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TRANSDERM®-NITRO
CONTROLLED DELIVERY OF NITROGLYCERIN VIA THE TRANSDERMAL ROUTE

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Introduction

The use of nitroglycerin in the acute treatment of angina has a long history dating back to the nineteenth century. Acute anginal attacks are quickly and effectively abated by fast dissolving linguet formulations as the drug is quickly absorbed by the sublingual mucosa, resulting in sufficiently high circulating concentrations of nitroglycerin to cause peripheral vaso-dilation and reduce cardiac preload and afterload. More recently, ointment formulations have been introduced and used as a prophylactic treatment for angina. However, use of conventional ointment formulations has several drawbacks. Accurate dosing of nitroglycerin from an ointment formulation is extremely difficult and is highly variable from patient to patient. Since nitroglycerin is quite permeable in human skin, the actual absorbed dose is

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not only dependent upon the concentration in the ointment but also related to the surface area of application. Hence, two inches of ointment spread over 50 cm^2 skin area will produce approximately twice the peak blood concentration as the same amount spread over 25 cm^2 skin area. Moreover, one would expect less duration of action as the same amount of ointment is spread over larger and larger areas.
In addition, because of the volatility of nitroglycerin, applied ointment must be occluded to prevent loss through evaporation. Finally, ointment formulations provide no input rate control and the patient is left to the mercy of his own skin permeability for the drug, a factor which is highly variable from patient to patient.

Transderm®-Nitro has been designed as a controlled release dosage form to replace the use of ointments in the prophylactic treatment of angina. This dosage form is constructed to provide accurate optimum dosing of nitroglycerin over prolonged periods of time with minimum patient intervention. Hence, surface area, rate of release and, as a result, total drug absorbed are all embodied within the system. In this paper, we would like to present the theoretical and experimental work undertaken at ALZA and CIBA-GEIGY which led to the development of Transderm®-Nitro and describe results of in-vitro and in-vivo evaluation of the system.

Diffusion Theory

Mass transport of nitroglycerin occurs in response to a spatial activity or concentration gradient. Movement of the drug either from the dosage form or through human skin can be represented by Fick's second law of diffusion,

$$\partial C/\partial t = D\partial^2 C/\partial x^2 \quad (1)$$

where we have assumed the diffusion coefficient, D, to be constant and transport is in one dimension only. We wish to consider the cumulative release profiles for two classes of nitroglycerin delivery systems which are in contact with an infinite sink for the drug. First, let us consider a monolithic system in which no rate controlling membrane separates the sink from the drug reservoir. These type systems have also been referred to as matrix systems. Since the concentration of nitroglycerin in the system is not constant as diffusion takes place, the fraction of the initial drug content which has been delivered at time t has a time dependence described by,

$$Q_t/Q_\infty = 1 - \sum \frac{8e^{-(2n+1)^2 \pi^2 Dt/a^2}}{\pi^2 (2n+1)^2} \quad (2)$$

where a is the device thickness. Figure 1 provides a graphical representation of the cumulative release profile for such a system. Consider now the case in which a rate controlling membrane separates the drug reservoir from the sink. In this case the boundary conditions are,

$$C = 0 \qquad x = 0$$
$$C = C_2 \qquad x = a,$$

where the membrane surface in contact with the sink is at x = 0. The amount of drug delivered is then given by,

$$Q_t = \frac{DC_2 t}{a} - \frac{aC_2}{6} - \frac{2aC_2}{\pi^2} \sum \frac{(-1)^n}{n^2} \epsilon^{-n^2 \pi^2 Dt/a^2} \quad (3)$$

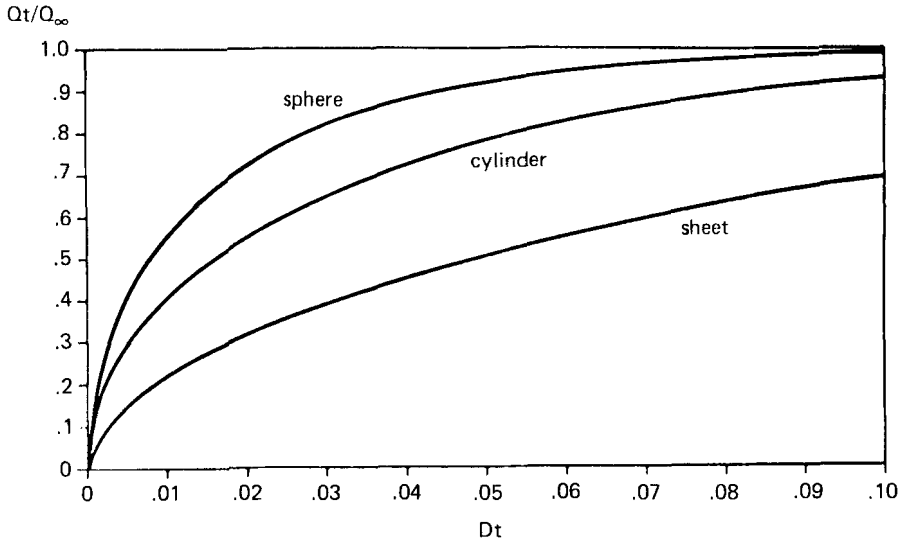

Figure 1 - Cumulative diffusion curves illustrating the quasi-first order mechanism of monolithic systems.

Equation (3) represents the case in which a constant concentration gradient exists across the membrane and the membrane is free of drug at time zero. Figure 2 depicts the delivery profile for such a system. The steady state portion of the delivery profile is given by,

$$Q_t = (DC_2/a)t - (aC_2/6) \quad (4)$$

the intercept, $aC_2/6$, being indicative of the time required for the membrane concentration to come to equilibrium with the reservoir. On the other hand, if a certain portion of drug has come to equilibrium solubility in the membrane, a so-called burst effect is observed as shown in Figure 3, where the quantity of drug immediately available has been expressed as a function of the reservoir concentration.

