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DEVELOPMENT OF TRANSDERMAL DRUG DELIVERY SYSTEMS

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I. Introduction

Continuous intravenous infusion at a programmed rate has been recognized as a superior mode of drug delivery not only to bypass the hepatic "first-pass" elimination, but also to maintain a constant, prolonged, and therapeutically-effective drug level in the body. A closely monitored intravenous infusion can provide both the advantages of direct entry of drug into the systemic circulation and also the control of circulating drug levels. However, such mode of drug delivery entails certain risks and, therefore, necessitates hospitalization of the patients and close medical supervision of the medication.

Recently, there is an increasing awareness that the benefits of intravenous drug infusion can be closely duplicated, without its potential hazards, by continuous transdermal drug administration through an intact skin (1).

In response to this new idea, several transdermal drug delivery (TDD) systems have recently been developed aiming to achieve the objective of systemic medication through topical application on the intact skin surface. It is exemplified first with the development of scopolamine-releasing TDD system (Transderm-Scop) for 72-hr prophylaxis or treatment of motion-induced nausea (2), and then by the successful marketing of nitroglycerin-releasing TDD systems (Deponit, Nitrodisc, Nitro-Dur, and Transderm-Nitro) as well as isosorbide dinitrate-releasing TDD system (Frandol tape) for once-a-day medication of angina pectoris (3,4), and most recently with the regulatory approval of clonidine-releasing TDD system (Catapres-TTS) for weekly therapy of hypertension (4) and of estradiol-releasing TDD system (Estraderm) for twice-a-week treatment of postmenopausal symptoms (5).

This review intends to discuss the origin and fundamentals of transdermal drug delivery as well as the development and evaluation of various TDD systems.

II. The Skin - Site for Transdermal Drug Administration

The skin of an average adult body covers a surface area of approximately 2 square meters and receives about one-third of the blood circulating through the body (6). It is one of the most readily accessible organs on the human body. Microscopically, the skin is a multilayered organ composing of many histological layers: the epidermis, the dermis, and the hypodermis (Figure 1). The epidermis is further divided into

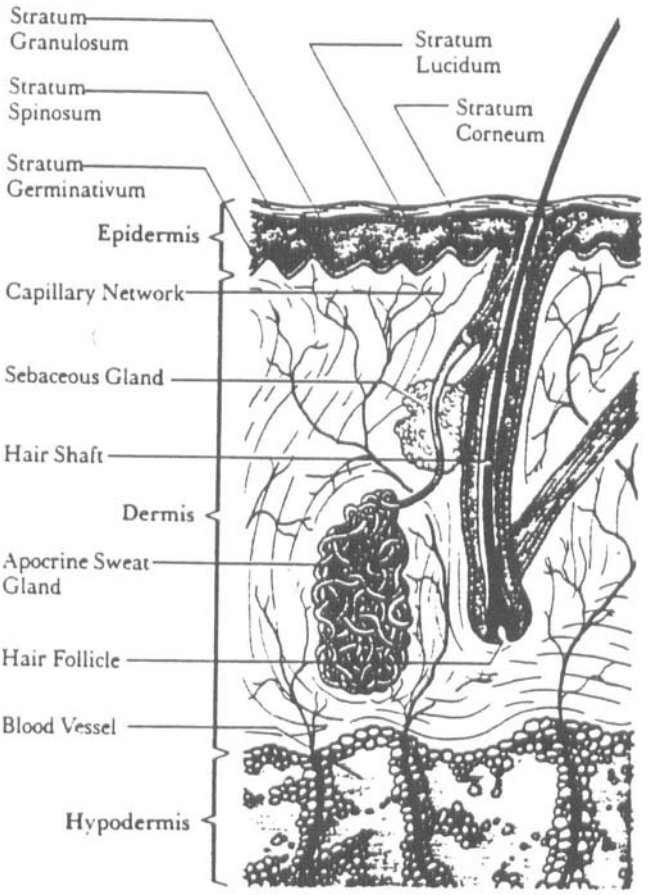


Figure 1: Cross-sectional view of human skin, showing various skin tissue layers and appendages (Reproduced from Zanowiak and Jacobs, 1982).

five anatomical layers with stratum corneum forming the outermost layer of the epidermis and exposing to the external environment.

