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PERCUTANEOUS TRANSPORT*

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Percutaneous transport involves the passage of molecules from the outer surface of the skin to the dermis, and through the dermal capillary walls into the circulation, from whence they are distributed throughout the body. The degree of penetration which is necessary varies with the clinical requirements. At one extreme, we may not want any percutaneous absorption, for example we may wish to do nothing more than protect damaged epidermis. Paraffin based ointments, containing such things as zinc oxide or calamine are typical examples of this type of treatment. At the other extreme, drugs are applied to the skin specifically for their systemic effect[1]. Most often however, we are concerned with intermediate situations where limited absorption is indicated, bactericides in cosmetic deodorants, fungistats for skin infections and steroids for psoriasis are

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typical examples. Systemic absorption is usually undesirable, the steroids come to mind in this respect, but there are more potent examples, in particular the tragedy in France in which infants, who had been treated for napkin rash, suffered extensive brain damage due to absorption of hexachlorophene. All too often we have to resort to the old English custom of compromise, using a preparation which just satisfies local requirements and gives a systemic effect which, although undesirable, is small enough to be acceptable.

Transport can take place by several routes, which are grouped under two general headings, transepidermal and pilosebaceous. Pilosebaceous transport, also known as shunt diffusion, occurs through the skin appendages, that is, through the hair follicles, sebaceous glands and sweat glands. These all provide openings through the stratum corneum, with access to the dermis through thin layers of epithelial cells. Transepidermal transport occurs across the stratum corneum, a barrier of flattened, keratinised cells, about 15 μm thick. Progress by this route is slower than by shunt diffusion, but since the stratum corneum covers 10^3 to 10^4 times the area covered by the appendages, transport is mainly transepidermal. However, during the initial lag period, when the first of the absorbed material is making its way across the stratum corneum, transport is exclusively pilosebaceous.

There are numerous factors which affect percutaneous transport; if the stratum corneum is damaged, as with cuts, ruptured blisters, eczema etc., substances will pass freely through these imperfections. Hydration has a profound effect, occlusion techniques can bring about a hundred fold increase in absorption.

The site of application is also important, absorption varies from the most rapid through posterior auricular skin, to the slowest through the soles of the feet. There are many other factors, but the one which most concerns the pharmacist is the nature of the preparation which is applied to the skin.

A biologically active solid suspended in a homogeneous ointment base can be represented diagramatically by Figure I. Transport from this particle involves four stages.

A. Solution of the solid in the thin layer of vehicle surrounding the particle.

B. Migration of the dissolved drug from the layer of vehicle surrounding the particle, to the skin surface.

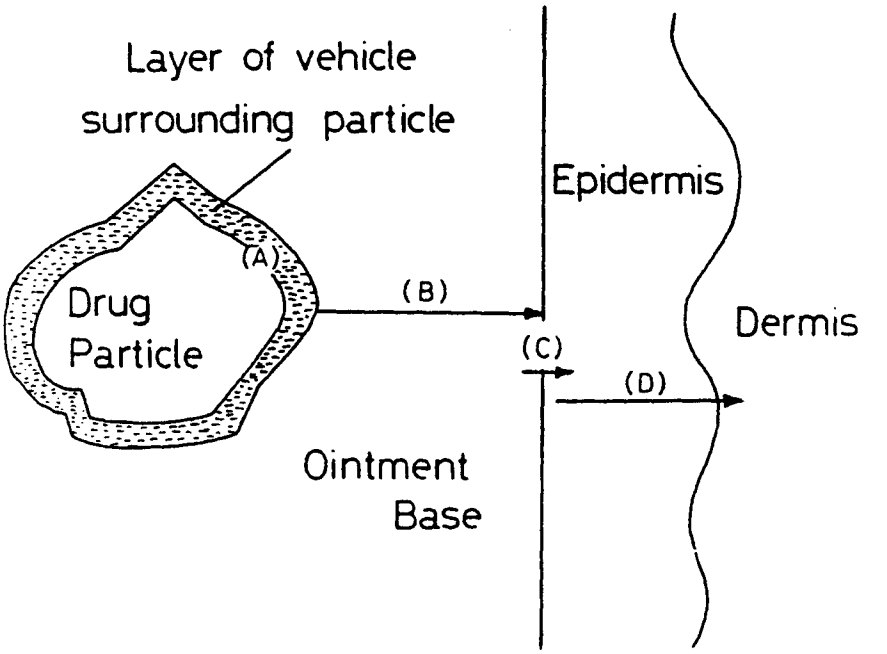


Figure 1 Migration route

C. Passage across the skin surface into the outer layers of the stratum corneum.

D. Migration through the stratum corneum to the inner epidermis, and thence into the dermis. Each step can be assessed in terms of definite physical laws. Step A will follow the Noyes-Whitney equation:-

