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In vitro assessments of transdermal devices containing nitroglycerin

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Summary

The in vitro rates of release of nitroglycerin from a number of products have been determined. The rates were measured in the absence of any skin, with dermatomed skin and skin that had been damaged by successive tape stripping. The results demonstrate the need for care in the interpretation of the data. If conventional Franz-type diffusion cells are used to monitor the rates of release where there is no rate-controlling membrane, it is possible to obtain erroneous results. This is caused by diffusion of additional drug from the polymer that is sandwiched between the ground glass edges of the cell. Considerable 'edge effects' are possible.

Introduction

In order to ensure batch to batch reproducibility and compare transdermal systems from different manufacturers, it is necessary to conduct in vitro release assessments. In the first instance, these can be conducted directly into a suitable receptor medium using an appropriate approved method (Shah et al., 1988). Care should be taken that the receptor phase does not interact with the polymeric constituents of the device since this would provide false results. In addition, the receptor solution should act as a perfect sink for the diffusant. If these criteria are adopted a kinetic analysis of the release profile can be performed. The calculations, with appropriate solutions of Fick's second law of diffusion, will provide values for the diffusion coefficient of the drug in the polymer. These can be compared with values within the skin to determine whether the device or the skin is the rate determining factor.

In any assessment the patches should also be compared by measuring the in vitro penetration rate across excised skin samples. This can be achieved using conventional Franz-type diffusion cells. The results can be compared to those obtained without the presence of the skin and a simple calculation performed to establish the relative resistances within the device and skin. If J_{tot}

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represents the flux observed both from the device (d) in contact with the skin (s) and J_d and J_s the respective individual fluxes

$$\frac{1}{J_{tot}} = \frac{1}{J_s} + \frac{1}{J_d} \quad (1)$$

The skin component can be further divided into the contributions from the stratum corneum (J_{sc}) and the viable tissue (J_{ve})

$$\frac{1}{J_s} = \frac{1}{J_{ve}} + \frac{1}{J_{sc}} \quad (2)$$

In some instances, it is possible that the transdermal device is placed onto a skin site where the barrier function has been compromised. In this case, J_{sc} will be large and drug input into the systemic circulation could be very much greater than anticipated especially if $J_d > J_{sc}$. This effect can be examined in vitro by mounting the device onto skin which has been tape stripped, thus damaging the stratum corneum. It is possible to conduct this type of experiment in conventional Franz-type diffusion cells and this paper details some of the difficulties involved.

Materials and Methods

The following transdermal delivery systems, all of which contain nitroglycerin (GTN) were examined: Transderm-Nitro (Ciba Geigy); Deponit and S917 (Schwarz Pharma); Nitrodur II (Key Pharmaceuticals) and Minitran (3M Riker). The patch details are presented in Table 1.

TABLE 1

Transdermal delivery systems examined

	GTN content (mg)	Area (cm^2)	Claimed in vivo release in 24 h (mg)
Transderm Nitro	50	20	10
Deponit	32	32	10
S917	10	16	7.5
Nitrodur II	80	20	10
Minitran	36	13.3	10

Dissolution test

The intrinsic release rates were determined using the FDA paddle method (Shah et al., 1988) with a paddle speed of 50 rpm and a receptor phase consisting of 900 ml distilled water thermostated to 32°C. The GTN concentrations in the receptor phase were determined using an HPLC method: apex ODS II 5 μm 25 cm column, mobile phase methanol:water (70:30) at a flow rate of 1.0 ml/min. Detection at 220 mm using these conditions gave a retention time of 4.0 min. The release characteristics for Deponit were also determined by clamping whole patches in all-glass Franz-type diffusion cells (available area for diffusion 1.77 cm^2, diameter 1.5 cm). The receptor phase was pH 7.4 phosphate-buffered saline thermostated at 37°C; the cells were designed such that the thermostating would provide a skin surface temperature of 32 ± 1°C when dermatomed epidermal membranes were mounted in them.

Skin permeation studies

Abdominal skin was dermatomed to 220 or 310 μm and placed in the Franz-type diffusion cells. The transdermal patches were adhered to the stratum corneum and the GTN flux through the skin monitored by HPLC over a 24 h period. In order to simulate damage to the stratum corneum experiments were also conducted in which abdominal skin samples were dermatomed to 310 μm and subsequently tape stripped 15 times. It was not possible to produce intact epidermal membranes by tape stripping after the skin had been dermatomed to a thickness of less than 310 μm.