The stratum corneum consists of many layers of compacted, flattened, dehydrated and keratinized cells. These cells are physiologically rather inactive and are continuously shed with constant replacement from the underlying viable epidermal tissue (7). The stratum corneum has a water content of only 20% as compared to the normal physiologic level of 70%, such as in the physiologically-active stratum germinativum (which is the regenerative layer of the epidermis).

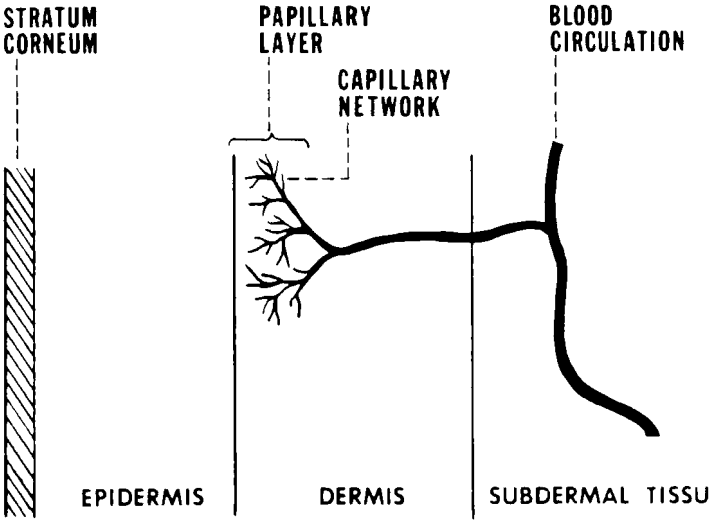


Figure 2: A simplified model of the human skin for mechanistic analysis of skin permeation (Reproduced from Y. W. Chien, 1983).

An average human skin surface is known to contain, on the average, 40-70 hair follicles and 200-250 sweat ducts on every square centimeter of skin area. These skin appendages, however, actually occupy, grossly, only one-tenth of one percent (0.1%) of the total human skin surface. Even though the foreign agents, especially the water-soluble ones, may be able to penetrate into the skin via these skin appendages at a rate which is faster than through the intact area of the stratum corneum, this trans-appendageal route of percutaneous absorption has, however, provided a very limited contribution to the overall kinetic profile of transdermal permeation. Therefore, the transdermal permeation of most neutral molecules at steady state can, thus, be considered as, primarily, a process of passive diffusion through the intact stratum corneum in the interfollicular region. So, for the fundamental understanding of transdermal drug infusion (8), the organization of the skin can be represented by a simplified multilayer model as shown in Figure 2.

For many decades, the skin has been commonly used as the site for the topical administration of dermatological drugs to achieve a localized pharmacologic action in the skin tissues. In this case, the drug molecule is considered to diffuse to a target tissue in the proximity of drug application to produce its therapeutic effect before it is distributed