$$\text{Rate of solution} = \frac{dQ}{dt} = SD(s_v - c) \qquad (1)$$

S is the surface area of the particle, D the diffusion coefficient, s_v the solubility in the vehicle and c is the concentration of the drug in the vehicle. Step B depends on the concentration gradient (Δc), the distance the dissolved molecules have to travel (d), and the diffusion coefficient of the particular molecules in that particular vehicle. These factors can be combined in the form of Fick's law:-

$$\frac{dQ}{dt} = \frac{DVc}{d} \qquad (2)$$

Step D can be considered in the same way as step B.

Higuchi[2] has combined the processes involved in steps A and B, and expressed the quan tity of drug (Q) transported in time t as :-

$$Q = (2A - Sv)\sqrt{\frac{Dt}{1 + 2\,(A-S_v)/S_v}} \qquad (3)$$

A is the total quantity of drug suspended in the base. Invariably, this is considerably greater than S_v so that the equation can be simplified to :-

$$Q = \sqrt{2ADcS_v} \qquad (4)$$

Step C involves the distribution coefficient K, between vehicle and skin, i.e.

$$K = C_s/C_v \quad (5)$$

where C_s is concentration in stratum corneum and C_v is concentration in vehicle. C_v is equivalent to Q, therefore :-

$$C_s = K\sqrt{2ADtS_v} \quad (6)$$

If suspensions having the same concentration are compared after the same interval of time, A and t will be constants. D. is a function of molecular weight and can be considered constant for a group of large molecules of similar size, e.g. steroids. Equation (6) can then be approximated to:-

$$C_s \propto Ks_v^{\frac{1}{2}} \quad (7)$$

Katz and Shaikh[3] plotted $Ks_v^{\frac{1}{2}}$ against log biological effect, in vivo for eleven anti-inflammatory steroids, and obtained a reasonably rectilinear relationship ($r = 0.86$), supporting this point of view.

Many workers have taken a more simplified approach and considered percutaneous transport to be directly related to distribution coefficient. A distribution coefficient of unity between stratum corneum and the vehicle would be expected to be optimum, because :-

(i) A coefficient less than one would mean a low affinity for the skin.

(ii) A coefficient greater than one would have too low a solubility in the base for a working concentration (C_v).

Lien and Tong[4] used Hansch analysis to correlate various partition coefficients e.g. octanol/water, for assorted groups of compounds, with in vitro and in vivo per-

meability rates. Quite good correlations were obtained in some cases, but not in others.

Precise quantitative relationships have not been forthcoming, for several reasons-

(i) The distribution coefficient is usually applied to solvent systems other than vehicle/s. corneum. There is evidence[5] to show that the distribution coefficient in one system is simply related to that in another, but there are numerous exceptions.

(ii) Properties other than distribution coefficient, are important, for example,diffusion coefficient. Molecular weights do vary significantly from substance to substance, even with steroids. Moreover, diffusion is also influenced by polar effects.

(iii) There is often doubt that biological results are truly representative of percutaneous absorption, e.g. measurement of blood or urine levels does not take into consideration metabolism or distribution elsewhere in the body. Threshold values are impracticable, because the absorption route changes in the early stages.

