Comparative Controlled Skin Permeation of Nitroglycerin from Marketed Transdermal Delivery Systems

Keyphrases □ Transdermal delivery—nitroglycerin, hairless mouse skin, comparison of three marketed systems □ Nitroglycerin—permeation of, comparison of marketed transdermal delivery systems □ Skin, hairless mouse—permeation of nitroglycerin, transdermal delivery systems

To the Editor:

The antianginal activity of nitroglycerin was discovered over 100 years ago by Murrel (1). Since then, nitroglycerin use has increased and it is now widely prescribed for the prevention and treatment of angina pectoris. Several types of pharmaceutical dosage forms, mainly the oral sustained-release capsules and tablets, sublingual tablets, topical ointments, and intravenous fluids, are available commercially. Unfortunately, oral administration of nitroglycerin leads to extensive hepatic first-pass metabolism to give several inactive metabolites (2). When administered sublingually, first-pass metabolism is eliminated, however the antianginal activity is of such short duration (10–30 min.), due to the inherently rapid elimination (half-life = 1.9–4.4 min.) of nitroglycerin (3), that repeated dosing every 5 min is recommended until the symptoms are relieved. On the other hand, the duration of antianginal activity of nitroglycerin can be substantially prolonged to 3–4 hr by topical administration of ointment formulations; however, the area covered and thickness of the ointment is variable and it is messy and inconvenient.

Recently, three one-a-day-type transdermal nitroglycerin delivery systems[1] (Products A, B, and C) were developed for transdermal-controlled administration of nitroglycerin over a 24-hr period. They were recently approved for marketing by the U.S. Food and Drug Administration for treatment of angina pectoris (4). Several articles have been published to compare these new delivery systems with the sublingual tablets and/or the topical ointment formulations (3, 5–7). However, the only data available to date are the results of studies conducted independently and under different conditions and protocols by the manufacturers, and controversy has surfaced concerning the interchangeability of these three nitroglycerin-releasing transdermal delivery systems (8, 9).

Since no results are available from studies that are designed to evaluate the performance of these transdermal delivery systems under identical conditions, the purpose of this investigation was to establish an *in vitro* skin permeation system to study and compare the controlled skin-permeation kinetics of nitroglycerin delivered by these controlled-release transdermal delivery systems. In our studies, pieces (3.5 × 3.5 cm each) of full-thickness abdominal skin were freshly excised from 5–7-week-old hairless mice[2] (10) and mounted individually on the 8-cell Franz diffusion assembly[3] (Fig. 1). After soaking the dermal side of the skin in the elution solution overnight (as the time-zero sample), the transdermal delivery system was applied to the stratum corneum side of the skin, and the skin permeation profile of nitroglycerin was followed by sampling and assaying the nitroglycerin concentration in the elution solution. A sensitive reverse-phase high-performance liquid chromatographic (HPLC) method was used with samples taken at 1, 2, 4, 8, 12, 16, 20, 24, and 30 hr postapplication. The elution solution was prepared from normal saline solution containing 20% polyethylene glycol 400 to enhance aqueous solubility of nitroglycerin for simulating the biological sink (11, 12). At least four experiments on each type of transdermal delivery system were performed in each run of the drug release and skin permeation studies.

The results of the skin permeation studies indicated that nitroglycerin penetrates through the abdominal skin of the hairless mouse at a rate profile which can be described fairly well by zero-order kinetics (Fig. 2). It appears that the rate of skin permeation for nitroglycerin delivered by system A (18.15 $\mu g/cm^2/hr$) is significantly greater than system C (14.55 $\mu g/cm^2/hr$). Interestingly, the rate of skin permeation of nitroglycerin from system B is between systems A and C rates, but it shows a shift at 12 hr from 16.67 $\mu g/cm^2/hr$ to 10.56 $\mu g/cm^2/hr$. However, a constant skin permeation is maintained in both phases. The rates determined in this investigation are quite in agreement with the data (10–25 $\mu g/cm^2/hr$) generated from human cadaver skins (13).