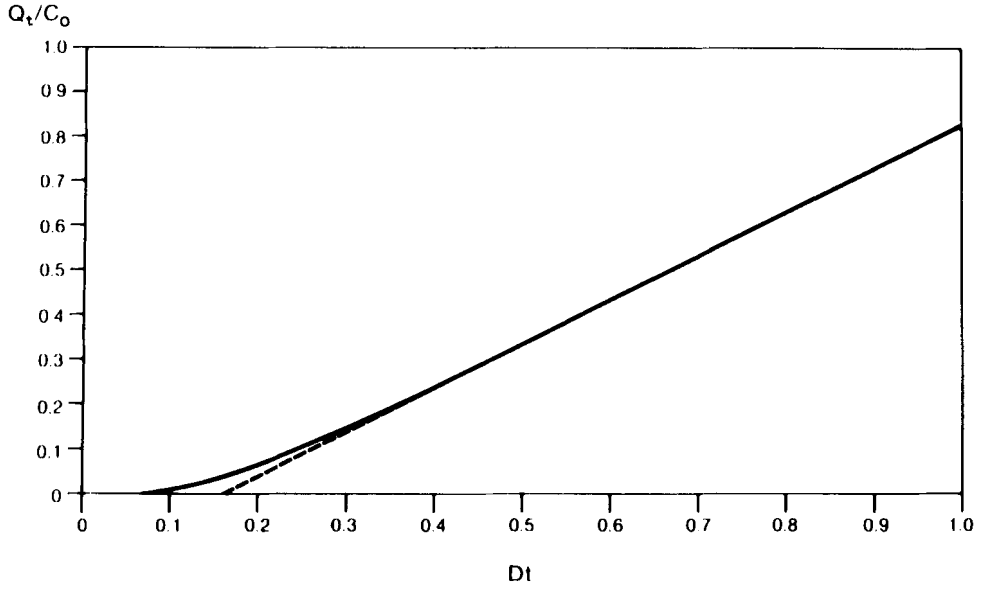

Figure 2 - Cumulative diffusion profile for a membrane controlled system with time lag.

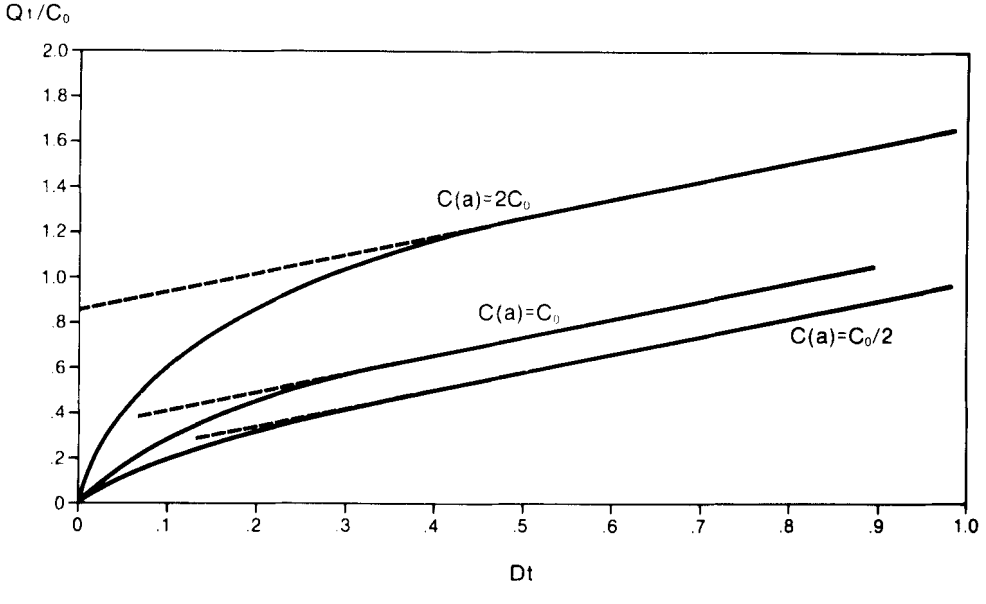

Figure 3 - Cumulative diffusion profiles for membrane controlled systems with burst effect. Legends on curves represent amount of burst in terms of reservoir concentration.

Skin Permeability

Permeability is defined in terms of the more basic parameters of diffusion coefficient, thickness and concentration. Although human skin can be differentiated into several specific cell layers, it has been found that the stratum corneum represents the prime barrier to nitroglycerin transport. The large variability of stratum corneum thickness and condition contributes to a fairly high variability in skin permeation of nitroglycerin. In-vitro skin permeability measurements indicate a mean value of approximately 25 $\mu g/cm^2$ hr using intact cadaver skin at 32°C. On the other hand, values less than 7 $\mu g/cm^2$ hr and greater than 50 $\mu g/cm^2$ hr are not uncommon. In a later section of this paper we will study the potential effects of skin permeability on the performance of transdermal nitroglycerin systems of both monolithic and membrane types.

Transderm®-Nitro: Characteristics and In-Vitro Performance

A cross-sectional diagram of Transderm®-Nitro is presented in Figure 4. A special silicone-based ointment is contained within an oblong shaped system consisting of a multilaminated impermeable backing heat sealed to the rate controlling membrane. The membrane is coated with an adhesive which

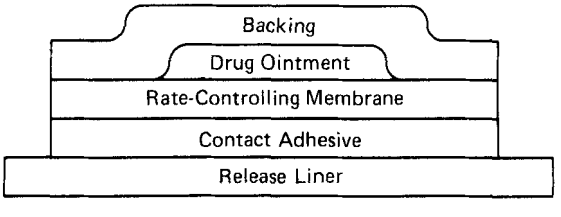

Figure 4 - Crossectional view of Transderm®-Nitro.

