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TRANSDERMAL ABSORPTION: A UNIQUE OPPORTUNITY FOR CONSTANT DELIVERY OF NITROGLYCERIN

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A recent important advance in biopharmaceutics has been the utilization of controlled delivery of drugs to the systemic circulation through the intact skin. With the conventional tablet and capsule dosage forms, the amount of drug absorbed through the gastrointestinal (GI) tract varies depending on the quantity and types of food in the stomach, on the GI motility and transit time, and on the GI microbial flora, which can destroy some agents. Furthermore, in the case of drugs with a high hepatic extraction ratio, the absorbed drug may be largely deactivated by first-pass metabolism before reaching the systemic circulation. Drug absorption through the GI tract can therefore result in variable and/or unpredictable blood levels. Some of this variability can be minimized by administering controlled-release tablet and capsule formulations. However, these dosage forms cannot eliminate the inherent variability associated with first-pass metabolism.

With the transdermal system the drug is absorbed from the skin into the capillaries that run under the skin and then into the

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general circulation. It is, therefore, possible to greatly minimize the absorption variability and to maintain a constant drug level in the blood. Transdermal drug delivery approaches zero-order drug input which is equivalent to administering a constant intravenous infusion.

The advantages of controlled transdermal drug administration include:

- Avoids the risk and inconveniences of intravenous therapy.
- Avoids the variable absorption and metabolism sometimes associated with oral therapy.
- Permits use of pharmacologically active agents with short biological half-lives.
- Permits lower daily dosage of drug, because of reduced liver metabolism and continuous drug input.
- Diminishes chance of over- or underdosing, because of prolonged, preprogrammed delivery of drug at the required therapeutic need.
- Provides for a simplified medication regimen.
- Allows rapid termination of drug input by removal of the system from the surface of the skin.

The transdermal route, however, is not suitable for drugs that irritate or sensitize the skin and is restricted by the surface

area of the delivery system to potent drugs that need to be administered on a chronic basis.

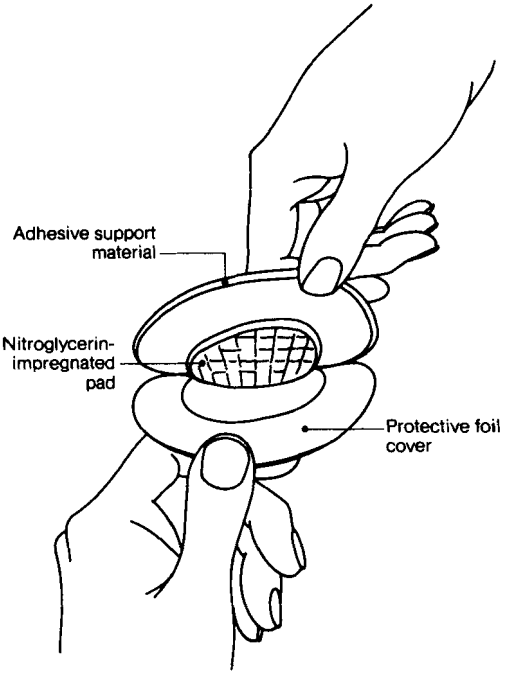
Controlled-Release Transdermal Systems:

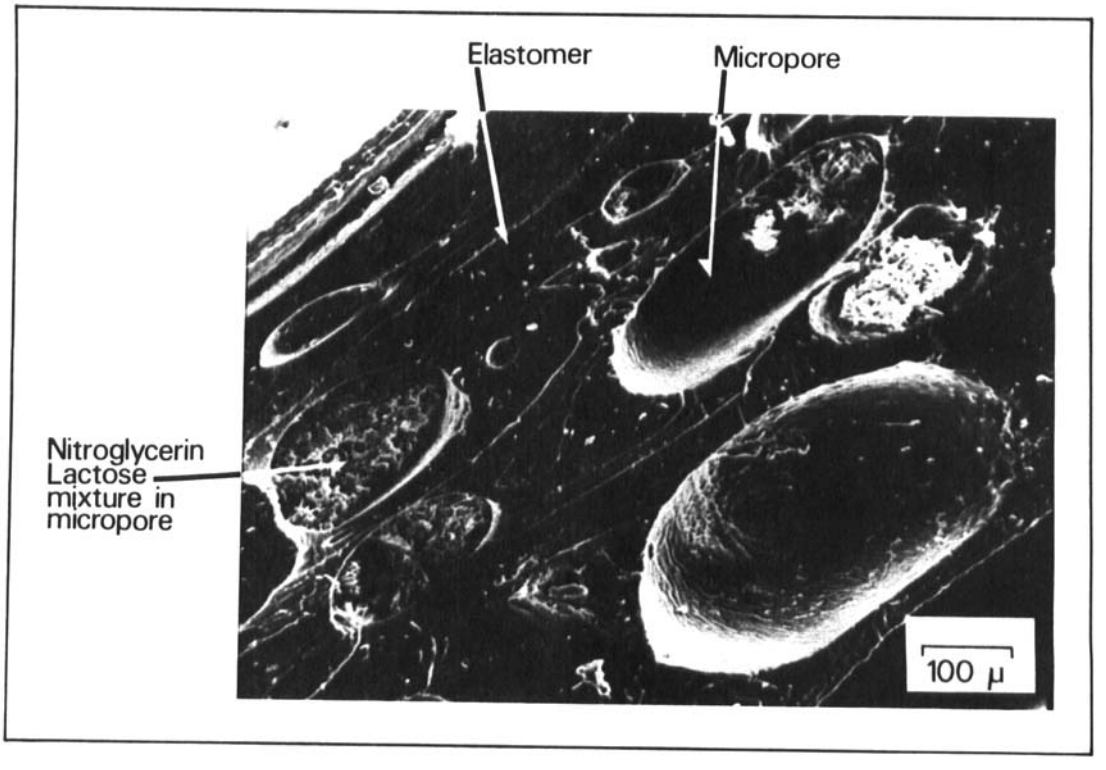
The controlled-release transdermal systems currently available fall into two main categories, namely those in which the drug is stored in a membrane sealed reservoir and those in which the drug is stored in a matrix.

