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Rapid Communication

In vivo-in vitro comparisons in the transdermal delivery of nitroglycerin

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Over the past decade there has been a considerable increase in the interest in transdermal drug delivery and it has become apparent that it would be desirable to be able to conduct in vitro experiments which provide indicators of in vivo performance. Two types of in vitro experiment can be conducted in order to evaluate transdermal delivery systems. In the simplest the transdermal device is placed in a modified dissolution apparatus and the intrinsic release characteristics measured as the drug diffuses from the delivery system into an aqueous receptor phase. This type of experiment is useful for determining batch to batch conformity. It cannot provide information about in vivo performance unless the device is the rate control in the total drug delivery into the systemic circulation (Guy and Hadgraft, 1992). In most transdermal systems that are currently on the market there is some control from the skin. In the case of matrix systems such as Nitrodur II, the relative control from the device and from the skin is 13:87 (Hadgraft et al., 1991). Clearly, in this situation an intrinsic release study using conventional dissolution apparatus will be of no use in estimating how the device will perform when it is placed in contact with skin.

The second technique is to place the device in contact with dermatomed skin mounted in a Franz-type diffusion cell. In this situation the drug diffuses out of the device and crosses the same barriers that it would in vivo. The major difference is that the skin used in vitro may not be metabolically viable. The question that needs to be addressed is whether or not the in vitro release profiles generated can be used to provide an indication of the plasma levels that are found in vivo.

The in vitro experiment gives the amount of drug that permeates through the skin as a function of time. It is possible to convert this to a rate which should be the same input rate for the drug when it is delivered to man. This being the case the input rate can be equated to the known clearance kinetics of nitroglycerin (gtn) to provide estimates for the plasma concentration time profile. Additionally, it should be possible to use the information to determine the residual content of the patch as a function of time and relate this to the observed figure.

It is the purpose of this publication to examine the in vitro-in vivo correlations for Deponit and Nitrodur II as examples of transdermal systems which have been examined in detail and for which published data are available.

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The in vitro release kinetics of the two devices across human skin (dermatomed to 220 μm) have been determined previously. The data are reproduced from Hadgraft et al. (1991) in Fig. 1 which shows the mean values $\pm$ standard deviation (n = 3).

With this information, it should be possible to calculate the variation that may be expected in the plasma levels in vivo that result from the variation in input function of the gtn into the systemic circulation. In order to estimate the input rate the data for the gtn levels at either extremes of the standard deviations have been taken and polynomial fits to the data obtained with the following equations:

Nitrodur II:

mean + SD

$m = 75.1 + 687.4t + 23.63t^2 - 0.98t^3 \quad r^2 = 0.999$

mean–SD

$m = -19.90 - 28.46t + 20.31t^2 - 0.47t^3 \; r^2 = 0.997$

Deponit:

mean + SD

$m = -121.19 + 733.76t - 17.83t^2 + 0.28t^3$

$r^2 = 0.998$

mean–SD

$m = -51.84 + 108.66t + 35.41t^2 - 1.08t^3$

$r^2 = 0.997$

where m (μg) is the amount permeated per patch in time t (h).

It is simple to differentiate the above equations to give the rate of penetration over the application time of 24 h.

STELLA software on the Apple Macintosh was used to equate the input rates with the published clearance kinetics of gtn. A mean value of 1044 lh^{-1} was taken for the clearance rate although it must be appreciated that this is also subject to inter-individual variation (Jaeger, 1986). In this publication this variation has not been taken into consideration, since it is not a variable probed by the in vitro experiment.

The STELLA software uses numerical integration to determine the loss of drug from the device and the plasma concentrations. In this simulation a Runge–Kutta method was used with a step time (dt) of 0.0025. Fig. 2 shows the expected plasma levels following the transdermal application of Nitrodur II. Also plotted on the graph are the mean C_{max} levels found in vivo $\pm$ SD (n = 24) (Noonan et al., 1986). There is a good correlation between the predicted and observed values.

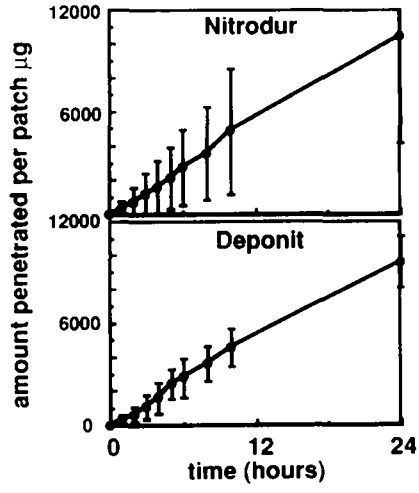

Fig. 1. Amount of gtn penetrated through dermatomed human skin from Nitrodur II and Deponit. Data from Hadgraft et al. (1991).