provides intimate contact when applied to human skin. The adhesive layer is protected during storage by a disposable liner which is impermeable to nitroglycerin. Upon manufacture, nitroglycerin is found only in the reservoir formulation. However, within a few hours of storage, nitroglycerin equilibrates according to its relative solubility into both the adhesive and control membrane. Distribution of nitroglycerin among these components is given in Table I. Clearly, the release of nitroglycerin, in-vitro, should more closely resemble a membrane system with the initial burst effect due to drug contained in the adhesive and membrane. Figure 5 represents the release profile for Transderm®-Nitro into an infinite sink of water at 32°C. Although these are provided for systems having a surface area of 10 cm^2, we report all data normalized to unit surface area. Figure 5 exhibits three regimes of different boundary conditions for diffusion. The first regime (0-2 hours) is indicative of the burst effect and can be characterized by an equation much like Equation (2). The second regime (2-16 hours) represents the steady state flux of nitroglycerin through the rate controlling membrane. The final regime (>16 hours) is a region of decreasing release rate in which the unit activity gradient

Table I

Distribution of Nitroglycerin in Transderm®-Nitro

Transderm®-Nitro	2.5	5	10
Surface Area (cm^2)	5.0	10.0	20.0
Nitroglycerin in:			
Drug Reservoir (mg)	11.5	23.0	46.0
Adhesive (mg)	1.0	2.0	4.0
Total Content (mg)	12.5	25.0	50.0

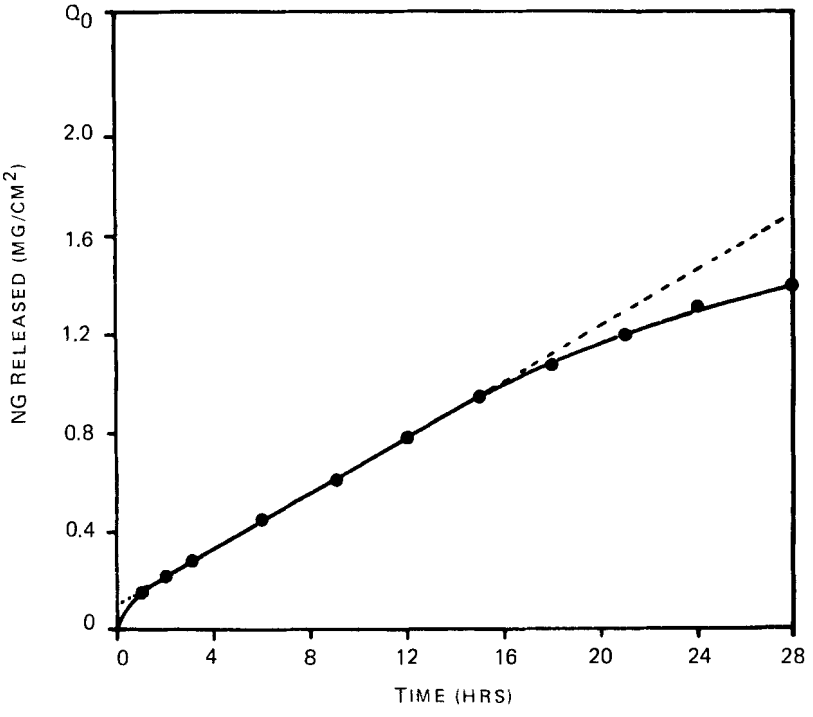

Figure 5 - Cumulative release profile of nitroglycerin from Transderm®-Nitro 5 into an infinite sink of water at 32°C. Data are normalized to system surface area.

has been lost due to diffusion of enough nitroglycerin to reduce its system concentration below saturation. The decreasing rate regime can be described by,

$$Q_t = Q_0 - (Q_0 - Q_z)\epsilon^{-k_1\tau} \quad (5)$$

where Q_0 is the total amount of drug in the system at zero time, Q_z is the amount of drug delivered at the point in time unit activity is lost and τ is the difference between the time of measurement and the time unit activity is lost,

t_z. The rate constant, k_1, is D/V_R, the ratio of the diffusion coefficient to the reservoir volume.

The time regimes $0 \leq t \leq t_z$ are characterized by a combination of Equations (2) and (3) which take into account both the burst effect and the steady state flux.

Absorption and Pharmacokinetics

Application of Transderm®-Nitro to human skin offers an intervening rate process between diffusion of nitroglycerin from the system and elimination from the body. Since the stratum corneum offers resistance to drug transport, the kinetics of absorption are modified by a combination of the barrier properties of skin and the ultimate barrier properties of the rate controlling system membrane. To assume the skin to be "rate controlling" is an over-simplification. Actual absorption kinetics can be characterized in response to a classification of skin permeability. For illustrative purposes we will define the following conditions for study,

$$P_s << P_T$$
$$P_s \lesssim P_T$$
$$P_s \gtrsim P_T$$
$$P_s >> P_T ,$$

where P_s is skin permeability and P_T is the permeability of nitroglycerin through the Transderm©-Nitro rate controlling membrane under infinite sink conditions in the steady state. In order to treat these conditions we must introduce the following parameters. The term flux, J, represents the rate per unit area of drug transport. If J_s and J_m represent skin flux and system flux, respectively, we have,

$$J_s = D_s C_1 / a_s \tag{6}$$

$$J_m = D_m C_2 / a_m \ , \tag{7}$$

where D_s, D_m, a_s and a_m represent diffusion coefficients and thicknesses of stratum corneum and system membrane as appropriate. C_1 and C_2 are concentrations in the adhesive and membrane, respectively. Because the adhesive presents virtually no barrier to nitroglycerin transport, we do not include it in the following definition of net flux, J_n,

$$J_n = \hat{J}_n C_m \tag{8}$$

where we have defined a useful parameter, $\hat{J}_n$, net unit flux as,

$$\frac{A}{D} = \frac{A_m}{D_m} + \frac{A_s}{D_s} = \hat{J}_n^{-1} = \hat{J}_m^{-1} + \hat{J}_s^{-1} \tag{9}$$