Reservoir System. In the reservoir system the drug is stored in a single compartment or reservoir from which it migrates through a rate-controlling membrane to the absorption site. The principal advantage of this system is the constant release rate of the drug. The disadvantage is that a tear or break in the rate-controlling membrane can result in "dose dumping" or a rapid release of the entire drug content.

Matrix System. In this system the drug is uniformly dispersed throughout a polymeric matrix through which it diffuses to the absorption site. Depending on the physicochemical parameters which define the system and the drug, release from such matrices may be via zero order or more complex kinetics. The advantage of matrix systems is the lack of danger of dose dumping since the polymer cannot be ruptured.

The "Microsealed Drug Delivery" (MDD) system, developed by Searle, combines the principles of the reservoir and matrix systems. In the MDD system the drug is dispersed throughout a polymer in microcompartments which serve as tiny reservoirs (Figure 1). The system allows for a zero-order release of a drug without the danger of dose dumping. The amount of drug released can be controlled by altering:





- the solubility of the drug in the liquid compartment
- the physicochemical properties of the system
- the size and/or structure of the silicone polymer

Transdermal Delivery of Nitroglycerin:

Nitroglycerin (NG) is an ideal candidate for transdermal drug delivery. NG is a potent, lipophilic, neutral compound with a low molecular weight. It undergoes extensive first-pass metabolism following oral administration (1). NG has a short elimination half-life of 2.8 minutes, a high apparent distribution volume of 3.3 liters/kg, and a high plasma clearance of 0.72 liters/min/kg (2). A topical dosage form of NG is already available as a 2% ointment (3,4). The ointment is messy to use and the applied dose, based on the concentration and the surface area, is subject to significant variability (5,6).

During the course of evaluating the transdermal absorption of NG, we have encountered several practical problems and unusual pharmacokinetics of the topically applied NG. For example:

- The reference standard of NG is not available as a pure crystalline chemical but as a 10% NG lactose adsorbate. The standard curve was prepared with pure NG collected by sublimation and weighed.

Figure 1: Microsealed Drug Delivery-Nitroglycerin (MDD-NG).

A = Circular MDD-NG system. The 8 cm^2 system contains 16 mg NG (2 mg/cm^2) and the 16 cm^2 system contains 32 mg NG (2 mg/cm^2).

B = Electron micrograph of MDD-NG system illustrating the presence of microcompartments which serve as tiny reservoirs for nitroglycerin.

- NG is rapidly adsorbed to (7) and hydrolyzed by (8) red blood cells. Therefore, immediate inhibition of the hydrolases, centrifugation and extraction of plasma samples following blood collection is necessary.

- The therapeutic plasma levels of NG are very low (<1 ng/ml) so a highly accurate and sensitive assay method capable of detecting 0.05 ng/ml level is required.

- NG has numerous side effects including headache, postural hypotension, flushing, tachycardia, and dizziness. The dose of NG used in a human bioavailability study therefore cannot be too high; otherwise the subject dropout rate may be excessive.

In the studies described below, plasma levels of NG were determined by a quantitative gas-liquid chromatographic method using isosorbide dinitrate as the internal standard and electron capture detection.