Tests on trimmed patches

Additional experiments on GTN release and skin permeation were conducted in which the patches were trimmed to a diameter of 2.1 cm such that they could be placed in the cells with a 3 mm overlap to ensure a good seal. This technique was possible for patches such as Deponit but could not be performed on Transderm-Nitro due to its construction.

Results and Discussion

The in vitro release profiles obtained using the FDA paddle method for the different systems are presented in Fig. 1. The data points represent the mean values from six determinations. The standard deviations were less than 5% of the quoted mean values and have been omitted from the graph for clarity. The results for Deponit and Nitrodur II are in good agreement with the one quoted by Shah et al. (1988); the values for Transderm-Nitro are less. For example, the 24 h time point in this study of 22.21 ± 1.29 mg released can be compared to 33.9 ± 2.1 and 28.0 ± 1.5 mg released in 23 h. The results in the present study show greater control of the drug released than those determined previously.

Both Nitrodur II and Minitran show rapid drug release with greater than 80% of the content being released within a 3 h period. Transderm-Nitro shows a classic membrane moderated profile with a small amount of drug being released rapidly followed by a zero-order process. Although Deponit does not contain a rate-controlling membrane it exhibits a similar release profile but the total amount released after 24 h is approximately half that for Transderm-Nitro.

S917 is somewhat different in that it has been designed to deliver the majority of its GTN content during the first few hours of application. 75% of the drug is released in the first 6 h.

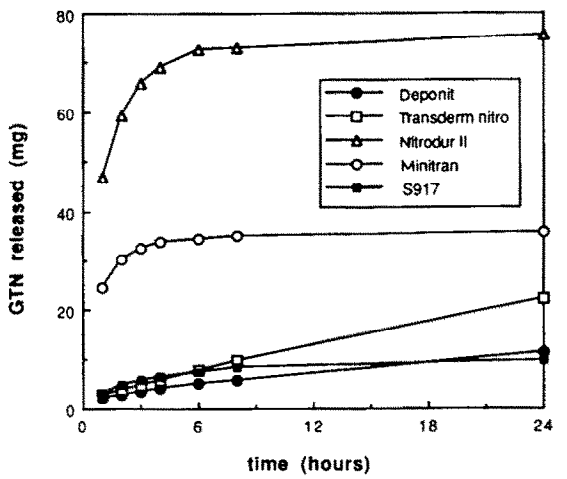

Fig. 1. In vitro release profiles, as determined by the FDA paddle method, for the different GTN containing transdermal systems.

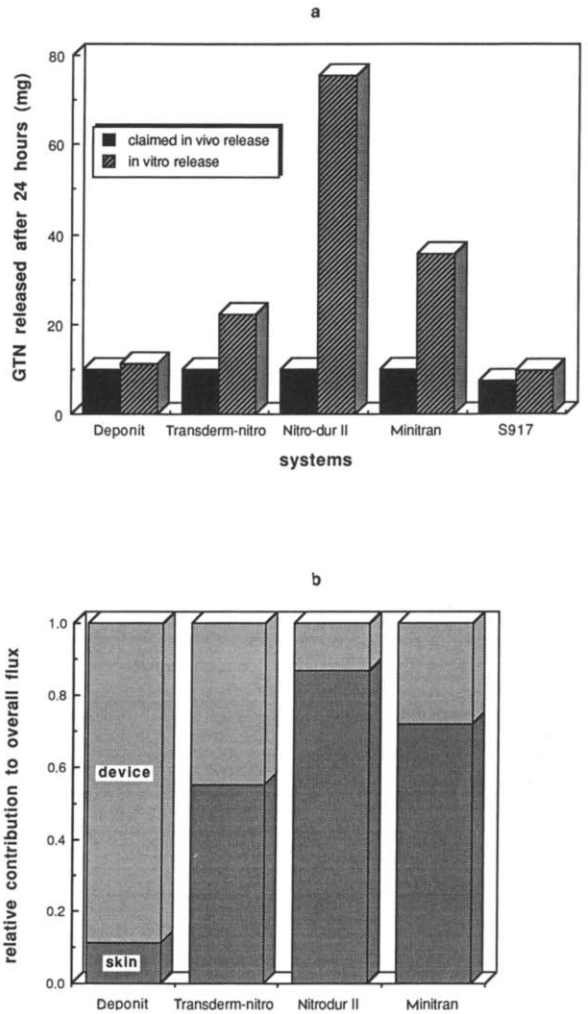

Fig. 2. (a) A comparison between the amount of GTN released in vitro after 24 h and the claimed in vivo uptake. (b) A comparison between the different contributions from the skin and from the device in controlling the overall absorption of transdermally delivered GTN.