This definition is derived in analogy to the well-known model[1] for composite membranes. Hence, we view the skin/-system combination as a 2-layer composite membrane. The unit fluxes are defined in such a way that the concentration terms are eliminated and have the advantage that transport of nitroglycerin can be characterized in terms of fundamental material properties of thickness and diffusion coefficient. Using these definitions and solving Fick's second law under the appropriate boundary conditions, we can now express the amount of nitroglycerin absorbed as a function of time,

For $0 \leq t \leq t_z$:

$$Q_{2s} = J_n T - \frac{A C_m}{6} - \frac{2 A C_m}{\pi^2} \sum \frac{(-1)^n \ \epsilon^{-n^2 \pi^2 D T / A^2}}{n^2} + Q_i \left[1 - \frac{8}{\pi^2} \sum \frac{\epsilon^{-(2n+1)^2 \pi^2 D_s T / A_s}}{(2n+1)^2} \right] \tag{10}$$

For $t \geq t_z$

$$Q_{2s} = Q_0 - (Q_0 - Q_{2z})\epsilon^{-K_{1s}\tau} \tag{11}$$

where $k_{1s} = \hat{J}_n k_1/\hat{J}_m$ and Q_i is the initial amount of nitroglycerin found in the adhesive as the loading dose. The last term in Equation (10) expresses burst effect, while the first term expresses the steady state or constant rate of release segment of the delivery profile. The time at which unit activity is lost, t_z, is highly dependent upon the skin permeability. Since the loss of constant delivery rate from the system coincides with the loss of unit activity, the term Q_{2z} in equation (11), amount of drug remaining at the onset of reservoir concentration depletion, is a constant under all conditions and may be used under the conditions that total amount delivered at $t = t_z$ ($\tau = 0$) require the equivalence of equations (10) and (11). At $t = t_z$ the infinite series in equation (10) converge or vanish and t_z may be evaluated from,

$$T_z = (Q_{2z} - Q_i + \frac{aC_m}{6} \quad \frac{C_m}{2})\hat{J}_n/C_m \tag{12}$$

The component properties of Transderm®-Nitro are given in Table II. Based on experience with in-vitro skin permeability

Table II

Some component properties of Transderm®-Nitro

Component	NG Solubility (mg/ml)	Thickness (μ)	Diffusion Coefficient (cm^2/hr)
Adhesive	50	∿30	6.0×10^{-4}
Membrane	6.0	50	4.56×10^{-5}
Reservoir	2.0	-	1.44×10^{-2}

measurements we have selected a range of skin fluxes from 7-150 μg/cm² hr to illustrate the effects of skin permeability on Transderm®-Nitro performance with respect to absorption of nitroglycerin. Table III defines the parameters used to generate the theoretical absorption data which follow.

Figure 6 provides a comparison of predicted absorption profiles from Transderm®-Nitro through skin types ranging in permeability from 7-150 μg/cm² hr. The delivery profile under sink conditions is also shown for comparison. Small arrows indicate the extent of constant absorption rate for each skin type. It is clear that the duration of constant absorption rate is dependent upon skin permeability. This conclusion is even more relevant if the transdermal system being considered is a monolithic device in which no rate control is inherent within the device. In addition, we make the point that even for relatively low permeable skin, the system exerts some influence on net flux or absorption. The influence of the system rate controlling membrane is,

Table III

Definitions of skin permeability used for theoretical calculations with resulting net flux and durations of steady state flux expected for systems with no rate control* compared to those expected upon application of Transderm®-Nitro⁺.

Skin Permeability	J_s* (μg/cm² hr)	t_z* (hrs)	J_n^+ (μg/cm² hr)	t_z^+ (hrs)
Low (L)	7	134	6.3	133
Moderate (M)	24	39	16.8	49
High (H)	63	15	29.4	28
Very High (VH)	150	6	40.7	20
Sink (S)	∞	0	55.7	15

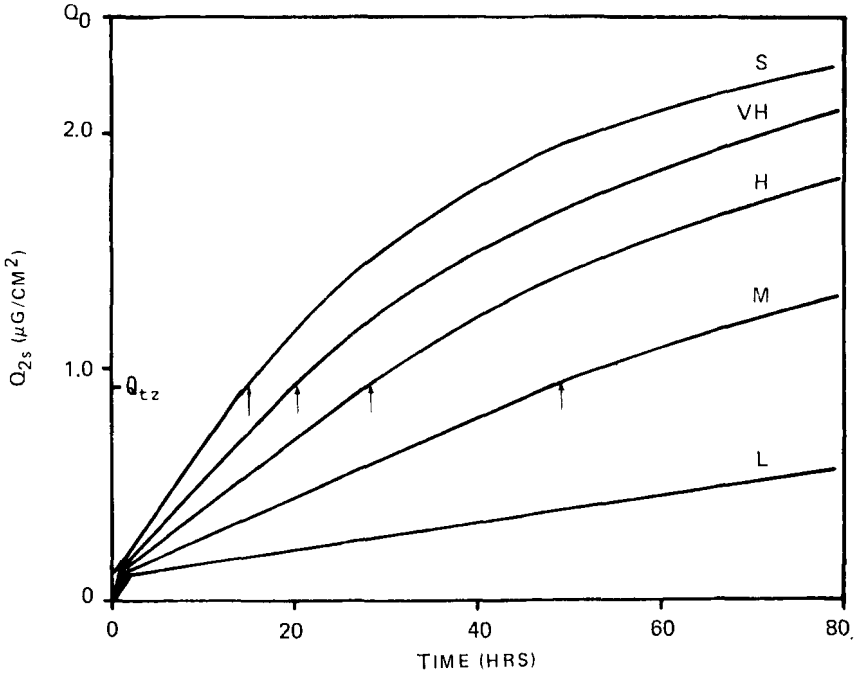

Figure 6 - Theoretical cumulative absorption profiles for nitroglycerin from Transderm®-Nitro through human skin having various permeabilites to nitroglycerin, Low (l), Moderate (M), High (H), Very high (VH) and infinite (S). Arrows indicate duration of steady state absorption.

however, most readily apparent for the high skin permeability cases. In these cases the rate controlling factor favors the system membrane as opposed to the skin permeability. In fact, Transderm®-Nitro provides an upper limit to absorption rates for nitroglycerin as defined for the net flux under sink conditions.