Surface Area and Concentration. The relationship between the transdermal absorption and the surface area or the concentration of NG applied on the skin was evaluated in healthy subjects with a study design outlined in Figure 2. MDD-NG (4 to 16 cm^2 containing 8 to 32 mg NG) or commercially available Nitro-Bid® ointment (1/2 to 1 inch over 53 cm^2 containing 8 to 16 mg NG) was applied on the volar surface of the left wrist and plasma levels of NG were determined in the ipsilateral and the contralateral antecubital forearm veins. Ipsilateral plasma levels were expected to be high and to reflect the drug levels near the site of absorption. The contralatral plasma levels representing the systemic levels were expected to be low due to the extensive

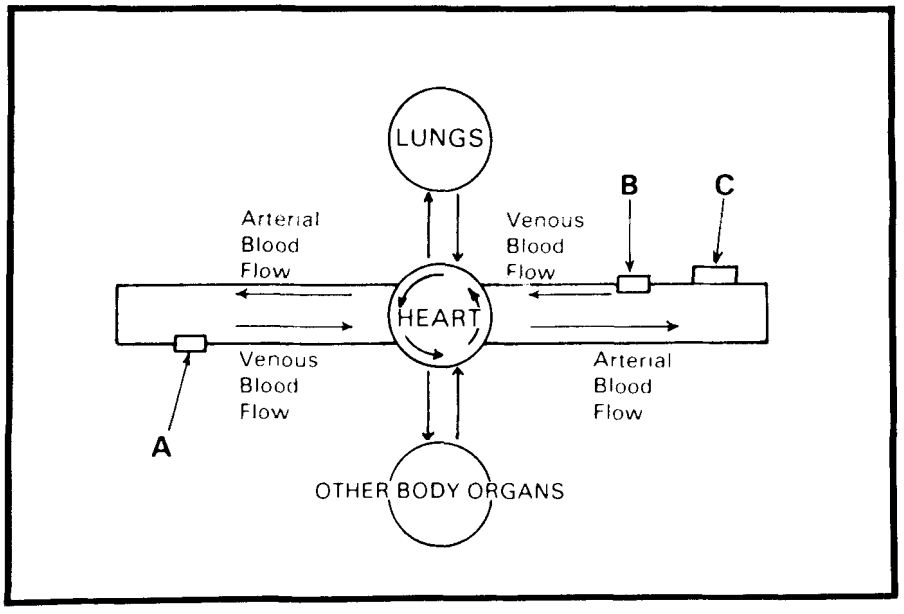


Figure 2: Procedure for evaluating transdermal absorption of nitroglycerin in man. MDD-NG is applied on the volar surface of the wrist (C) and NG plasma levels are determined in the ipsilateral (B) and the contralateral (A) forearm antecubital veins.

distribution and metabolism of NG. The study design in Figure 2 permitted evaluation of the kinetics of transdermal absorption as well as the kinetics of the systemic NG levels. However, Figure 3 shows that with application of either MDD-NG (32 mg over 16 cm^2) or a therapeutic dose (9) of Nitro-Bid® ointment [one inch (16 mg) over 53 cm^2], the systemic plasma levels were below the limit of detection even though the ipsilateral levels were as high as 12 ng/ml.

Figure 4 shows that the ipsilateral plasma levels of NG increased as the surface area of the applied MDD-NG was increased from 4 to 16 cm^2. An approximately linear relationship was found between the area under the plasma concentration-time curve (AUC) and the surface area of the applied MDD-NG.

