International Journal of Pharmaceutics, 82 (1992) R1–R6

IJP 10047

Rapid Communication

Rate control in transdermal drug delivery?

Richard H. Guy [a] and Jonathan Hadgraft [b]

[a] *University of California, San Francisco, Departments of Pharmacy and Pharmaceutical Chemistry, San Francisco, CA 94143 (USA)* and [b] *University of Wales, College of Cardiff, The Welsh School of Pharmacy, Cardiff CF1 3XF (UK)*

(Received 28 February 1992)
(Accepted 11 March 1992)

Key words: Transdermal drug delivery; Skin absorption; Rate control; Nitroglycerin; Penetration enhancement

There have been numerous claims made concerning the existence or lack of rate control provided by transdermal drug delivery systems. Because, in most cases, the term rate-controlling has been either vaguely defined or completely unspecified, the validity of the various claims is often difficult to assess. It is the objective of this paper to specify a simple method to quantify the degree to which a transdermal delivery system controls the overall input kinetics of drug into the body across the skin. The reason for revisiting this issue lies in the fact that the demonstration of bioequivalence between transdermal delivery systems containing the same drug is not as easily performed as that for (e.g.) oral dosage forms. It is not unusual for transdermal devices to differ significantly in drug content and surface area, yet still deliver basically the same amount of drug over the same period of application (illustrated most vividly, perhaps, for the nitroglycerin systems) (Hadgraft et al., 1991).

Previous efforts to address the issue of rate-control in drug delivery across the skin have considered the impact of a 'rate-controlling' membrane on inter-subject variability (Shaw and Theeuwes, 1985), the validity and utility of in vitro assessments of nitroglycerin release from transdermal systems (Hadgraft et al., 1991), and the general principles relating to drug transfer across diffusive barriers in series (Chien et al., 1983; Chien, 1987). In this communication, we focus upon the central issue of rate control as it relates to the safety and efficacy of a transdermally delivered drug. In particular, we offer a simple algorithm, by which the fractional contributions to rate control of the patch and of the skin can be measured from two simple experiments conducted for a period equivalent to the planned application time of the transdermal system: (i) the in vitro release of the drug into an aqueous sink, and (ii) in vitro delivery of the drug from the patch and across a piece of excised human skin. The degree to which the calculated values will change if the skin has elevated permeability (caused by either a pathologic condition, or induced deliberately using a penetration enhancer) is considered, and the utility of the approach, with respect to the calculation of maximum plasma levels achievable (and, hence, with respect to safety and efficacy), is illustrated.

Two in vitro experiments (Fig. 1) are typically considered necessary to characterize drug deliv-

Correspondence: J. Hadgraft, University of Wales, College of Cardiff, Cardiff CF1 3XF, U.K.

ery when a transdermal device is applied to the skin:

(Expt 1) measurement of drug release from the device into an aqueous sink;
(Expt 2) assessment of drug delivery from the patch and through the skin.

Under steady-state conditions, the total resistance (R_T) to drug delivery through the skin in Expt 2 is given by:

$$R_T = R_d + R_s \quad (1)$$

where R_d and R_s are the resistances to drug release from the device and to drug transport across the skin, respectively. It has been common to rewrite Eqn 1 in terms of reciprocal fluxes

$$\frac{1}{J_T} = \frac{1}{J_d} + \frac{1}{J_s} \quad (2)$$

and to estimate, from the results of Expts 1 and 2, the values of J_d and J_T. Basically, Expt 1 provides J_d, Expt 2 yields J_T; J_s is calculated from Eqn 2, and the fractional contributions to control are then determined from Eqns 3 and 4:

$$\text{Fractional control by device (Fd)} = \frac{R_d}{R_T} = \frac{J_T}{J_d} \quad (3)$$

$$\text{Fractional control by skin (Fs)} = [1 - \text{Fd}] = \frac{R_s}{R_T} = \frac{J_T}{J_s} \quad (4)$$