Of particular interest is the effect of the burst quantity of nitroglycerin in the early time period. Figure 7 depicts the same skin conditions for the first 3 hours of delivery from Transderm®-Nitro. Again, we see an upper

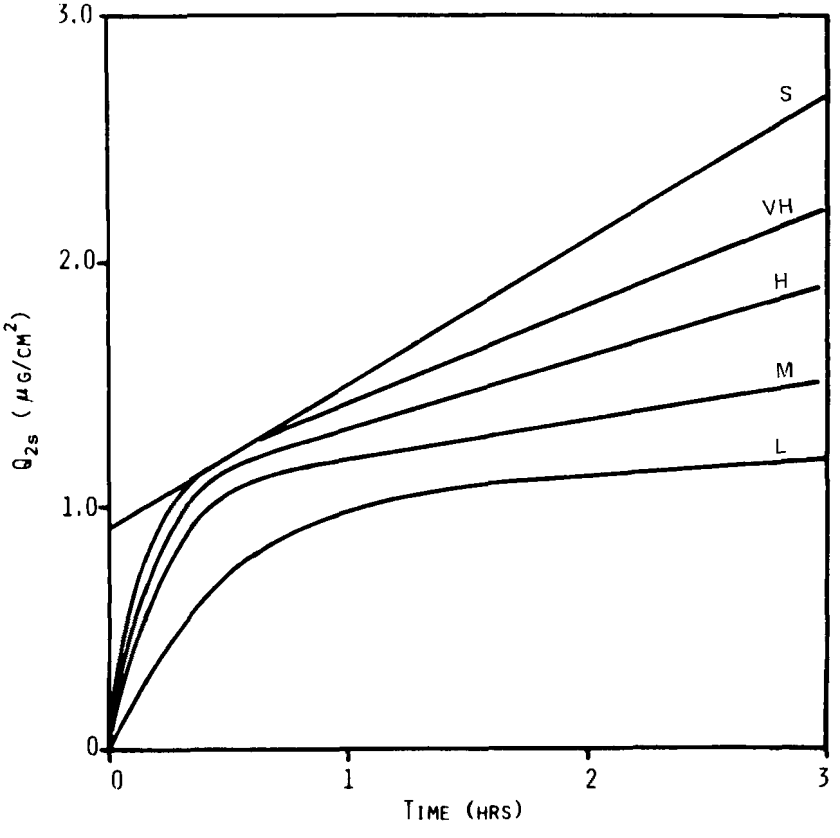

Figure 7 - Theoretical cumulative absorption profiles of nitroglycerin through human skin of various permeability during the burst regime for Transderm®-Nitro.

limit to absorption defined by the line marked sink conditions. In this case, the upper limit of absorption due to the burst is defined by the quantity of nitroglycerin found in the adhesive and skin permeability. It is also interesting to note that steady state absorption is attained easily within 1-2 hours for all skin conditions.

Pharmacokinetic analysis of drugs applied transdermally are, in principle, quite simple. The one compartment model perturbed by constant rate infusion is well known and serves

as the basis for modelling the absorption and elimination of nitroglycerin from plasma. We have utilized a modified version of this model to take into account the burst effect, steady state delivery and decreasing rate regimes of Transderm®-Nitro. For convenience our equations are expressed in terms of amount of drug in the central compartment as a function of time, ignoring distribution volume terms as we are interested in illustrating the theoretical plasma profiles qualitatively under differing skin permeability conditions. In order to simplify the calculations we have truncated the infinite series found in the absorption equations to one term. This simplification will not alter the qualitative aspects of the central compartment profiles and, in fact, is virtually quantitative as one proceeds to times greater than a few hours. The amount of nitroglycerin found in the central compartment, Q_3, is given by,

For $t \leq t_z$

$$Q_3 = \frac{J_n(1 - \epsilon^{-K_3 T})}{K_3} + \frac{2J_n(\epsilon^{-K_3 T} - \epsilon^{-K_n T})}{(K_3 - K_n)} - \frac{J_s(\epsilon^{-K_b T} - \epsilon^{-K_3 T})}{(K_b - K)} \qquad (13)$$

For $t \geq t_z$

$$Q_3 = \frac{K_{1s}(Q_0 - Q_{2z})(\epsilon^{-K_{1s}\tau} - \epsilon^{-K_3\tau})}{(K_3 - K_{1s})} + \frac{J_n \epsilon^{-K_3\tau}}{K_3} \qquad (14)$$

WHERE : $K_n = \pi^2 D/A^2$

$K_b = \pi^2 D_s/A_s^2$

$K_{1s} = \hat{J}_n K_1/\hat{J}_m$

$\tau = T - T_z$

The steady state plasma level is given by,

$$Q_{3ss} = \frac{J_n}{k_3} \qquad (15)$$

where k_3 is elimination constant for nitroglycerin. The half life of nitroglycerin in the body is known to be exceedingly short and has been reported to be between 3 minutes and 10 minutes. In the following illustrations we have taken the half life to be 5 minutes and calculated anticipated plasma profiles for the skin permeability conditions given in Table III. Figure 8 demonstrates the effect of skin permeability