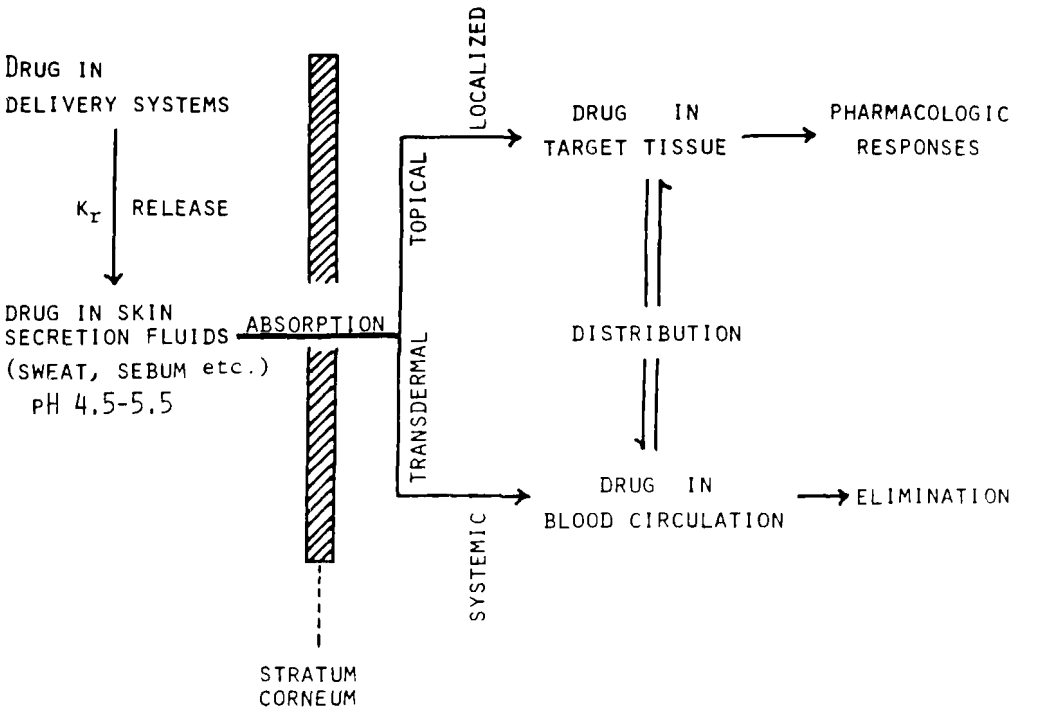


Figure 3: Schematic illustration of drug release and absorption across the skin tissues for localized therapeutic actions in the tissues directly underneath the site of drug administration or for systemic medications in the tissues remote from the site of topical drug application (*Reproduced from* Y. W. Chien, 1983).

to the systemic circulation for elimination (Figure 3). The use of hydrocortisone for dermatitis, benzoyl peroxide for acne, and neomycin for superficial infection (9) are few examples of the application.

In the case that the skin serves as the port of administration for systemically-active drugs, the drug applied topically is distributed, following absorption, first into the systemic circulation and then transported to target tissues, which could be relatively remote from the site of drug application, to achieve its therapeutic action (Figure 3). This new application is exemplified by the transdermal controlled delivery of nitroglycerin to myocardium for the treatment of angina pectoris, of scopolamine to the vomiting center for the prevention of

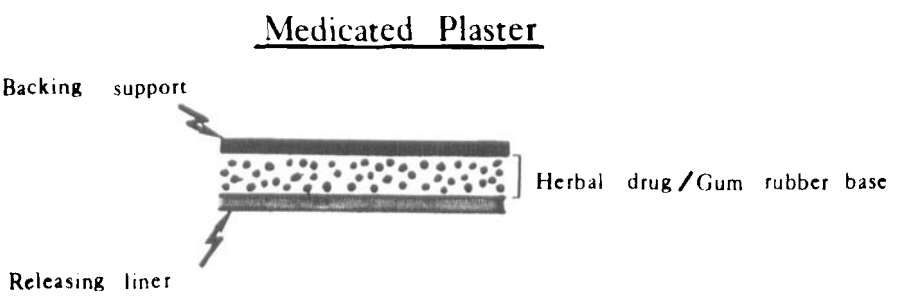


Figure 4: Cross-sectional view of a medicated plaster, showing various major structural components.

motion-induced sickness, and of estradiol to various estradiol-receptor sites for the relief of postmenopausal syndromes (10-12).

III. Conceptual Origin of Transdermal Drug Delivery

The potential of using the intact skin as the port of drug administration has been recognized for several decades as evidenced by the development of medicated plasters. By definition, the plaster is also a drug delivery system designed for the external applications. It is made of natural adhesive materials and with proper balance of cohesive strengths, the adhesive is bonded to the backing support (Figure 4). Such a proper balance also provides a good bonding to the skin as the plaster is applied and a clean adhesive break from the skin surface when the plaster is removed. Historically, the medicated plaster could be viewed as the first development of human's idea of transdermal drug delivery. It is designed to bring medication into close contact with the skin, so drug can be delivered transdermally (13).

To date, the historic development of the medicated plasters has not been well documented. However, the use of medicated plasters can be traced several hundred years back to Ancient China. One representative of the Chinese medicated plasters, which are now still available on the marketplace for medical practice, is shown in Figure 5. As shown in Table I, these early generations of medicated plasters tend to contain multiple ingredients of herbal drugs and are indicated for localized action in the tissues directly underneath the site of application.