There are some significant problems with the above approach if the interpretation of the data is carelessly performed. Firstly, there is an assumption that steady-state conditions hold under all circumstances – simple examination of some recently published data for transdermal nitroglycerin devices shows that this is not always the case (Hadgraft et al., 1991). Secondly, if a true steady

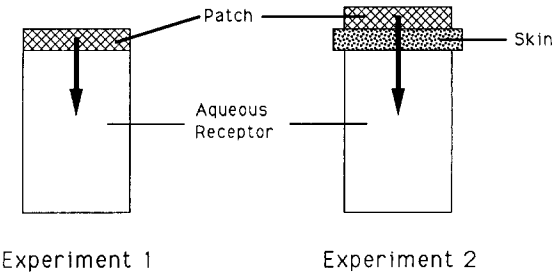

Fig. 1. In vitro experiments which are used to characterize drug delivery when a transdermal device is applied to the skin: (Expt 1) measurement of drug release from the device into an aqueous sink; (Expt 2) assessment of drug delivery from the patch and through the skin.

state is established across two barriers in series (the patch and the skin, in this case), then the fluxes of drug through each component of the total transport system *must be the same*. Thus, if we measure, for example, in Expt 2, that $J_T = 10$ mg/24 h per [area of patch], then it is physically impossible for J_d to exceed this value during Expt 2, irrespective of the release kinetics observed in Expt 1. In fact, when a residual analysis of drug content in the patch is performed at the end of the application period, mass balance demands, and experiment shows, that 10 mg will have been depleted from the system. The discussion can be illustrated using information for four of the marketed nitroglycerin devices (Table 1) (Hadgraft et al., 1991).

Obviously, the four systems differ significantly in size and drug loading, yet they all deliver basically the same amount of drug (10 mg) in the same amount of time (24 h) (Hadgraft et al., 1991). This has to be the case, of course, because they are each expected to achieve the same thera-

TABLE 1

Delivery characteristics of four marketed nitroglycerin patches (from Hadgraft et al., 1991)

System	Drug content (mg)	Area (cm^2)	Delivered dose (mg) in 24 h
Transderm-Nitro	50	20	10
Nitrodur II	80	20	10
Deponit	32	32	10
Minitran	36	13.3	10

peutic effect, and the dose delivered per unit area ($A_{T;24}$) must satisfy the basic equation of steady-state pharmacokinetics, i.e.,

$$\frac{S \cdot (A_{T;24})}{t_{app}} = CL \cdot C_{ss} \quad (5)$$

where S is the area of the patch, t_{app} represents the application time of the patch, C_{ss} is the target plasma concentration required, and CL denotes the clearance of the drug. How, then, to assess the relative degree to which each of the patches controls nitroglycerin input across the skin? The simplest solution to this question, in our opinion, can be presented as follows. Suppose a hypothetical patch of surface area 10 cm^2 releases, in Expt 1, 10 mg of nitroglycerin into an aqueous sink in 24 h. The amount of drug released in the intended application period ($A_{d;24}$) is, therefore, 1 mg/cm^2. Further, in Expt 2, when placed in contact with a 10 cm^2 piece of skin, over 24 h, 10 mg of drug is delivered from the patch across the skin (in other words, $A_{T;24} = 1$ mg/cm^2); i.e., an amount exactly equivalent to $A_{d;24}$. In this case, the equality between $A_{T;24}$ and $A_{d;24}$ implies that drug delivery across the skin is completely controlled by drug release from the delivery system. If $A_{T;24}$ were less than $A_{d;24}$, a contribution to rate control by the skin would be evident, the larger the difference, the greater the value of Fs. We therefore propose that the following definitions of fractional rate control be employed

$$\text{Fractional control by device (Fd)} = \frac{A_{T;tapp}}{A_{d;tapp}} \quad (6)$$