The release kinetics of nitroglycerin from the transdermal delivery systems were also evaluated under the same conditions without the hairless mouse skin. Results indicated that nitroglycerin is released at a constant rate profile from system C but not from systems A nor B (Fig. 3). System C is a membrane permeation-controlled drug delivery system in which a rate-determining microporous

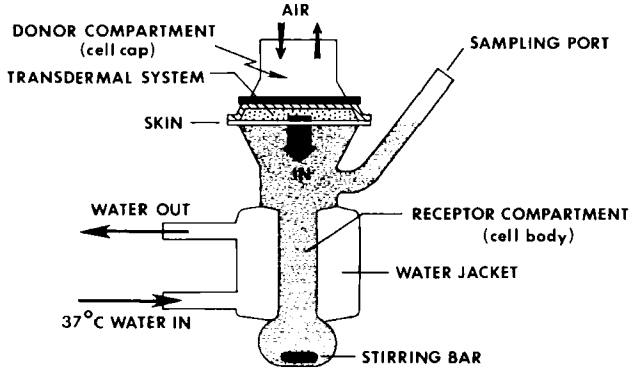

Figure 1—*Schematic illustration of the* in vitro *skin permeation system with skin sample and transdermal system sandwiched in between the donor and receptor compartments of the Franz diffusion cell assembly. The stratum corneum of the skin sample faces the donor compartment and is in close contact with the transdermal system. The dermal tissue faces the receptor compartment and is soaked in an elution solution at 37°.*

[1] System A, Nitrodisc, G. D. Searle & Co.; System B, Nitro Dur, Key Pharmaceuticals; System C, Transderm-Nitro, Ciba Pharmaceuticals.

[2] Male, HRS/J strain, Jackson Laboratories, Bar Harbor, Maine.

[3] Crown Glass Co., Somerville, N.J.

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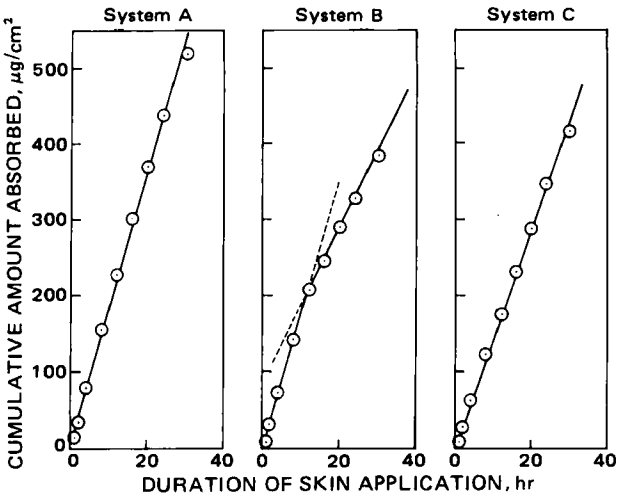

Figure 2—*Permeation profiles of nitroglycerin through the abdominal skin of the hairless mouse, following its controlled release from each of the three commercial transdermal delivery systems (each data point is the mean of at least eight determinations). The rate of skin permeation for nitroglycerin is calculated to be 18.15 μg/cm²/hr (system A), 16.67 (<12 hr) and 10.56 (>12 hr) μg/cm²/hr (system B), and 14.55 μg/cm²/hr (system C).*