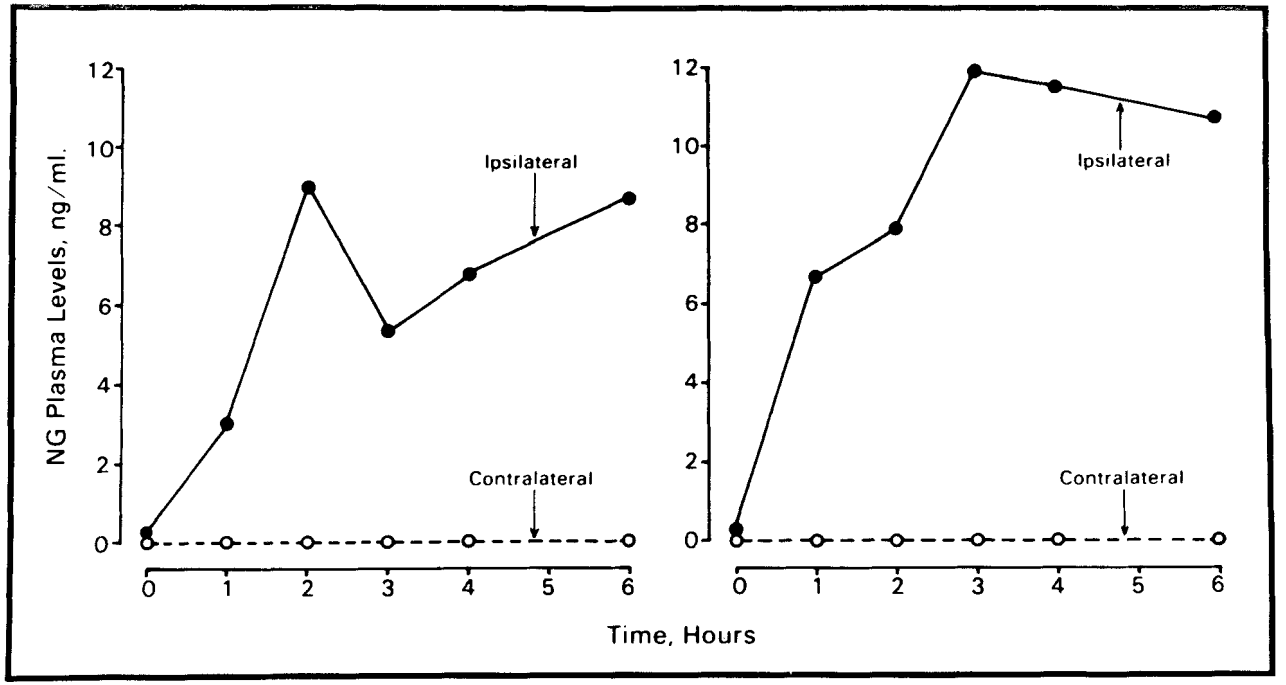


Figure 3: Relationship between plasma levels of NG in the antecubital vein of the ipsilateral and contralateral forearms. Each value is a mean of five healthy male subjects. MDD-NG (32 mg NG over 16 cm^2) or 2% ointment (one inch, 16 mg NG over 53 cm^2) were applied on the volar surface of the left wrist in a crossover study. The sensitivity of the assay was 0.1 ng NG/ml.

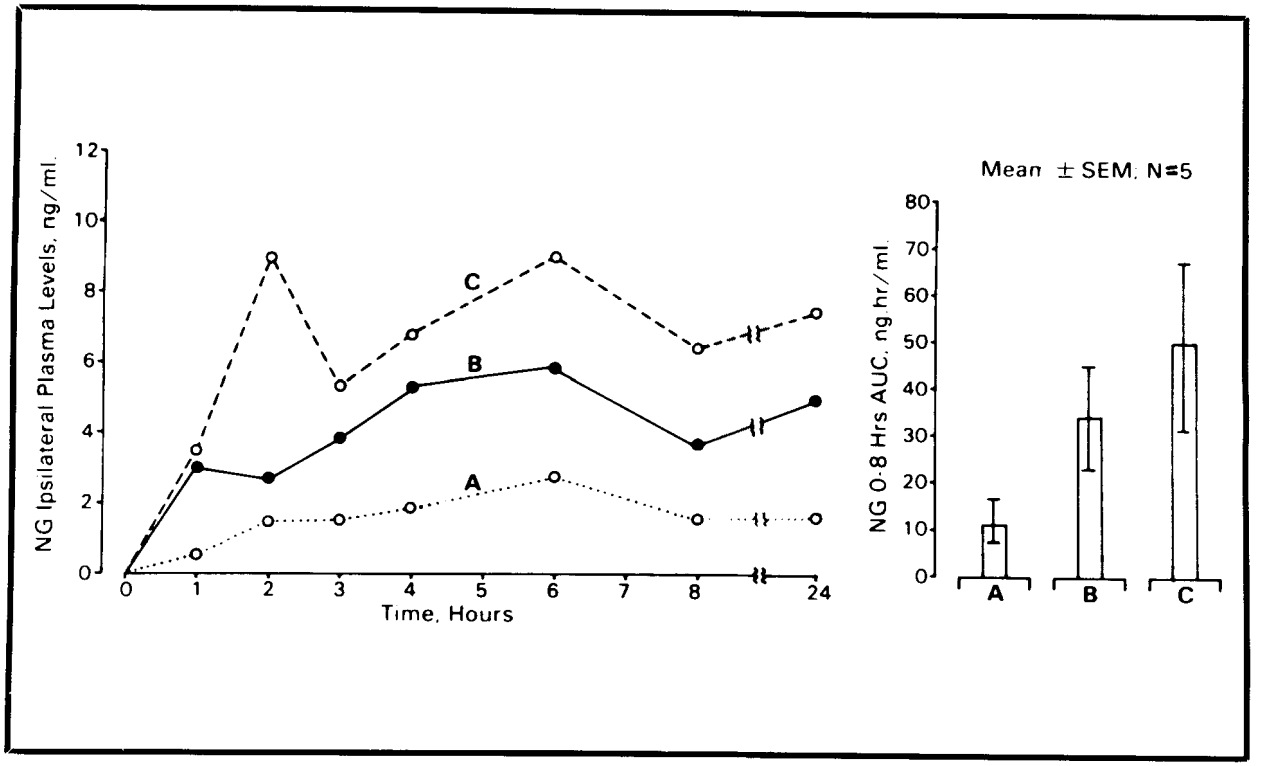


Figure 4: Relationship between the surface area of the application site and the ipsilateral plasma levels of nitroglycerin. Each value is a mean of five healthy male subjects and vertical bars represent SEM. MDD-NG systems were applied on the volar surface of the left wrist in a crossover study.