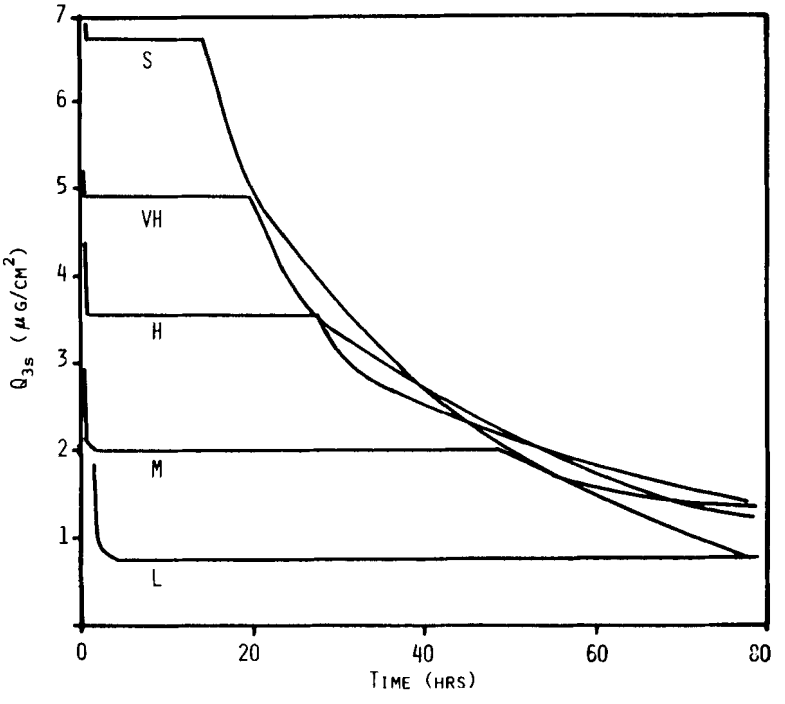

Figure 8 - Theoretical plasma profiles for nitroglycerin delivered through variously permeable human skin from Transderm®-Nitro. Data are calculated without distribution volume term assuming a half-life of 5 minutes for nitroglycerin.

on predicted plasma profiles as Transderm®-Nitro is applied at time zero. The most significant aspect of this illustration is the effect skin permeability has on duration of steady state plasma levels. These durations range from less than 20 hours under sink conditions to 133 hours for low permeable skin. This affect is even more dramatically illustrated in Figures 9 and 10 where we compare projected profiles for system controlled delivery versus monolithic delivery having only skin control for absorption. For low permeable skin, steady state level and duration are nearly the same for both cases. On the other hand, it is clear that highly permeable skin limits duration of steady state to a very short time

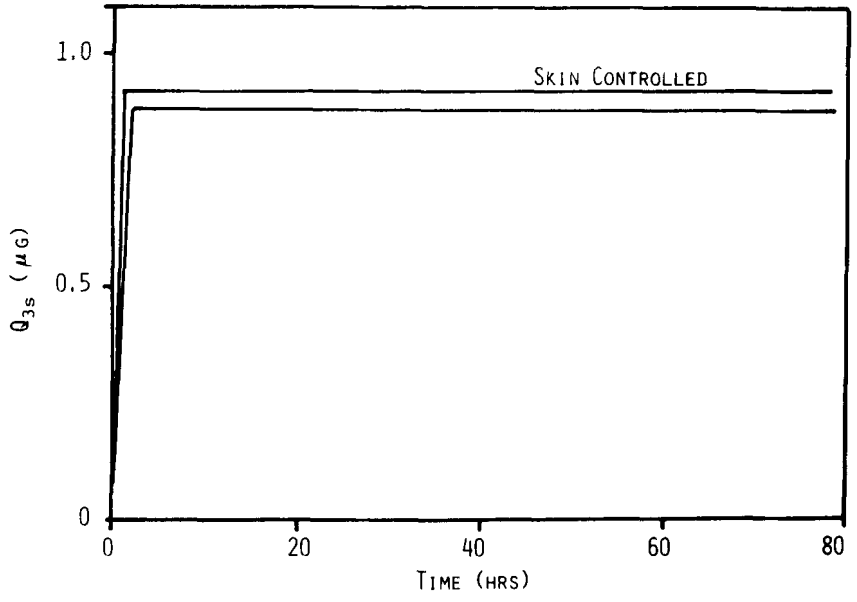

Figure 9 - A comparison of theoretical plasma profiles of nitroglycerin resulting from absorption from a monolithic system (skin controlled) and Transderm®-Nitro through hypothetical skin having permeability of 7 μg/cm² hr. Data are normalized to unit surface area.

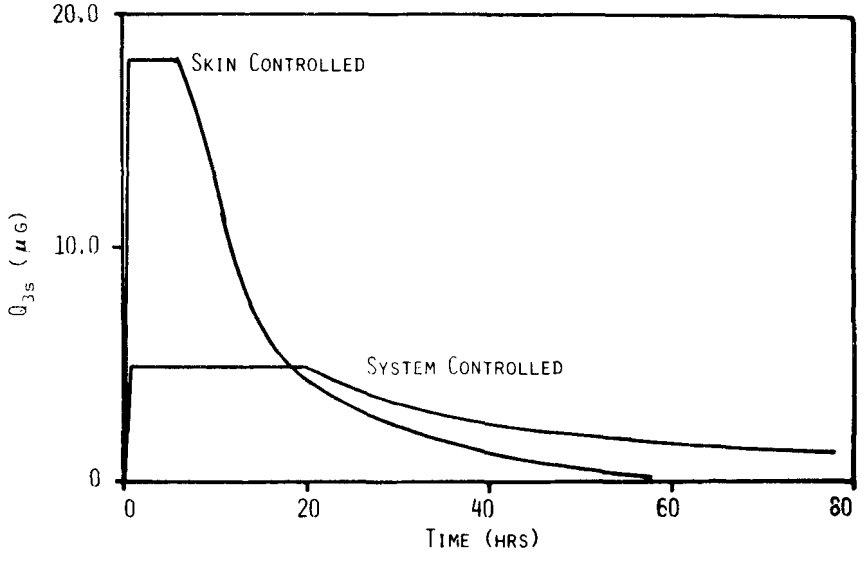

Figure 10- A comparison of theoretical plasma profiles of nitroglycerin resulting from absorption from a monolithic system (skin controlled) and Transderm®-Nitro (system controlled) through hypothetical skin having permeability of 150 µg/cm² hr.

and generates quite high plasma levels relative to the system controlled case. In the high skin permeability case it is clear that some system rate control is highly desirable to extend duration and avoid excessive blood levels.