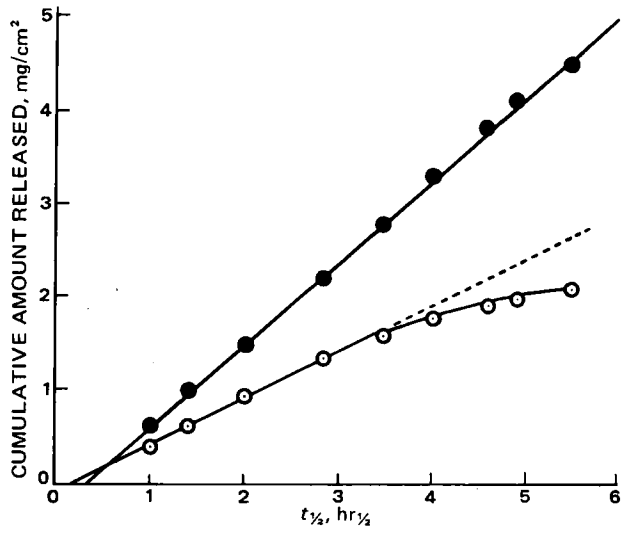

Figure 4—*Linear* Q versus $t^{1/2}$ *relationship for the controlled release of nitroglycerin from system B (●) and system A (○). (The* $Q \sim t^{1/2}$ *linearity is followed in system A for up to 12 hr in which 78% of the loading nitroglycerin dose is released, as compared with 30 hr duration and 89% release in system B). Each data point is the mean value of four determinations.*

ethylene–vinyl acetate membrane controls the release of nitroglycerin from a suspension-type drug reservoir (5, 6), and, as expected (11), a constant drug-release profile results. It is interesting to note that nitroglycerin is released from system C at a rate (35.8 μg/cm²/hr) which is more than two times greater than the rate of skin permeation (14.55 μg/cm²/hr). These results suggest that the skin tissues provide an additional diffusional barrier for the permeation of nitroglycerin.

On the other hand, the release profiles of nitroglycerin from systems A and B can be better defined by a *Q versus* $t^{1/2}$ relationship (Fig. 4), indicating that nitroglycerin is released under a matrix diffusion-controlled process from both systems A and B (11, 12, 14–16). System A is, in its original development (17–19), a partition-controlled drug delivery system with the drug reservoir microsealed as microscopic liquid compartments homogeneously dispersed in a cross-linked polymer matrix, and a constant drug release profile is expected (20). The incorporation of a hydrophobic solvent, like isopropyl palmitate (21), which is a good solvent for nitroglycerin, into the polymer matrix during fabrication, could affect the interfacial partitioning kinetics of nitroglycerin from the microscopic *liquid* compartment, leading to the shift in drug-release kinetics from the partition-controlled process to the matrix-controlled process (11, 22).

Similarly, system B is a matrix diffusion-controlled drug delivery system in which nitroglycerin–lactose triturate is homogeneously dispersed in a hydrophilic gel matrix (23); and, as expected (11), the release profile of nitroglycerin from system B follows the *Q versus* $t^{1/2}$ linearity. Again, the drug release fluxes from both systems A and B are maintained at magnitudes that are much greater than

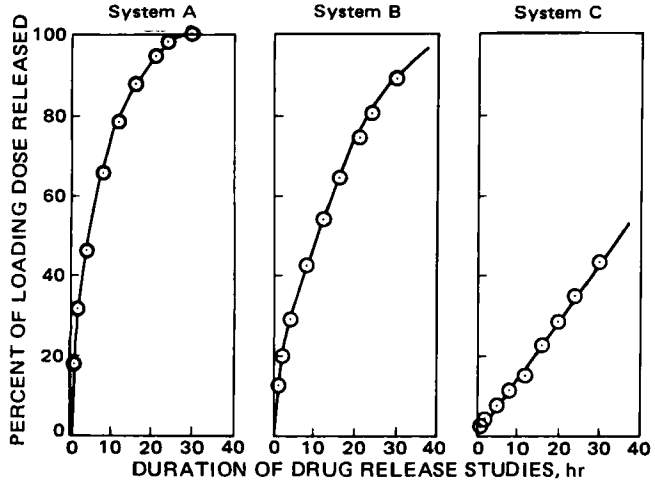

Figure 3—*Release profiles of nitroglycerin from the transdermal delivery systems into normal saline solution at 37° as drug elution solution (containing 20% polyethylene glycol 400 w/w to maintain a sink condition). Each data point is a mean value of four determinations.*

Table I—Comparison in Drug Release Kinetics and Skin Permeation Profiles of Nitroglycerin from Commercial Transdermal Delivery Systems