The medicated plasters are also very popular in Japan as over-the-counter pharmaceutical dosage forms and they are also commonly called

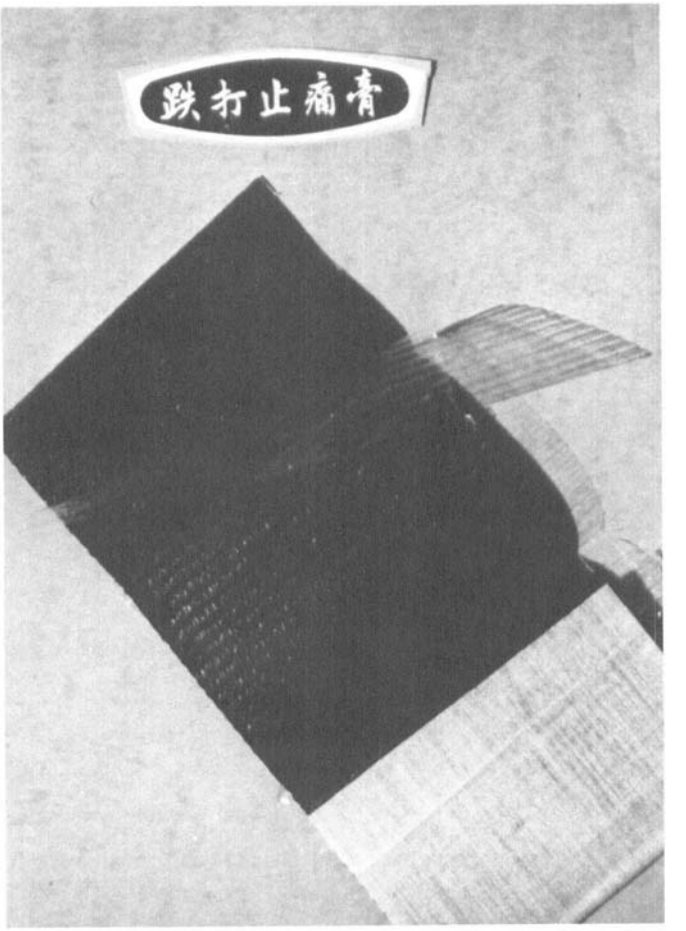


Figure 5: A representative Chinese medicated plaster, named Yang-Cheng® Plaster (manufactured by The United Pharmaceutical Manufactory, Kwangchow, China). Its composition is outlined in Table I.

cataplasms (14). Salonpas is a typical example (Figure 5). Although it is still formulated from multiple ingredients, including six therapeutically-active agents (Table II), the formulation has been so improved as to contain only the purified drugs.

Medicated plasters have also been existing in Western medicine for several decades. In the United States, for instance, three medicated

TABLE I: CHINESE MEDICATED PLASTER

Main Ingredients:

Fossilia Ossis Mastodi	10.42%
Eupolyphagasinensis Walker	10.42%
Sanguis Draconis	4.17%
Catechu	6.25%
Myrrha	6.25%
Rhizoma Drynariae	4.17%
Radix Dipsaci	4.17%
Flos Carthami	9.17%
Rhizoma Rhei	8.33%
Herba Taraxaci	8.33%
Mentholum	20.00%
Methylis Salicylas	8.32%

Description and Action:

This plaster is prepared on the basis of the dialectic therapeutics of traditional Chinese medicine. The elements of various drugs and herbs, when applied to the skin, will penetrate into the subcutaneous tissues to stimulate circulation and produce a local analgesic effect. This plaster helps to cure the inflammation in the muscles and to promote the healing of bone fractures.

Indications:

Bruises, Fractures, Sprains, Swelling and Pains, bad circulation of blood, Injuries and wound, rheumatic arthritis, Neuralgia, Limb languor etc.

Directions:

Cut a piece of desired-size from the roll, remove the cellophane and apply it to the affected part. Medicinal effect last 24 hours.

Figure 6: A representative Japanese medicated plaster, named Salonpas® medicated plaster (manufactured by Hisamitsu Pharmaceutical Co., Inc., Saga, Japan). Its composition is outlined in Table II.

plasters have been listed in the official compendia since as early as almost 40 years ago (15, 16):

1) Belladonna Plaster - Which contains belladonna root extract (0.275%) and has been listed in National Formulary, since 1946, as a local analgesic.
2) Mustard Plaster - Which contains black mustard powder and is capable of delivering allyl isothiocyanate after moistening

TABLE II: SALONPAS® MEDICATED PLASTER

Active Ingredients (per 250 cm^2)

Methyl Salicylate	330 mg.
Glycol Salicylate	50 mg.
ℓ-Menthol	300 mg.
dℓ-Camphor	65 mg.
Thymol	42 mg.
Tocopherol Acetate	6 mg.

