 ± 0·02	0·9995	0·62 ± 0·03	1·45 ± 0·28	0·9999
47·6	0·64 ± 0·03	0·9995	0·65 ± 0·04	0·09 ± 0·18	0·9999

*$Q/Q_0 = kt^n$. †$Q/Q_0 = k(t - t_{lag})^n$. ‡Correlation coefficient of the regression line. N = 4, mean ± s.d.

The course of the drug release from a dosage form can be expressed by a semi-empirical function (Peppas 1985):

$$Q/Q_0 = kt^n \quad (7)$$

Where Q/Q_0 has the same meaning as in equations 3 and 6, k is the release-rate coefficient, and n is an exponent which describes the kinetics. If release is delayed, neglecting the lag-time can lead to incorrect conclusions about the penetration kinetics. In this circumstance equation 8 offers a better approach:

$$Q/Q_0 = k(t - t_{lag})^n \quad (8)$$

The release exponent (n) and the lag-time can be determined by a computer-aided, iterative method. Here the lag-time is established by a progressive shift of the experimental curve to the left parallel to the abscissa, beginning with data from 5 h onwards, inserting in the logarithmic form of equation 7 and subsequent linear regression to obtain the best curve fit (Lindner 1994). Table 3 shows the liberation parameters determined directly with equation 7 and iteratively with equation 8.

Neglecting the lag-phase normally leads to overestimation of the release exponent n and a worse fit of the calculated curve to the experimental data; this is reflected in a lower correlation coefficient. With the exception of the lacquer containing 47·6% chloramphenicol, the lag-time ranges from 1·4 to 3·3 h and agrees with the values determined graphically from Fig. 1. The iterative exponents (0·50 to 0·62, Table 3) are in the range expected for pure matrix release (n = 0·5) and confirm the visual assessment of the profiles. The exponent of the 47·6% lacquer is significantly different from unity which is expected for completely membrane-controlled release from a saturated vehicle. These results, on the other hand, correspond with the assumption of initial membrane control changing to matrix control as the drug content of the lacquer decreases.

Fluxes from nail lacquers compared with liquid vehicles

The profile between the first and the sixth hours after the start of the experiment was evaluated to determine the fluxes through the hoof membrane. Here the penetration rate is highest and there is an approximately linear relationship between the amount penetrated and time. This behaviour, not typical of matrix control, corresponds to the initial membrane-control. The expected first order kinetics (only dissolved drug in the lacquer) results in a more or less linear course for an amount penetrated of 10% at the most (pseudo steady-state). For saturated solutions (real steady-state), zero order kinetics prevail, which causes a linear increase of the concentration in the acceptor. Not before a sufficiently large emptying zone of the drug has developed, causing also a decrease in concentration in the membrane, does the process become matrix-controlled.

As the maximum flux is, in addition to antifungal power, the most important parameter for predicting the therapeutic efficacy of antimycotics, the penetration of chloramphenicol through the nail in man was investigated with a single formulation (31·3%). Fig. 3 shows the low penetration rate and large lag-time in comparison with the thinner hoof membrane. The lag-time (about 400 h) is significantly longer than for penetration from an aqueous suspension (about 200 h). Because both fluxes do not differ from each other in the steady-state (Table 4), the distinction cannot be explained by the different diffusion coefficients. Possibly the initially dry nail plate is slowly hydrated under the occlusive lacquer after contact with the acceptor medium, whereupon the partition equilibrium between polymer and nail plate and, therefore, the formation of the maximum concentration gradient, is delayed. The flux was calculated from the steady-state values between t = 670 and 940 h. Because of the lower penetration rate it should stay constant over a longer period than for the hoof membrane, for which the emptying area in the matrix widens after a short time and then the course of diffusion corresponds to classical $\sqrt{t}$-kinetics. Thus, the hoof membrane has to be