$$\text{Fractional control by skin (Fs)} = [1 - \text{Fd}] \quad (7)$$

In Table 2, the recently published results for the four nitroglycerin systems in Table 1 are analyzed with the above approach and values of Fd and Fs are calculated using Eqns 6 and 7. These values are in complete agreement with the findings of Hadgraft et al. (1991), who used Eqns 2–4 to determine the values of Fd and Fs; in this latter work, attention was focussed specifically upon the results applicable at 24 h; and the calculations were, therefore, essentially identical to those of the general approach outlined above. The danger in using the reciprocal flux equation to calculate Fd and Fs is the temptation to extrapolate, or interpolate, to different periods of application – if drug release from the system is not zero order, significant errors may result. Another inherent assumption of this analysis is that the patch is not exhausted of drug during the application period (Table 1 shows that this is not a problem for the nitroglycerin systems, for which, at most, only one-third of the initial drug content is delivered in 24 h). If there is significant depletion of the drug load, then rate control may be a significantly varying function of time; this point is treated in more detail below.

TABLE 2

Relative control of nitroglycerin delivery from four marketed patches (data from Hadgraft et al., 1991)

System	$A_{d;24}$ [a] (mg/cm^2)	$A_{T;24}$ [b] (mg/cm^2)	Fd [c]	Fs [d]
Transderm-Nitro	1.11	0.50	0.45	0.55
Nitrodur II	3.78	0.50	0.13	0.87
Deponit	0.35	0.31	0.87	0.13
Minitran	2.69	0.75	0.28	0.72

[a] Measured amount released into an aqueous sink in 24 h divided by area of patch (Hadgraft et al., 1991).
[b] Measured amount released into and across the skin in 24 h divided by area of patch (Hadgraft et al., 1991).
[c] Determined from Eqn 6.
[d] Determined from Eqn 7.

In the above discussion, the inherent variability associated with human skin permeability (Barry, 1983) has not been addressed. It is reasonable to ask, therefore, whether the approach described can be used to predict the impact of, for example, high-permeability skin upon drug delivery from devices which exert different levels of control. The increased permeability may be the result of a pathologic condition, or (e.g.) the perturbation induced by a penetration enhancer. For the purpose of illustration, we define high-permeability skin as that having a permeability which is an order of magnitude greater than the average normal, intact barrier. This means that the value of R_s in Eqn 1 is reduced to $R_s/10$.

The ratio of the total resistance to drug transport from a patch across high-permeability skin (R_T^i) to that from the same patch across normal skin (R_T) is, therefore:

$$\frac{R_T^i}{R_T} = \frac{\frac{R_s}{10} + R_d}{R_T} = \frac{Fs}{10} + Fd \qquad (8)$$

The degree of enhancement of transdermal delivery (EF, enhancement factor) which will result from this perturbation to the skin is equivalent to the reciprocal of the above ratio, i.e.,

$$EF = \frac{R_T}{R_T^i} \qquad (9)$$

Furthermore, the amount of drug delivered into the body during the application time of the patch to the high-permeability barrier can be calculated by multiplying the dose delivered across intact skin by EF. Table 3 contains calculations showing how the input of nitroglycerin from four marketed delivery systems is predicted to increase when the skin at the application site is compromised. Also shown in Table 3 are the predicted values of C_{ss}^i which would result from the application of the different patches to the more permeable skin. The values of C_{ss}^i are calculated from Eqn 5 using the $A_{T;24}^i$ values determined from the EF parameters defined above, and a published, average clearance for nitroglycerin of 1044 l/h (Jaeger, 1986). Through normal, intact skin, for each of the four systems, the 'control' value of C_{ss} is 0.40 ng/ml (again calculated from Eqn 5 with $S \cdot A_{T;24} = 10$ mg). In this way, given knowledge of a drug's therapeutic index, it should be possible to make a first-order estimate of the potential ramifications of applying a transdermal patch to a compromised skin surface.