Directions:

Clean and dry affected area. Remove SALONPAS plaster from the cellophane film and apply to affected area. Change plaster once or twice a day. SALONPAS plaster is more effective if used after a hot bath. Keep unused portions in a cool place.

with warm water. It has been listed in National Formulary, since 1950, as an effective local irritant.

3) Salicylic Acid Plaster - Which contains salicylic acid (10-40%) and has been listed in United States Pharmacopeia, since 1950, as a keratolytic agent.

It is interesting to note that these Western-type medicated plasters are rather simple in formula and all contain only a single active ingredient, which is in great contrast to the Oriental-type medicated plasters (Tables I and II). However, like the Oriental plasters, the Western medicated plasters have also been developed mainly for local medication.

IV. RECENT DEVELOPMENT IN TRANSDERMAL DRUG DELIVERY

The potential of using an intact skin as the port for continuous transdermal infusion of drug has been recently recognized beyond the boundary of topical medication. The development of female syndromes in male operators working in the manufacturing areas for estrogen-containing pharmaceutical dosage forms has challenged the old theory that the skin is an impermeable barrier, and also triggered the research curiosity of several biomedical scientists to evaluate the feasibility of trans-

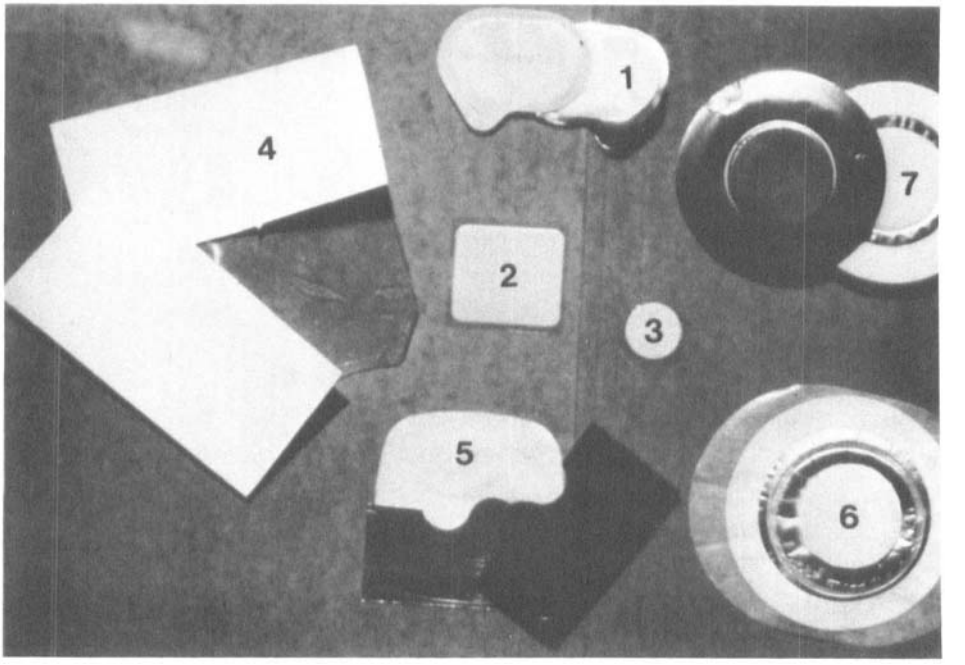


Figure 7: Photographic illustration of various newly-developed transdermal therapeutic systems

(A) Membrane permeation-controlled TDD systems:
(1) Transderm-Nitro® system (3) Transderm-Scop® system
(2) Catapres-TTS® system

(B) Adhesive dispersion-type TDD systems:
(4) Frandol® tape (5) Deponit® system

(C) Matrix diffusion-controlled TDD systems:
(6) Nitro-Dur® system

(D) Microreservoir dissolution-controlled TDD systems:
(7) Nitrodisc® system

dermal delivery of systemically-effective drugs. The findings accumulated over the years have practically revolutionized the old concept of impermeable skin barrier and also motivated a number of pharmaceutical scientists to develop patch-type drug delivery systems for transdermal rate-controlled administration of drugs for systemic medication (1, 2, 17).