It is interesting to compare the measured in vitro release after 24 h with the claimed in vivo uptake during a similar time period. The comparisons are made in Fig. 2a. In the cases of Deponit and S917 the in vivo uptake and in vitro release are very similar showing that the J_s and J_d in Eqn 1 are very similar. For the other systems the skin resistance is the dominant factor. This can

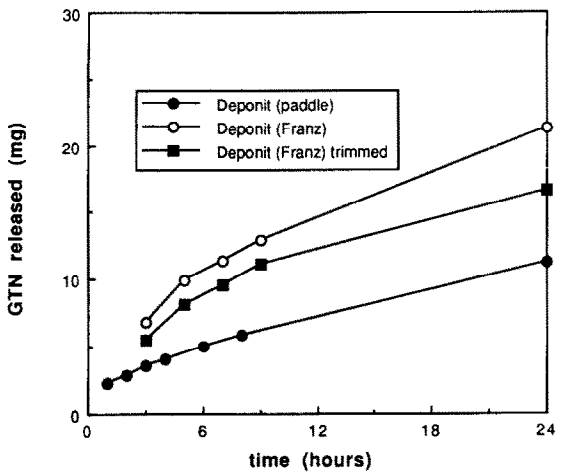

Fig. 3. The GTN release profiles for Deponit showing the differences obtained between the paddle method, the patch supported in a Franz-type diffusion cell and a trimmed patch mounted in a Franz diffusion cell.

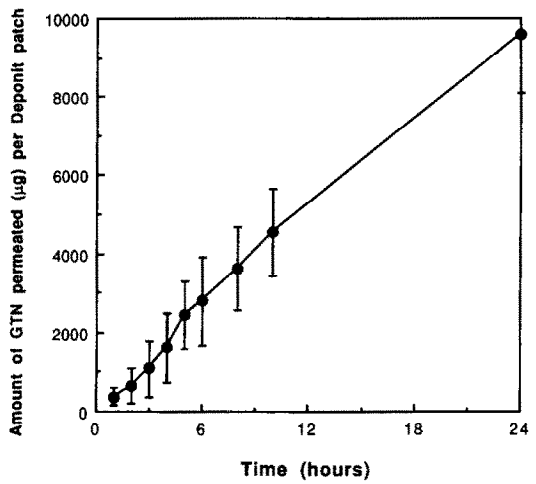

Fig. 4. The release and transfer of GTN from a Deponit patch through human skin dermatomed to 220 μm.

be seen by analysing the data using Eqn 1. It is possible to calculate the relative resistances due to the release of drug from the device and drug penetration through the skin. The comparisons are made in Fig. 2b. There is a wide range of relative contributions with 10% of the resistance attributable to the skin in the case of the application of a Deponit system and 90% Nitrodur II.

The release profiles for whole Deponit patches clamped into Franz-type diffusion cells are presented in Fig. 3. The receptor phase data have been scaled in proportion to the total patch area divided by the area available for diffusion such that comparisons with Fig. 1 can be made. It is immediately apparent that using this technique provides overestimates of the amount of drug released. The reason for this is that GTN can diffuse radially in the patch and drug not immediately above the active diffusion area in contact with the receptor phase is also available. Consideration of the data in Fig. 3 suggests that the effective area of diffusion is 3.6 cm^2 rather than the measured 1.8 cm^2. Care needs to be taken in the design of this type of release study to minimise edge effects. In an attempt to achieve this the Deponit patches were trimmed so that there was a 3 mm overlap with the ground glass joints of the diffusion cells. The results for the trimmed patches are also shown in Fig. 3. There is an improvement in cutting down the size of the patches but there still appear to be considerable edge effects.

These problems do not manifest themselves when a skin barrier is incorporated into the cells. The release of GTN across excised human abdominal skin dermatomed to 220 μm was determined for Deponit, Nitrodur, Transderm-Nitro and Minitran. The experiments were conducted in triplicate and are presented in Figs 4–7. Where

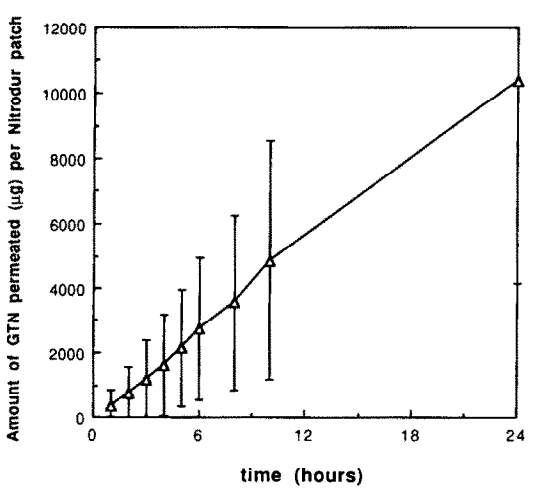

Fig. 5. The release and transfer of GTN from a Nitrodur patch through human skin dermatomed to 220 μm.