TABLE 3

Nitroglycerin delivery from four marketed patches across high-permeability [a] skin

System	$\frac{R_T^i}{R_T}$ [b]	EF [c]	$S \cdot A_{T;24}^i$ [d] (mg)	C_{ss}^i [e] (ng/ml)
Transderm-Nitro	0.51	1.98	19.8	0.71
Nitrodur II	0.22	4.61	46.1	1.66
Deponit	0.88	1.13	11.3	0.41
Minitran	0.35	2.84	28.4	1.14

[a] High-permeability skin is defined as that which has a barrier function 10-fold less than normal skin (i.e., $R_s^i = R_s/10$).
[b] Determined using Eqn 8.
[c] Determined using Eqn 9.
[d] The dose delivered in 24 h across normal skin (i.e., 10 mg) multiplied by EF.
[e] Calculated from Eqn 5 using the $S \cdot A_{T;24}^i$ values in the preceding column, and CL = 1044 l/h (Jaeger, 1986). The corresponding C_{ss} for drug delivery through intact skin from each of the four patches is 0.4 ng/ml.

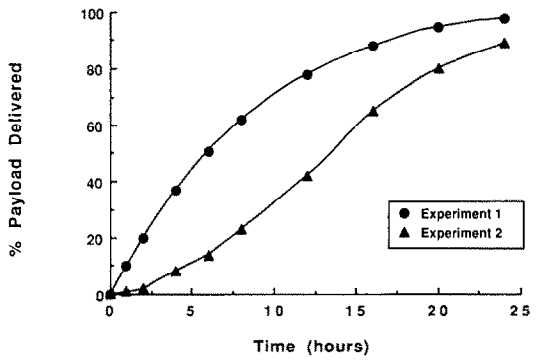

Fig. 2. Simulated data from Expts 1 and 2 for a transdermal delivery system which is essentially fully depleted of its payload by the end of the application period.

Analysis for transdermal systems which deliver a large fraction of their payload: For controlled substances (e.g., fentanyl), and for very potent drugs, for which continual delivery over (for example) 24 h is sub-optimal, it may be beneficial to design a transdermal patch that delivers all (or a large percentage) of its payload during the application period. Simulated data from Expts 1 and 2 for such a system are shown in Fig. 2. Because 'steady state' per se is not achieved in this case, and because the patch is exhausted by the end of the application period, the application of Eqn 6 can be misleading. Clearly, for the hypothetical situation illustrated in Fig. 2, at 24 h, $A_{d;24}$ and $A_{T;24}$ are equal; hence, Eqn 6 predicts that Fd $\approx$ 1 and Fs $\approx$ 0. At 24 h, this must be the case – the patch is essentially depleted of drug, there is hardly any concentration gradient remaining across the skin, and the resulting negligible input of drug into the

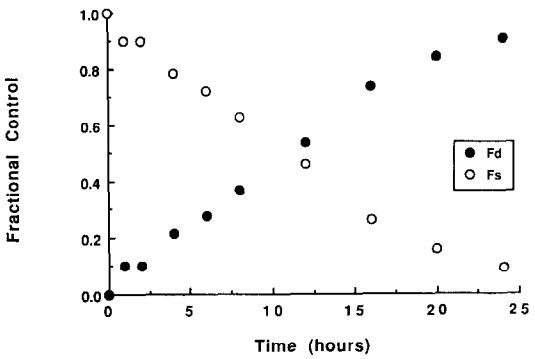

Fig. 3. Values of Fd and Fs, calculated as a function of time (using equations analogous to Eqns 6 and 7), for the transdermal system having the release and delivery characteristics shown in Fig. 2.

skin dominates the rate at which compound can ultimately show up in the systemic circulation. Contrast this situation with that which exists a few moments after the patch is applied: at this point, the patch is full of drug, whereas the skin is essentially devoid of compound. There is no supply problem to the skin surface (as is the case at 24h), and the appearance of the first molecules into the blood is therefore controlled completely by their rate of passage across the skin. Thus, close to $t = 0$, Fs ≈ 1, and Fd ≈ 0. It follows that, over the application period of a fully depleting device, the fractional control levels exerted by patch and skin are continually varying; the form of these time-dependent functions can be calculated from the individual data points collected during Expts 1 and 2. For the simulated data in Fig. 2, the calculated values of Fd and Fs as a function of time are plotted in Fig. 3. In a manner comparable to that outlined above, one can also analyze the impact of patch application to high-permeability skin, and how the resulting blood levels of the drug will be affected.