Over a decade of intensive research and development efforts, several rate-controlled transdermal drug delivery (TDD) systems have been successfully developed and commercialized (Figure 7). They can be

classified, according to the technological basis of their approach, into the following 4 categories:

A) Membrane Permeation-controlled TDD Systems
- Transderm-Scop system - Scopolamine-releasing TDD system
- Transderm-Nitro system - Nitroglycerin-releasing TDD system
- Catapres-TTS system - Clonidine-releasing TDD system
- Estraderm system - Estradiol-releasing TDD system

B) Adhesive Dispersion-type TDD Systems
- Deponit system - Nitroglycerin-releasing TDD system
- Frandol tape - Isosorbide dinitrate-releasing TDD system
- Nitro-Dur II system - Nitroglycerin-releasing TDD system

C) Matrix Diffusion-controlled TDD Systems
- Nitro-Dur system - Nitroglycerin-releasing TDD system
- NTS system - Nitroglycerin-releasing TDD sytem

D) Microreservoir Dissolution-controlled TDD Systems
- Nitrodisc system - Nitroglycerin-releasing TDD system

By now, there are 7 TDD systems have been launched on the world-wide prescription drug market: Transderm-Scop® system (Ciba), Transderm-Nitro® system (Ciba), Catapres-TTS® system (Boehringer-Ingelheim), Estraderm® system (Ciba), Nitro-Dur® system (Key) and Nitrodisc® system (Searle) in the United States, Deponit® system (Pharma-Schwarz) in Europe, and Frandol® tape (Toaeiyo-Yamanouchi) in Japan (Figure 7).

The difference in structural components between the newly-developed transdermal drug delivery systems and the medicated plasters is compared side-by-side in Table III.

V. MECHANISMS OF RATE-CONTROLLED TRANSDERMAL DRUG DELIVERY

For a systemically-active drug to reach a target tissue, which is remote from the site of drug administration on the skin surface, it has to possess some physicochemical properties which facilitate the sorption of drug by the stratum corneum, the penetration of drug through the viable epidermis, and also the uptake of the drug by microcirculation in the dermal papillary layer (Figure 8). The rate of permeation, dQ/dt, across various layers of skin tissues can be expressed in mathematical form (18) as:

$$\frac{dQ}{dt} = P_s (C_d - C_r) \qquad (1)$$

TABLE III: TRANSDERMAL PATCHES vs. MEDICATED PLASTERS

Structural component	Composition and Functionality	
	Medicated plaster	Transdermal patch
Backing support	Non-occlusive (fabric, paper etc.)	Occlusive (drug-impermeable plastic film, metallic plastic laminate)
Drug reservoir	Dispersion of multiple drugs in adhesive natural gum rubber base	Dispersion of single drug in liquid- or solid-state synthetic polymer base
Drug release mechanism	Matrix diffusion	Membrane permeation, microreservoir dissolution, or matrix diffusion
Adhesive film	No (adhesiveness derived from gum rubber base)	Yes (surface coating with pressure-sensitive adhesive polymer)
Release liner	Cellophane Gauze	Occlusive (drug-impermeable plastic film, metallic plastic laminate with releasing surface)

Where C_d and C_r are, respectively, the concentrations of a skin penetrant in the donor phase, e.g., the drug concentration on the stratum corneum surface, and in the receptor phase, e.g., systemic circulation; and P_s is the overall permeability coefficient of the skin tissues to the penetrant and is defined by:

$$P_s = \frac{K_s D_{ss}}{h_s} \qquad (2)$$

Where K_s is the partition coefficient for the interfacial partitioning of the penetrant molecule from a transdermal drug delivery system onto the stratum corneum; D_{ss} is the apparent diffusivity for the steady-state diffusion of the penetrant molecule through skin tissues; and h_s is the overall thickness of the skin tissues for penetration. The perme-