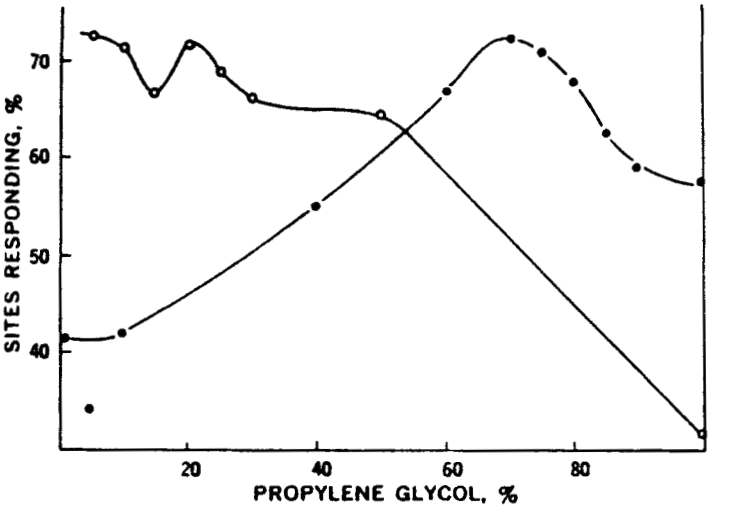
(iv) When comparing compounds, C_v is not an adequate representation of the influence of concentration. The thermodynamic activity a_v is required. This can be calculated approximately from $a_v = C_v/S_v$[6]

The considerations so far have assumed a dynamic process. An alternative is to assume that when the

steady state of absorption is reached, the various steps outlined above will take the form of a series of equilibria, linking a migration of active material from a reservoir which is the suspended solid, and a sink, represented by the systemic uptake of the drug. Poulsen[7] considered percutaneous absorption under such conditions. If a solid drug is in suspension in a vehicle on the skin, at the steady state, the concentration in solution will be its solubility in the vehicle S_v, and its concentration in the skin will be given by equation (8) as follows.

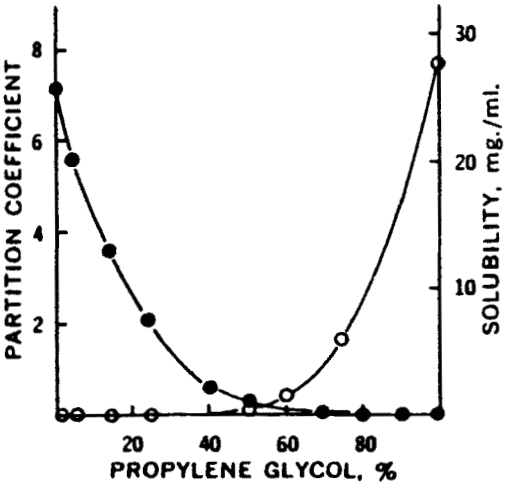
$$C_s = K\ C_v = K\ S_v \qquad (8)$$

Poulsen supported his views with results obtained with fluocinonide and fluocinolone acetonide in various water-propylene glycol mixtures[8]. These compounds gave different plots of biological effect against percentage propylene glycol, reproduced in Figure 2. Considering fluocinolone acetonide first, aqueous solubilities and distribution coefficients formed two 'mirror image' plots, shown in Figure 3. Such a situation would normally be anticipated. Poulsen explained the biological results for this compound on the basis of these plots. Arbitrary results, shown in Table 1, can be chosen to fit the plots in Figure 3. Abstracting from this table, for 20% glycol, $C_s = KS_v = 5o \times 0.2 = 10\%$ of steroid, but since the preparation contains only 0.1% steroid, $C_s = 50 \times 0.1 = 5\%$. The dotted line, shown in Figure 4 is obtained if this argument is continued on through the glycol concentration range, but for higher concentrations of suspended steroid, a plateau is obtained initially. This profile also shown in Figure 4, is similar to that obtained with the biological responses to fluocinolone acetonide.



In vivo ***response (24-hr. vasoconstriction) as a function of vehicle composition. Key:*** **O,** ***fluocinolone acetonide; and*** **●,** ***fluocinonide.***

Figure 2



Isopropyl myristate/propylene glycol-water partition coefficients **(●)** ***and propylene glycol-water solubilities*** **(O)** ***for fluocinolone acetonide.***

Figure 3

(Both figures reproduced from J. Ostrenga, C. Steinmetz & B. Poulsen J. Pharm. Sci. 60 1175 (1971))

TABLE I.

Arbitrary results for fluocinolone acetonide.