In summary, it has been the goal of this communication to de-mystify the concept of rate control in transdermal drug delivery, and to present a very simple approach by which the contributions of the device and of the skin to drug input control can be calculated from readily available experimental data. It should be clear from the analysis that drug delivery across the skin is directly dependent upon the area of skin contact, but may be less sensitive to drug loading in the patch, particularly if the skin provides a significant contribution to the control of delivery. Furthermore, the patch design does not predetermine the location of the rate-controlling step in drug delivery; for example, the presence of a polymeric membrane between a drug reservoir and the skin surface does not guarantee that the patch will be rate-controlling. It follows that the amount of drug present in a transdermal system, and the mechanism by which drug is released from the system, are inappropriate parameters for the establishment of bioequivalence criteria. One of the key parameters, which must be matched in transdermal drug delivery, is the amount of drug absorbed in a specified time period. It is interesting that a wide range of drug loading in the device can produce the same apparent dose absorbed (see Tables 1 and 2). In the design of new systems, it is important for safety reasons (see Table 3) to attempt to make the drug loading as close as possible to the amount absorbed. Finally, while experiments which measure drug release from transdermal systems into an aqueous sink (Expt 1 – see Fig. 1) are useful for quality control and quality assurance (Shah et al., 1986, 1989), they give no indication of the system's ability to determine rate control of drug input across the skin. It follows that, unless the drug is released from the device at a rate slower than its absorption across the skin, studies of the type exemplified by Expt 1 cannot be used in in vitro-in vivo correlations.

Acknowledgement

This work was supported in part by a grant (HD-23010) from the U.S. National Institutes of Health.

References

Barry, B.W., *Dermatological Preparations: Percutaneous Absorption*, Dekker, New York, 1983, pp. 235–236.

Chien, Y.W., Development concepts and practice in transdermal therapeutic systems. In: Chien, Y.W. (Ed.), *Transdermal Controlled Systemic Medications*, Dekker, New York, 1987, pp. 25–81.

Chien, Y.W., Keshary, P.R., Huang, Y.C. and Sarpotdar, P.P., Comparative controlled skin permeation of nitroglycerin from marketed transdermal delivery systems. *J. Pharm. Sci.*, 72 (1983) 968–970.

Hadgraft, J., Lewis, D., Beutner, D. and Wolff, H.-M., In vitro assessments of transdermal devices containing nitroglycerin. *Int. J. Pharm.*, 73 (1991) 125–130.

Jaeger, H., Absolute bioavailability of GTN patches. In: Jaeger, H., Mosberg, H., Plettenberg, H and Klingmann, I. (Eds.), *Transdermal Drug Delivery*, ipa Verlag GmbH, Neu-Ulm, 1986, pp. 142–150.

Shah, V.P., Tymes, N.W. and Skelly, J.P., In vitro release profiles of clonidine transdermal therapeutic systems and scopolamine transdermal patches. *Pharm. Res.*, 6 (1989) 346–351.

Shah, V.P., Tymes, N.W., Yamamoto, L.A. and Skelly, J.P., In vitro dissolution profile of transdermal nitroglycerin patches using paddle method. *Int. J. Pharm.*, 32 (1986) 243–250.

Shaw, J.E. and Theeuwes, F., Transdermal dosage forms. In: Prescott, L.F. and Nimmo, W.S. (Eds), *Rate Control in Drug Therapy*, Churchill Livingstone, Edinburgh, 1985, pp. 65–70.