A = 8 mg NG over 4 cm^2 (2 mg/cm^2)

B = 16 mg NG over 8 cm^2 (2 mg/cm^2)

C = 32 mg NG over 16 cm^2 (2 mg/cm^2)

With the ointment, the ipsilateral plasma levels of NG increased with the increase in the concentration of NG applied on the skin. With the constant surface area of 53 cm^2, ipsilateral plasma levels increased approximately 1.5-fold when the concentration of NG applied on the skin was increased from 0.15 to 0.30 mg/cm^2 (Figure 5). However, this finding only applied to the concentration range studied. At higher concentrations saturation in the transdermal absorption process may occur.

Intersubject Variability in Transdermal Absorption. Figure 6 demonstrates the mean ± SEM ipsilateral plasma levels of NG over a period beyond 24 hours in 23 subjects following application of MDD-NG (16 mg over 8 cm^2) on the volar surface of the wrist. Slow and continuous NG transdermal absorption occurred resulting in constant mean ipsilateral plasma levels of about 4 ng/ml for a period up to 32 hours. A high intersubject variability in the transdermal absorption was found and this variability was largely attributed to the differences in the skin characteristics of individuals because the relationship between ipsilateral AUC MDD-NG versus AUC ointment was approximately linear (Figure 7).

Bioavailability. Using each subject as his own control, NG absorption from a half inch of ointment (8 mg over 53 cm^2) was equivalent to that from MDD-NG (16 mg over 8 cm^2) (Figure 8). However, it was shown earlier that both the concentration and the surface area are important in evaluating the transdermal absorption of NG. When the dose plus the surface area adjusted ipsilateral AUC were compared then the transdermal absorption of NG from MDD-NG was 1.8 times that from the ointment.

Systemic Plasma Levels. Since the systemic plasma levels of NG were below the detection limit of the assay following application

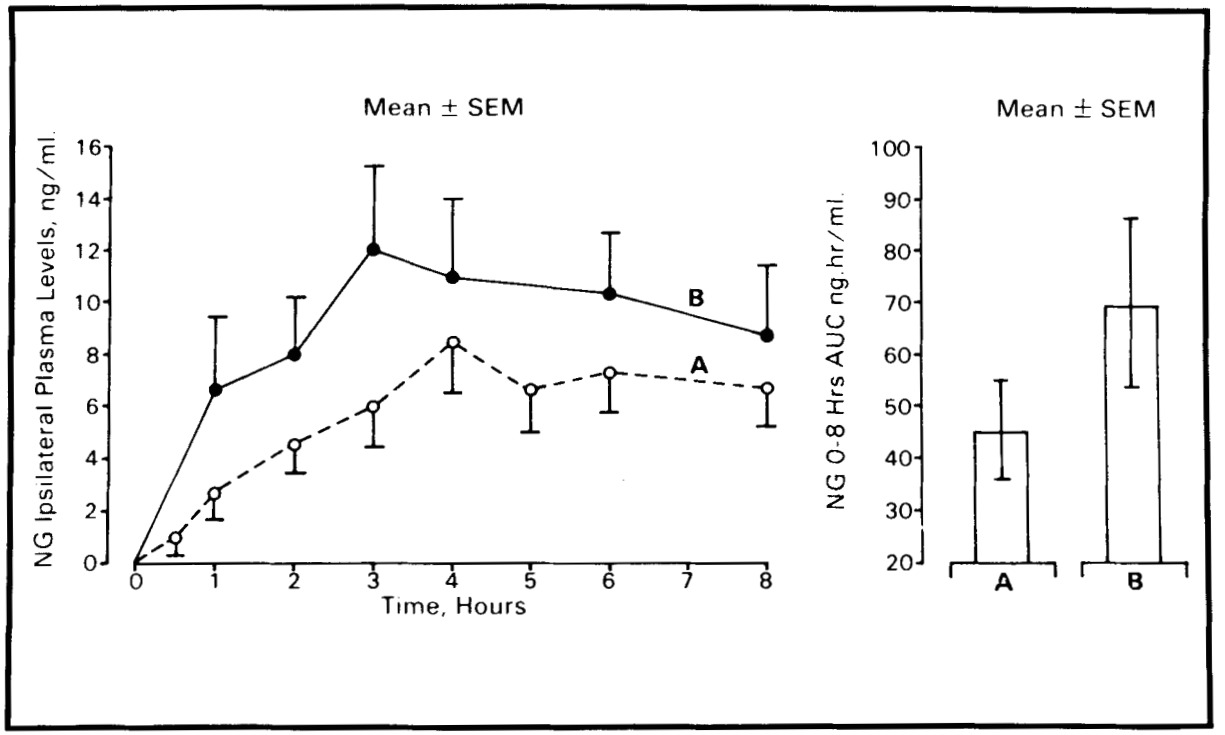


Figure 5: Relationship between the concentration and the ipsilateral plasma levels of nitroglycerin. 2% Nitro-Bid ointment was applied on the volar surface of the left wrist.