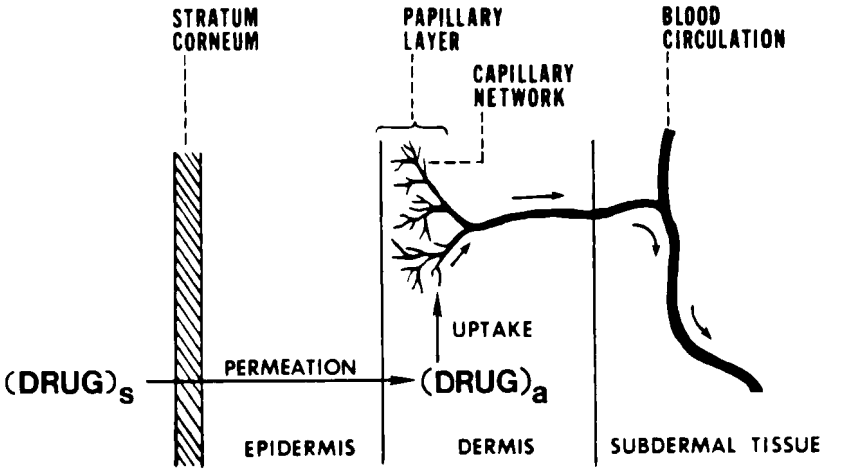


Figure 8: A multilayer skin model showing the sequence of transdermal permeation of drug: sorption by stratum corneum, permeation across viable epidermis and then uptake by the capillary network in the dermal papillary layer for systemic distribution.

ability coefficient (P_s) for a skin penetrant can be considered as a constant value, if K_s, D_{ss} and h_s terms in Equation (2) are essentially constant under a given set of conditions.

Analysis of Equation (1) suggests that in order to achieve a constant rate of drug permeation, one needs to maintain a condition in which the drug concentration on the surface of stratum corneum (C_d) consistently and substantially greater than the drug concentration in the body (C_r), i.e., $C_d >> C_r$; under such a condition, Equation (1) can be reduced to:

$$\frac{dQ}{dt} = P_s C_d \tag{3}$$

and the rate of skin permeation (dQ/dt) should become a constant, if the magnitude of C_d value remains fairly constant throughout the course of skin permeation. To maintain the C_d at a constant value, it is necessary to make the drug to be delivered at a rate (R_d) that is either constant or always greater than the rate of skin absorption (R_a), i.e., $R_d >> R_a$ (Figure 9). By making R_d greater than R_a, the drug concentration on the skin surface (C_d) is maintained at a level which is equal to or