In-Vivo Experience

We would like to report results of two separate studies using Transderm®-Nitro in healthy human volunteers to assess plasma concentration-time profiles and, ultimately, system performance.

In order to study performance and confirm the relationship between surface area of the applied Transderm®-Nitro and plasma concentration, 6 subjects wore Transderm®-Nitro 5

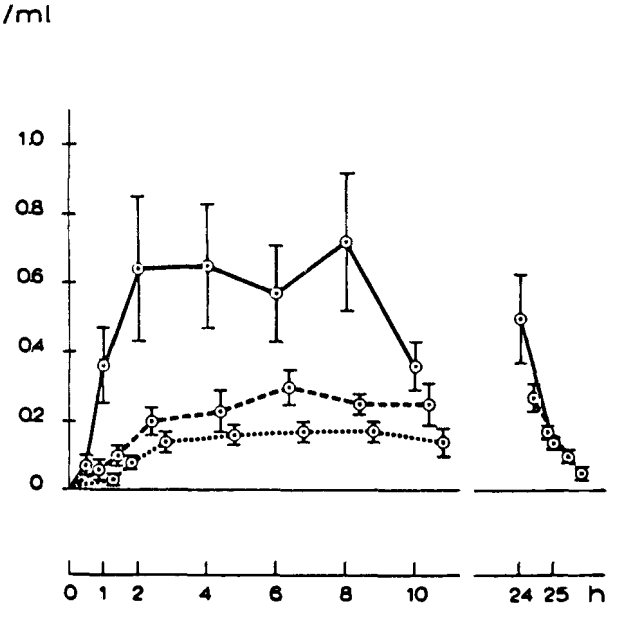

Figure 11 - In-vivo plasma concentrations of nitroglycerin resulting from 24-hour applications of Transderm®-Nitro over 10 cm^2 (·····), 20 cm^2 (----) and 40 cm^2 (———) surface area. N = 6.

(10 cm^2 area) for 24 hours. The same subjects underwent 24 hour applications of 2 systems (20 cm^2) and 4 systems (40 cm^2). The plasma profiles achieved from each application are shown in Figure 11. Dose proportionality can by demonstrated by correlating surface area with area under the plasma curve or surface area with mean steady state plasma concentration. Figures 12 and 13 provide these correlations and confirm surface area proportionality.

An assessment of system functionality and plasma profiles was performed in 12 healthy volunteers in which Transderm®-Nitro 5 was compared to 3 successive applications of a commercial ointment formulation. The ointment was applied and occluded over 10 cm^2 area 3 times consecutively every 8

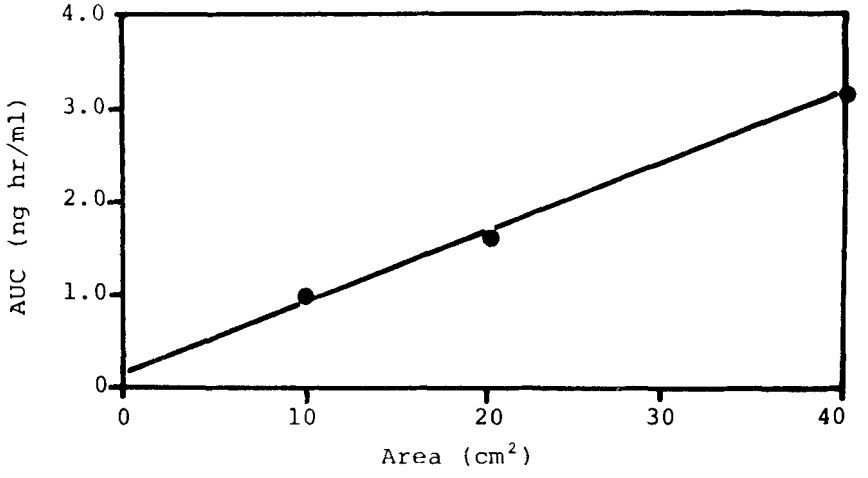

Figure 12 - Correlation of area under the plasma curves with surface area of application of Transderm®-Nitro. N = 6.

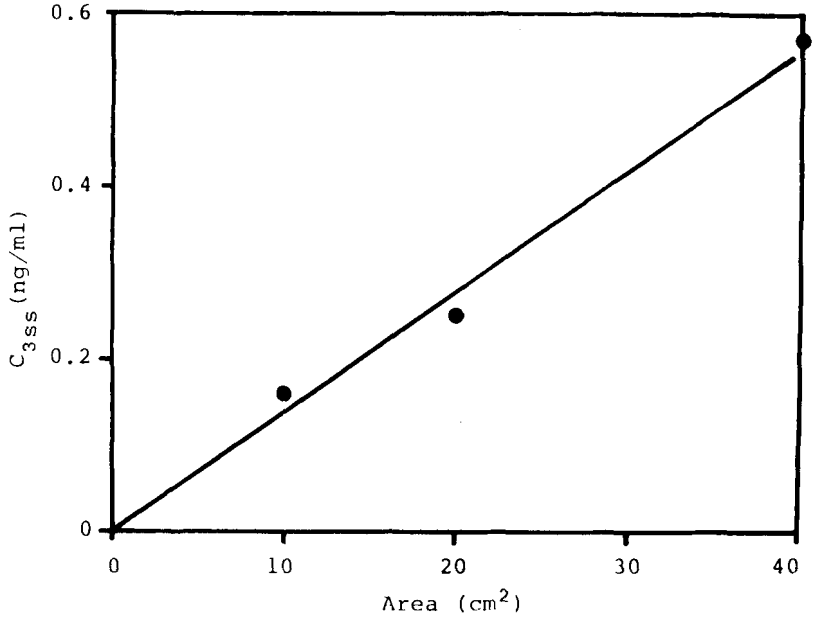

Figure 13 - Correlation of steady state plasma concentrations of nitroglycerin with surface area of application of Transderm®-Nitro. N = 6.