% GLYCOL	K	S_v	0.1%		1.0%	
			C_v	KC_v	C_v	KC_v
0	100	0.1	0.1	10.0	0.1	10.0
20	50	0.2	0.1	5.0	0.2	10.0
40	20	0.5	0.1	2.0	0.5	10.0
60	10	1.0	0.1	1.0	1.0	10.0
80	2	4.0	0.1	0.2	1.0	2.0
100	1	10.0	0.1	0.1	1.0	1.0

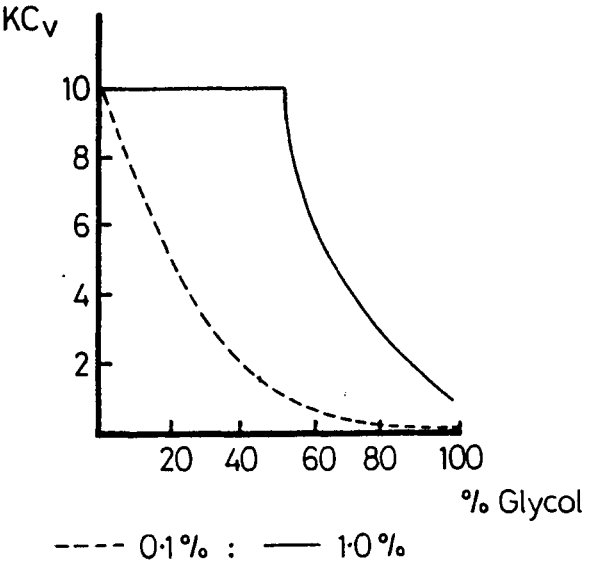


Figure 4 Theoretical percutaneous transport of fluocinolone acetonide

These distribution coefficients are not between propylene glycol and water, but instead, between a saturated solution of water in propylene glycol and a saturated solution of propylene glycol in water. Distribution behaviour can be influenced by the solute complexing with either the dissolved water or the dissolved propylene glycol, or both. This evidently occurs with fluocinonide, because the solubility and distribution coefficient plots are no longer symmetrically opposite[8]. A similar situation can occur in vivo, when the vehicle changes the solvent properties of the skin. Arbitary results, selected to fit this situation (Table2), yield a different set of biological response profiles (Figure 5), which fit the observed results for fluocinonide.

TABLE 2

Arbitrary results for fluocinonide.

% GLYCOL	K	S_v	0.1%		1.0%	
			C_v	KC_v	C_v	KC_v
0	100	0..	0.1	10	0.1	10
20	60	0.2	0.1	6	0.2	12
40	40	0.6	0.1	4	0.6	24
60	25	1.6	0.1	2.5	1.0	25
80	15	4.0	0.1	1.5	1.0	15
100	10	10.0	0.1	1.0	1.0	10

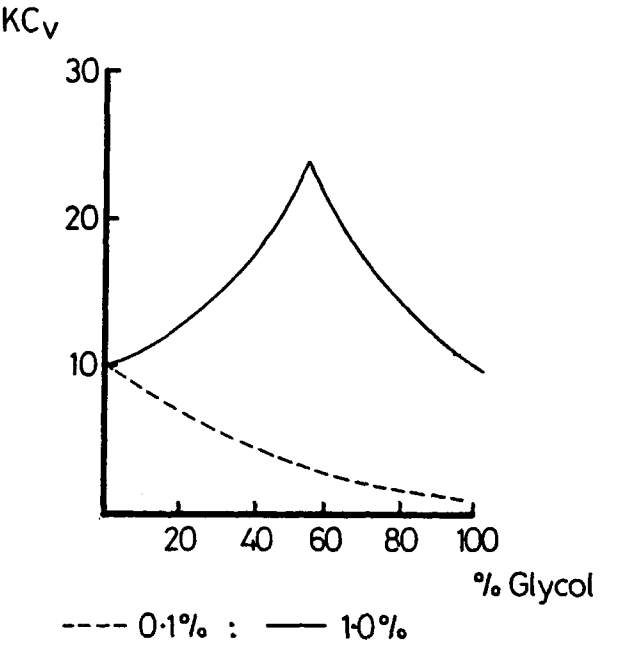


Figure 5 Theoretical percutaneous transport of fluocinonide

If the drug is in solution in the base, rather than in suspension, the migration into the skin will simply follow Equation[5] but the rate will be reduced with time, because C_v falls with time.

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