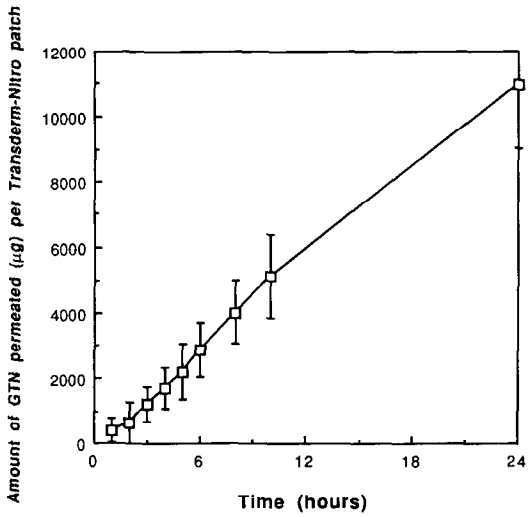

Fig. 6. The release and transfer of GTN from a Transderm-Nitro patch through human skin dermatomed to 220 μm.

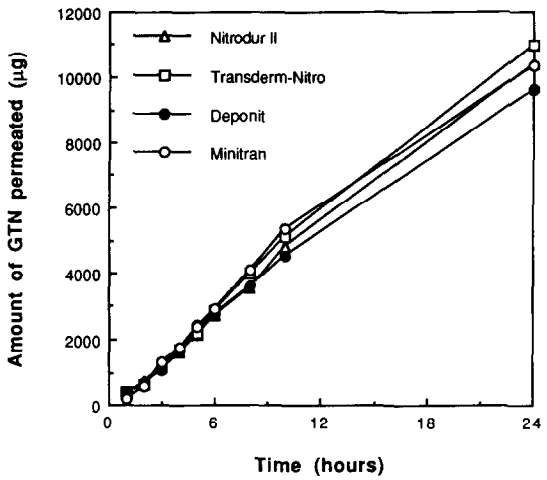

Fig. 8. A comparison of the release and transfer of GTN from the four patches through human skin dermatomed to 220 μm.

the device rather than the skin controls the rate of delivery, the error bars are smaller. A comparison of all four systems is given in Fig. 8. It shows that the in vitro system with skin present is predictive of the in vivo transfer rate with 10 mg penetrating over the 24 h period. When a rate-limiting membrane is included in the Franz-type diffusion cell there is no problem due to edge effects and in vitro-in vivo correlations are good.

Subsequent tape stripping experiments could only be performed on skin which had been dermatomed to 310 μm. It was therefore necessary to verify that, under the experimental conditions described above, there were no significant differences between the amounts of GTN that permeate skin dermatomed to 220 and 310 μm. A single experiment with Transderm-Nitro, Deponit and S917 was conducted using whole patches and the results presented in Fig. 9. There are no apparent differences between the data presented

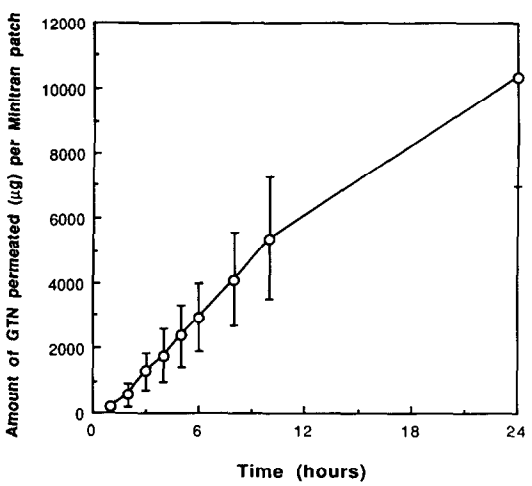

Fig. 7. The release and transfer of GTN from a Minitran patch through human skin dermatomed to 220 μm.