hours for a total of 24 hours. Each new application was done at a different nearby site and the remainder of the previous application was removed. Transderm®-Nitro 5 (10 cm^2) was left in place for 28 hours. Plasma was analyzed out to 30 hours and each removed system was assayed for residual nitroglycerin. A comparison of mean plasma concentrations found for ointment application and Transderm®-Nitro is shown in Figure 14. It is quite clear that the Transderm®-Nitro 5

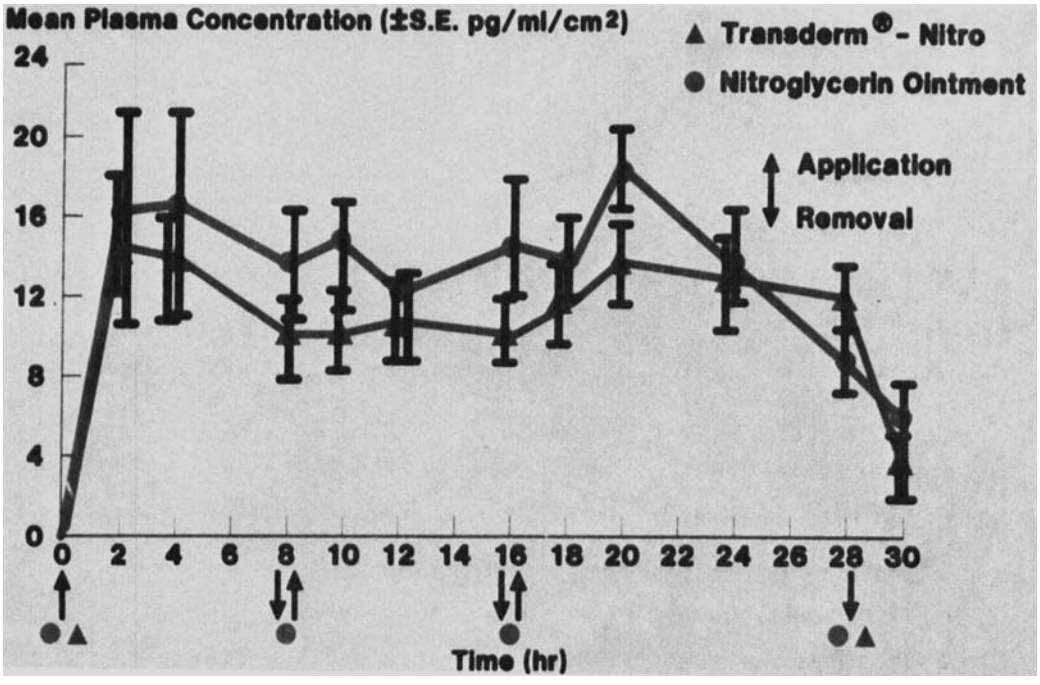

Figure 14 - In-vivo plasma concentrations of nitroglycerin resulting from 2 successive 8-hour applications followed by a 12-hour application of an occluded commercial ointment over 10 cm^2 surface area of skin as compared to a single 28 hour application of Transderm®-Nitro 5. Data are normalized to unit surface area. N = 12.

Table IV

Pharmacokinetic properties derived from in-vivo plasma concentrations found in a study comparing Transderm®-Nitro to a commercial ointment formulation.

	Transderm®-Nitro	Ointment
Dose Absorbed (mg/cm^2)	0.788 ± 0.320	0.977 ± 0.278
C_3 (ss) ($pg/ml\ cm^2$)	12.7 ± 2.0	14.7 ± 2.1
$AUC\Big|_0^{28}$ ($pg\ hr/ml\ cm^2$)	353 ± 96	410 ± 164
Apparent Clearance (l/min)	42.7 ± 11.3	47.8 ± 15.2

performed as anticipated, providing significant blood concentrations for 28 hours at least equivalent to 3 consecutive applications of the commercial ointment. In Table IV we have summarized some pharmacokinetic parameters along with the mean total dose absorbed over 28 hours for each dosage form determined from residual analysis. An assessment of the amount absorbed at 24 hours together with several other results from pilot studies established that the average amount of nitroglycerin provided from the system is 0.5 mg/cm^2 over 24 hours, hence, the name Transderm®-Nitro 5 (10 cm^2 area).

We can use the data from Table IV to estimate the net flux for both the Transderm®-Nitro system and the ointment formulation. Having measured the actual absorbed dose and the steady state plasma concentrations, there are two methods available to calculate the net absorption flux, J_n,

$$J_n = (\text{Total Dose})/t_a = Cl \cdot C_3(ss),$$

where t_a is the time of administration, Cl is apparent plasma clearance and $C_3(ss)$ is the steady state plasma concentration. Using the mean plasma levels and clearances

Table V

Apparent net flux of nitroglycerin through human skin derived from in-vivo plasma concentrations* and analysis of residual nitroglycerin+ found in applied ointment and Transderm®-Nitro.

	J_n* (µg/cm² hr)	J_n+ (µg/cm² hr)
Transderm®-Nitro	32 ± 6	28 ± 11
Ointment	42 ± 6	35 ± 10

we have obtained the data in Table V for both formulations. Agreement in apparent flux calculated by either method seems reasonable and a comparison of net fluxes indicates that rate control in these subjects is approximately 20-25% system related and 75-80% skin related with a fairly high variability, probably due to differences in skin permeability from subject to subject.

Conclusion

If we have learned anything about transdermal delivery of drugs over the duration of development of this product, it is that human skin can serve as an effective route of administration for drugs targeted for systemic action. However, the barrier properties of the stratum corneum can be highly variable and in order to provide optimum therapy it is extremely important that the transdermal system be designed with adequate delivery rate control so as to take into account these variations. It is simply not adequate to assume that skin can serve as the rate controlling membrane. We have experienced first hand with Transderm®-Nitro the need for inherent system rate control and, as we advance to

other transdermal applications, we will continue to develop systems which deliver their contents on the basis of maximum safety and optimum therapeutic rate.

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