A = 1/2 inch, 8 mg NG over 53 cm^2 (0.15 mg/cm^2), n=23

B = 1 inch, 16 mg NG over 53 cm^2 (0.30 mg/cm^2), n=6

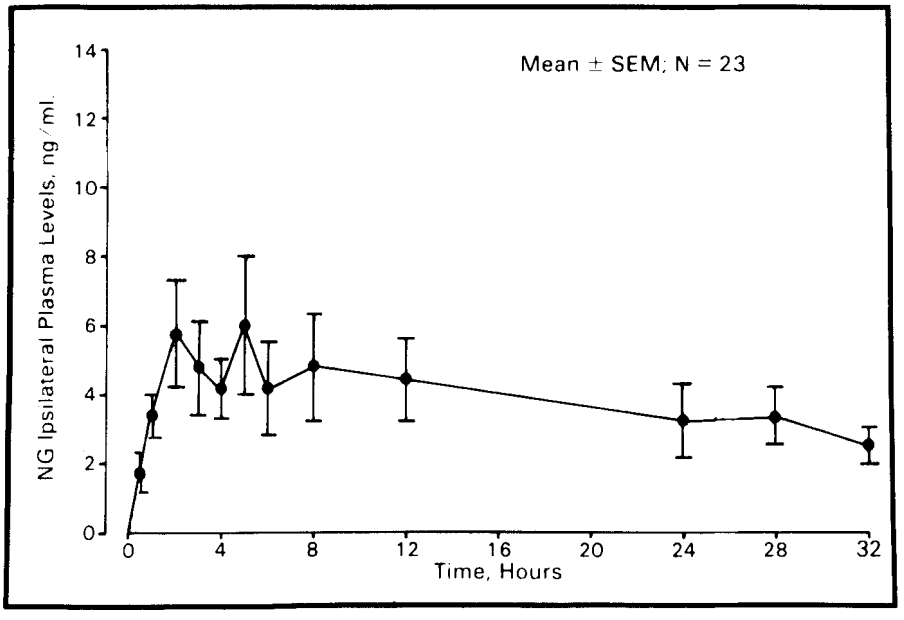


Figure 6: Mean ipsilateral plasma concentration-time curve of nitroglycerin in 23 healthy male subjects following application of MDD-NG (16 mg over 8 cm^2) on the volar surface of the left wrist.

of either MDD-NG or ointment, the absorption study was repeated in an additoinal 12 subjects each of whom received MDD-NG (32 mg over 16 cm^2) and Nitro-Bid® ointment [one inch (16 mg) over 53 cm^2] in a randomized, balanced, crossover manner. The application site was the precordial region of the chest.

With the chest application, plasma levels of NG in the left and the right forearm veins should be similar if systemic levels were indeed achieved. The concentration-time curves in Figure 9 show that about 0.3 ng/ml plasma levels were attained in the left and right forearm veins with application of MDD-NG on the chest (Figure 10).

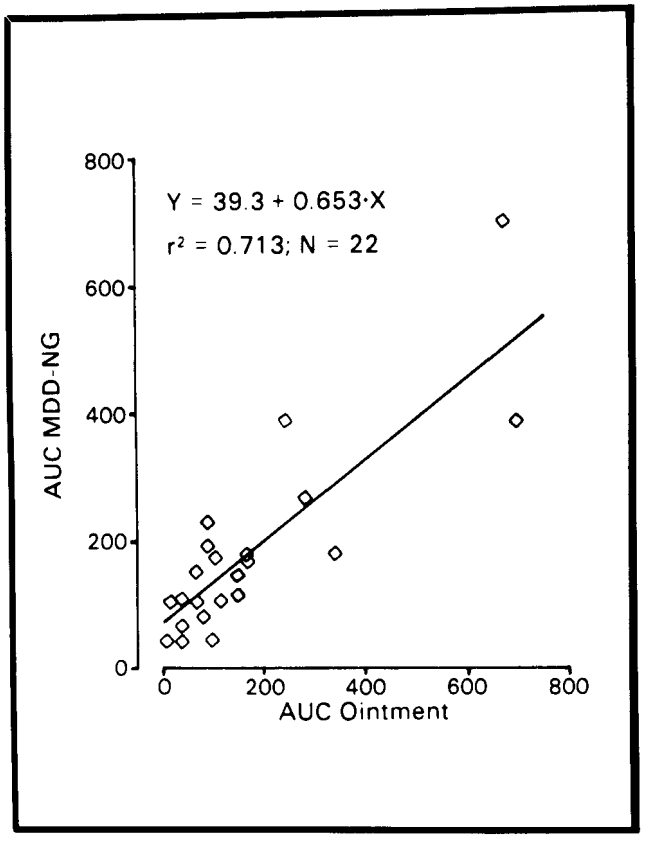


Figure 7: Relationship between 0-48 hour ipsilateral area under the plasma concentration-time curves (AUC, ng.hr/ml) following application of MDD-NG (16 mg over 8 cm^2) or 2% ointment (8 mg over 53 cm^2) on the volar surface of the left wrist of 22 healthy male subjects in a randomized, crossover study.