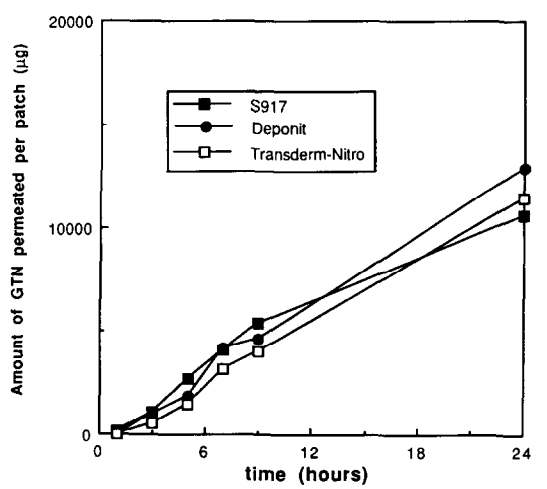

Fig. 9. A comparison of the release and transfer of GTN from Deponit, Transderm-Nitro and S917 patches through human skin dermatomed to 310 μm.

in Figs 8 and 9 indicating that the skin tissue within the depths 220–310 μm does not contribute to the control of the GTN flux, in terms of Eqn 2 ($1/J_{sc}$) dominates.

The effect of trimming the patches to an area of 2.3 cm^2 was also examined. All systems were treated in this way except Transderm-Nitro which could not be cut. Fig. 10 shows the results where the experiments were conducted in triplicate. A comparison between the amounts penetrated at 24 h was made between Figs 8 and 10. Statistical analysis (Duncans New Multiple Range analysis of variance) showed no significant difference ($p < 0.01$), confirming that patch trimming and the skin dermatome procedures did not have any significant effect when skin was present in the diffusion cell.

For some transdermal patches it is clear that the rate controlling step is in the skin and not in the delivery system. The final experiments involved a study in which skin dermatomed to 310 μm was damaged by tape stripping 15 times. This would simulate inadvertent placing of a delivery system on to skin whose barrier function had been compromised. In order to minimise edge effects patches were trimmed to an area of 2.3 cm^2 with the exception of Transderm-Nitro which was used intact. The results for this patch could therefore be influenced by edge effects.

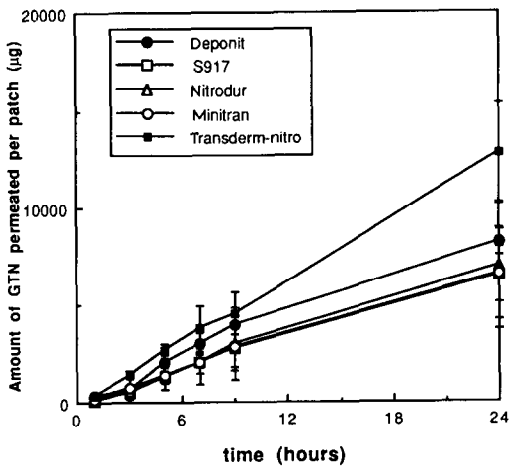

Fig. 10. A comparison of the release and transfer of GTN from Transderm-Nitro (whole patch), Deponit, Nitrodur, Minitran and S917 patches trimmed to 2.3 cm^2 through human skin dermatomed to 310 μm.

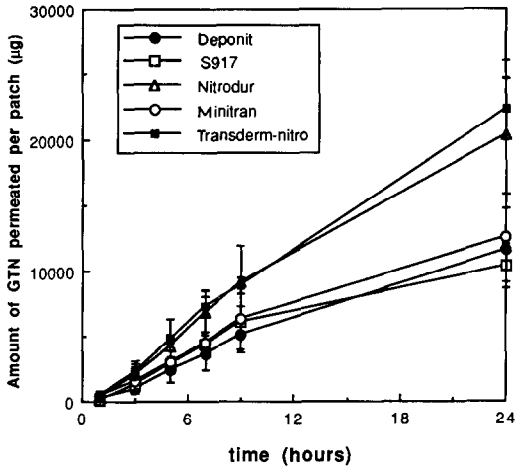

Fig. 11. A comparison of the release and transfer of GTN from Transderm-Nitro (whole patch), Deponit, Nitrodur, Minitran and S917 patches trimmed to 2.3 cm^2 through human skin dermatomed to 310 μm and tape stripped 15 times.

Fig. 11 shows the data obtained. Analysis of variance of the amount penetrated after 24 h was performed to compare the data in Fig. 11 with that in Fig. 10. In the cases of Deponit, S917 and Minitran there was no significant difference ($p < 0.01$).

Conclusions

The data generated demonstrate the need for careful experimental design particularly where release profiles for transdermal patches are obtained in Franz-type diffusion cells. Edge effects cannot be ignored. The technique can be used to examine damaged skin and provides information about the relative contributions to the overall GTN flux from the patch and from the skin.

References

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