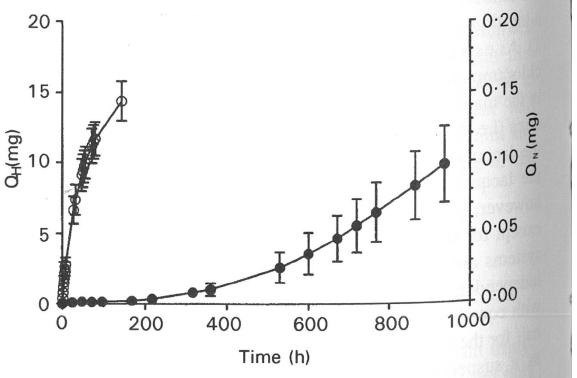

FIG. 3. Penetration of chloramphenicol (C_L = 31.3%) from Eudragit RL lacquer through the hoof membrane (thickness, d_B, = 104 µm) and the nail plate (d_B = 953 µm) at 32°C (n = 4, mean ± s.d.). Q_H and Q_N are, respectively, the amounts of drug penetrated through hoof membrane (○) and nail plate (●).

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Table 4. Flux of chloramphenicol through the hoof membrane and the nail plate at 32°C from Eudragit RL lacquers containing different concentrations of drug, C_L, and from a saturated solution in pH 7·4 phosphate buffer.

Concentration in the lacquer (%)	Maximum flux of chloramphenicol ($J(1000\,\mu m)$; $mg\,cm^{-2}\,s^{-1}$)	
	Hoof membrane	Nail plate
2·2	$3{\cdot}10 \pm 0{\cdot}39 \times 10^{-7}$	n.d.*
18·5	$4{\cdot}34 \pm 1{\cdot}27 \times 10^{-6}$	$8{\cdot}02 \pm 1{\cdot}81 \times 10^{-8}$
31·3	$7{\cdot}26 \pm 1{\cdot}75 \times 10^{-6}$	n.d.
47·6	$8{\cdot}11 \pm 2{\cdot}16 \times 10^{-6}$	n.d.
Saturated solution in phosphate buffer	$5{\cdot}32 \pm 1{\cdot}62 \times 10^{-6}$	$8{\cdot}21 \pm 2{\cdot}11 \times 10^{-8}$

*Not determined. Results are standardized to $d_B = 1000\,\mu m$. n = 3–7, mean ± s.d.

used with caution as a model for studying controlled-release systems for application on nails.

The fluxes of chloramphenicol, standardized to a barrier thickness of 1000 μm are in the same range as the maximum fluxes from aqueous suspensions (Table 4). Firstly, it is surprising that the flux through the hoof membrane from the more highly concentrated lacquers (for the 47·6% lacquer it is even statistically significant, $P = 0{\cdot}05$) is greater than that from an aqueous suspension. This can only be explained by the assumption of the formation of a supersaturated solution in the barrier. For the 31·3% Eudragit RL lacquer the development of a thermodynamically unstable supersaturated solution could be proved by polarization microscopy. This state seems also to be formed on the donor side of the hoof membrane, because of the distribution equilibrium, and remains until crystallization starts or the concentration falls below the solubility as a result of the emptying of the matrix. As the flux from the 18·5% lacquer is not significantly lower than the maximum flux from water, it has to be assumed that the solubility of chloramphenicol in the poly(methyl methacrylate) lacquer is in the same range. These findings are confirmed by the results of the nail plate—the flux from the 18·5% lacquer equals the maximum flux from water.

The lacquer presented, consisting of a highly permeable quaternary poly(methyl methacrylate) (Eudragit RL) and dibutyl sebacate as a plasticizer, is, therefore, a suitable dosage form for achieving high drug fluxes through the nail plate and the hoof membrane. By addition of a sufficiently high concentration of drug it is possible to achieve penetration rates which correspond to those from saturated liquid vehicles (water or non-aqueous solvents) or even exceed those owing to the temporary formation of a supersaturated system. Because of the low permeability of the nail plate the release rate of the lacquer is not important in this instance. The rapid development of the partition equilibrium between lacquer and barrier is, however, significant and so high-swelling polymers (Eudragit RL) have to be preferred. It must, however, be considered that the dried lacquer remains water-insoluble when it becomes more hydrophilic-otherwise it would be removed by washing and, therefore, the application intervals have to be shortened. On the other hand, the occlusivity of the nail lacquer is of some importance; this is probably increased for poorly swelling polymers with low water-vapour permeability.

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