Comparison of AUC MDD-NG with AUC ointment indicated that the systemic availability of NG from MDD-NG (32 mg over 16 cm^2) was equivalent to one inch of the ointment (16 mg over 53 cm^2). Therefore, the MDD-NG bioavailability parameters obtained from the systemic plasma levels were similar to those obtained from the ipsilateral plasma levels.

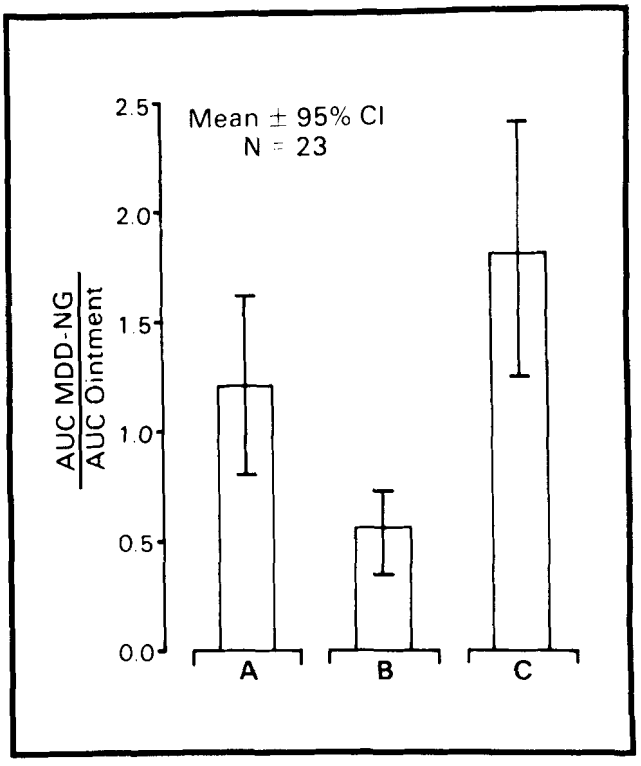


Figure 8: Evaluation of transdermal absorption of nitroglycerin from MDD-NG (16 mg over 8 cm^2) relative to the 2% ointment [1/2 inch (8 mg) over 53 cm^2] from the ratio of ipsilateral AUC following dermal application on the volar surface of the left wrist of 23 subjects in a randomized, crossover study.

A = 0-48 hr AUC ratio without adjustment of the dose or the surface area differences.

B = 0-48 hr AUC ratio adjusted for dose difference.

C = 0-48 hr AUC ratio adjusted for dose and surface area differences.

Is There a Site-Related Difference in the Systemic Availability?

The above findings suggest a site-related difference in the systemic availability of the transdermally applied NG. This difference cannot be attributed to differences in the amount of NG released from the MDD-NG systems since about 70% of NG was released in 48 hours and available for dermal absorption when