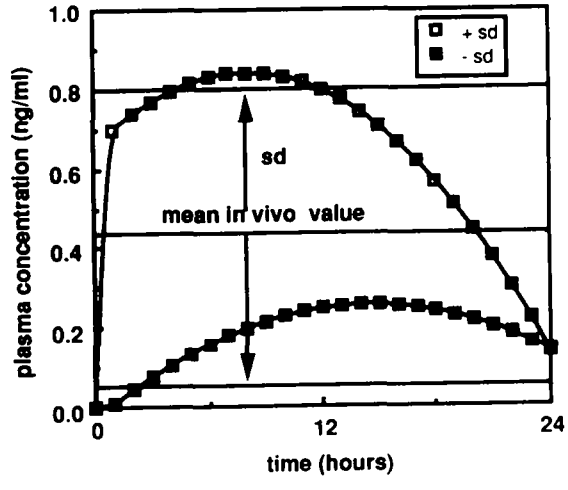

Fig. 2. Mean in vivo C_{max} levels $\pm$ SD (data from Noonan et al., 1986) for Nitrodur II and the predicted plasma levels using the in vitro penetration data and known clearance kinetics.

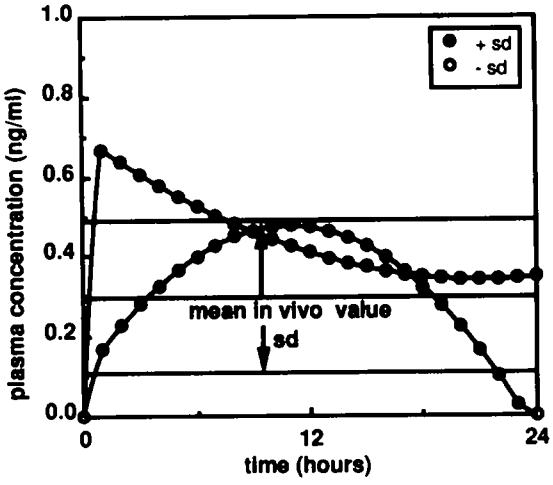

Fig. 3. Mean in vivo C_{max} levels ± SD for Deponit and the predicted plasma levels using the in vitro penetration data and known clearance kinetics.

It is interesting that the spread of results for both the in vitro and in vivo experiments are very similar but most importantly the in vitro experiments were able to be used together with the known clearance kinetics of the drug to estimate plasma levels.

Similar results were obtained for Deponit (Fig. 3).

Again the correlation between the levels predicted from the in vitro experiments and those determined from a volunteer study is good.

The other parameter that can be examined is the residual amount left in the patch and hence the amount, by difference the quantity of gtn, that has been delivered to the skin. After 24 h both the Nitrodur II system and the Deponit are designed to deliver 10 mg gtn. The values determined from volunteer studies were Nitrodur II, 10.67 ± 4.78 mg ($n = 24$) (Noonan et al., 1986) and Deponit, 8.9 ± 1.3 ($n = 22$). This can be compared with the values generated using the in vitro data and the STELLA modelling. In the simulations the range of values for the apparent dose delivered were as follows: Nitrodur II, 4.6–16.6 mg; Deponit, 8.1–11.2 mg.

The agreement again is very good and the ranges also provide valuable predictors for the

TABLE 1

Apparent dose of gtn as a function of time

Time (h)	Apparent dose (mg)	SD	n
6	3.6	0.6	4
12	5.5	1.4	4
18	7.6	1.2	4
24	8.6	0.5	4
12	5.4	1.2	11

observed in vivo scatter in the data. For Deponit additional data are available for the way in which the apparent dose varies as a function of application time: in a smaller volunteer study ($n = 4$), Deponit patches were applied to the skin of healthy human volunteers and removed at 6, 12, 18 and 24 h after application. At the 12 h point a further study was conducted generating 11 additional data points. The apparent dose was determined by assaying the residual gtn in the patch. The results are shown in Table 1 and Fig. 4. Fig. 4 also shows the predicted way in which the apparent dose is expected to vary with time as a result of analysing the in vitro data as described above.

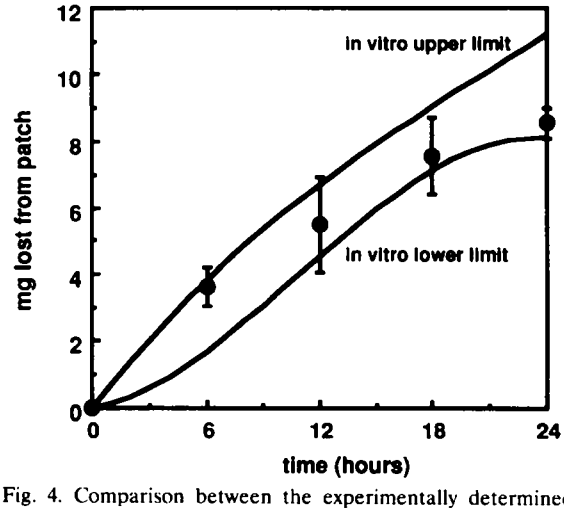

Fig. 4. Comparison between the experimentally determined levels of gtn lost from the Deponit patch as a function of application time and those calculated from the in vitro data.

There is very good agreement between the predicted and experimentally determined values. This shows that the in vitro technique linked with the clearance kinetics can provide information about the delivery of the drug over the entire time course of application.

For the delivery of transdermal nitroglycerin the in vitro technique in which the release of drug is assessed with the patch in contact with human skin dermatomed to 220 μm, there appears to be very good in vitro-in vivo correlation. This correlation should be good for other systems provided the experimental protocols are designed correctly and that there is no significant difference in the transfer rate of the drug through 'dead' skin compared to viable skin. Problems may be encountered if there are significant metabolic events occurring as the drug diffuses through the skin in vivo.

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