	System A	System B	System C
System Characteristics			
Surface area, cm²	8	10	10
Loading dose, mg	16	51	25
Release Kinetics			
Flux or rate of release	500 μg/cm²/hr 1/2	875 μg/cm²/hr 1/2	35.8 μg/cm²/hr
Dose released (24 hr)[a]			
Percent	98.1 (±0.1)	80.3 (±0.2)	34.4 (±1.4)
Milligrams	15.7 (±0.02)	40.9 (±0.1)	8.6 (±0.35)
Skin Permeation Profiles			
Rate of permeation, μg/cm²/hr	18.15	16.67 (<12 hr) 10.56 (>12 hr)	14.55
Dose absorbed (24 hr)			
Percent	21.93 (±3.86)[b]	6.41 (±1.19)[b]	13.88 (±2.65)[c]
Milligrams	3.51 (±0.62)[b]	3.27 (±0.60)[b]	3.47 (±0.66)[c]

[a] Mean (± standard deviation) of four determinations. [b] Mean (± standard deviation) of eight determinations. [c] Mean (± standard deviation) of 12 determinations.

the rate of skin permeation (Table I), so a constant skin-permeation profile can be achieved. By calculation, systems A and B release nitroglycerin at a flux ($Q/t^{1/2}$) of 500 and 875 $\mu g/cm^2/hr^{1/2}$, respectively (Fig. 4). The difference in release fluxes between these two systems is expected from the difference in drug-loading doses in the devices (11).

In summary, the results generated from the present investigation suggest that even though nitroglycerin is released at different rate profiles from these three transdermal delivery systems (Figs. 3 and 4), it penetrates through the hairless mouse skin under, basically, the same rate process (Fig. 2). Additionally, the total nitroglycerin dose delivered through the abdominal skin at 24 hr by each of these transdermal delivery systems is fairly close in magnitude and the difference is statistically insignificant [$F = 0.33$, $F_{0.95}(2,25) = 3.39$] (Table I), although the loading dose varies greatly from one system to another, and the percentage of the loading doses released during a 24-hr elution study is substantially different.

Additional studies are currently underway to generate evidence on the feasibility of using hairless mouse skin as the viable substitute for human skin in studying the transdermal controlled administration of systemically active drugs from novel drug delivery systems. A more detailed report will be written when more data become available.

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Organ Perfusion Studies

Keyphrases □ Organ perfusion—pharmacokinetics, importance of volume replenishment □ Pharmacokinetics—organ perfusion studies, importance of volume replenishment

To the Editor:

Single-pass and recirculating perfused organ systems have been used to study how specific organs of the body handle drugs. The single-pass system has been used extensively to study the influx and efflux of drugs by various organs, whereas recirculating systems have been used more commonly to study metabolism and/or excretion of drugs by these organs. Although both systems are useful, the conservation of drug and perfusion media associated with the recirculating system makes it more economical and allows for longer perfusion experiments even with limited volumes of perfusion medium. However, in recirculating perfusion systems, there are problems associated with volume depletion due to excretion in open systems (*i.e.*, liver and kidney) and sample withdrawal in both closed (*i.e.*, heart, muscle, and lung) and open systems, which must be considered when performing pharmacokinetic analyses of the data derived from these experiments. The following discussion will address these problems.

It has been shown that the rate of elimination of a drug from an isolated organ perfusion system is a function of the perfusate volume (1) according to the following equation:

$$\frac{dC_i}{dt} = \frac{Q}{V_R}(C_i - C_o) \qquad \text{(Eq. 1)}$$

where C_i and C_o are the inflow and outflow concentrations, Q is the perfusate flow, and V_R is the reservoir volume. The elimination rate constant (K) varies inversely with perfusate volume changes since $K = Q/V_R$. Several authors have published on this observation (1–5), and some have attempted to correct the elimination rate for perfusate volume changes (2–5). Other authors have discussed perfusate volume and nutrient replenishment as a means of maintaining the viability of open perfused organ systems, such as the kidney or liver, where there is loss of water and energy sources due to urine and bile excretion (6–8). Two

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