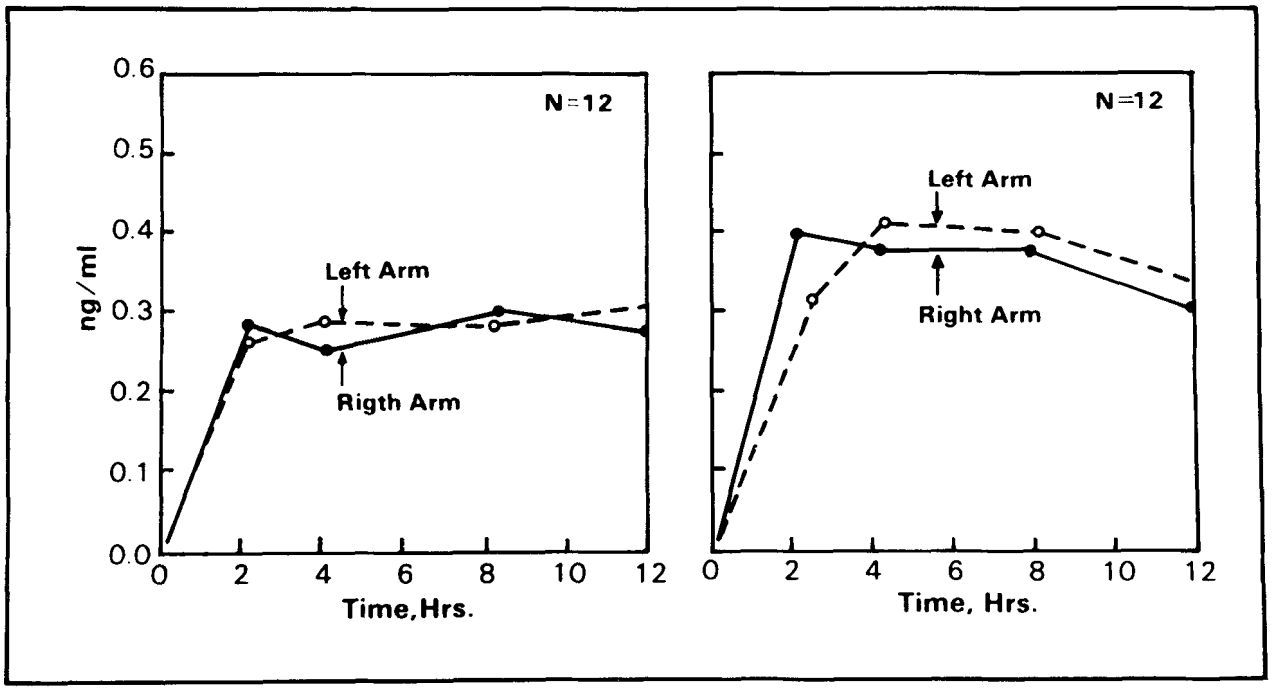


Figure 9: Plasma concentrations of nitroglycerin in the left and right forearm antecubital veins following application of MDD-NG (32 mg over 16 cm^2) (left panel) or 2% ointment (one inch, 16 mg over 53 cm^2) (right panel). Each point is a mean of 12 subjects in whom the two preparations were applied on the precordial region of the chest in a randomized, balanced, crossover study.

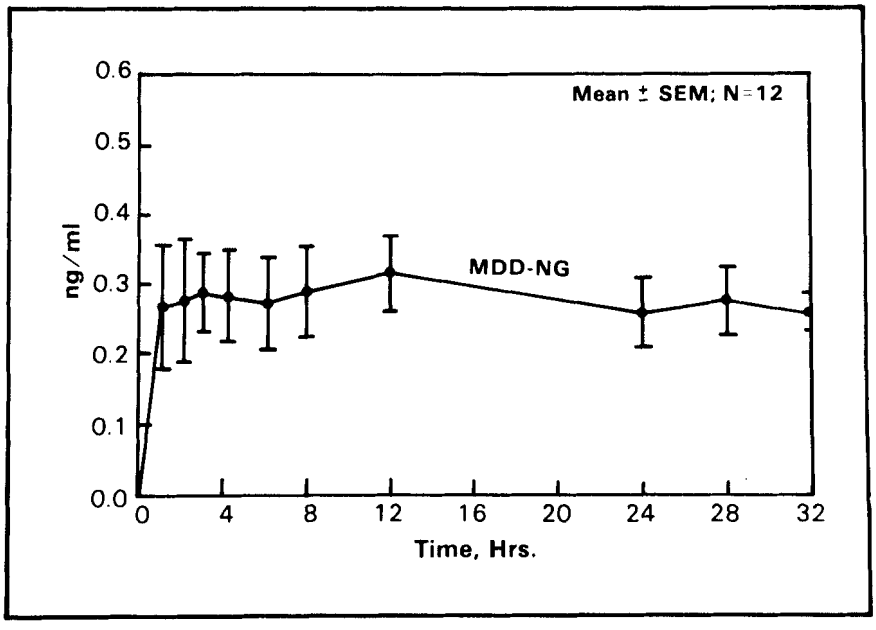


Figure 10: Mean systemic plasma concentration-time curve of nitroglycerin in 12 healthy male subjects following application of MDD-NG (32 mg over 16 cm^2) on the precordial region of the chest.

MDD-NG was placed either on the volar surface of the wrist or on the precordial region of the chest.

Recently a first-pass blood vessel uptake of NG has been demonstrated (10,11) in rats when the drug was injected directly in the lumens of blood vessels. Furthermore, the uptake of NG in the aorta was less extensive than the uptake in the inferior vena cava. The site-related systemic availability differences of NG may be attributed to the differences in the blood vessel uptake and/or metabolism of topically applied NG. These results support the clinical observations of Hansen et al (12) who noted significant differences in the responses of normal subjects to NG ointment when the same dose was applied to different body sites.

Of the three sites studied (the mid-forehead, the left lower anterior chest, and medial left ankle), the forehead uniformly produced the greatest response in terms of magnitude and time of onset of changes in systolic blood pressure and incidence of subjective complaints. The chest site produced slightly lessened responses, but they paralleled the responses for the forehead site. With application to the ankle, the responses of the subjects were markedly less in comparison with either the forehead or chest site, and were nearly indistinguishable from the control.

Future Application of Transdermal Drug Delivery:

The transdermal delivery of additional drugs could play an important role in many fields of medicine. A major constraint in the application of the transdermal system is a need for drugs that are therapeutically potent in doses on the order of a few milligrams a day. Fortunately, a wide range of important potent drugs already exist in several significant areas of medicine that are suitable for transdermal delivery. In the cardiovascular area, the transdermal system may prove valuable in administering drugs to treat hypertension and peripheral vascular disease. Other possibilities include treatment of central nervous system and respiratory malfunctions, and conditions related to steroidal hormone deficiency.

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