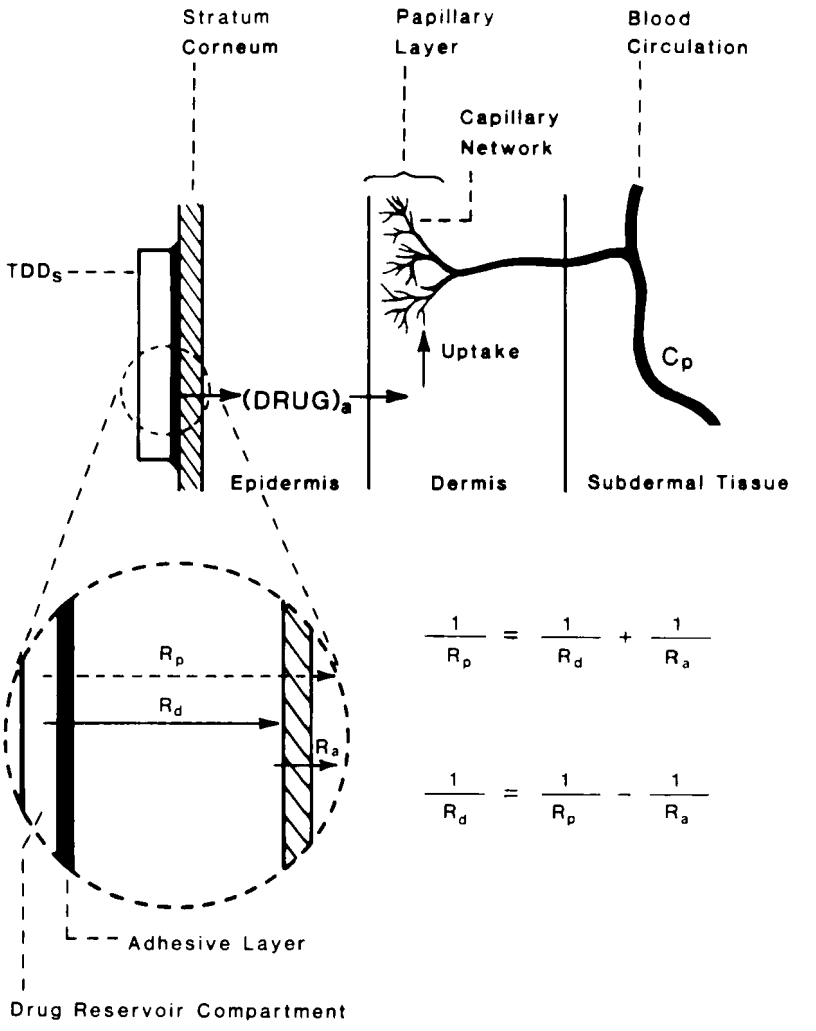


Figure 9: Schematic illustration of the relationship among the rate of skin permeation (R_p) of a drug, the rate of drug delivery (R_d) from a TDD system, and the rate of drug absorption (R_a) by the skin.

greater than the equilibrium (or saturation) solubility of the drug in the stratum corneum (C_s^e), i.e., $C_d \geq C_s^e$; and a maximum rate of skin permeation $(dQ/dt)_m$, as expressed by Equation (4), is thus achieved:

$$\left(\frac{dQ}{dt}\right)_m = P_s C_s^e \tag{4}$$

Apparently, the magnitude of $(dQ/dt)_m$ is determined by permeability coefficient (P_s) of the skin to the drug and equilibrium solubility of

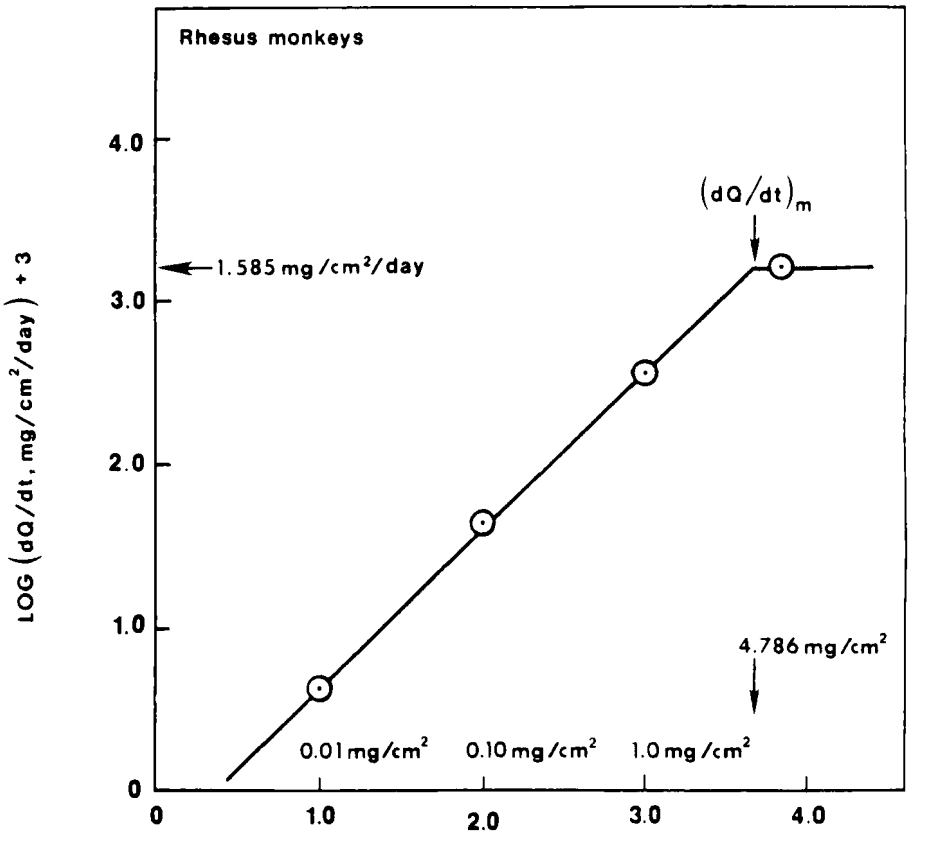


Figure 10: Linear relationship between the skin permeation rate of nitroglycerin (dQ/dt), determined from the daily urinary recovery data, and the nitroglycerin dose applied to the rhesus monkey skin (C_d) (plotted from the data by Sanvordeker et al., 1982).

the drug in the stratum corneum (C_s^e). This concept of stratum corneum-limited skin permeation was investigated by depositing various doses of pure nitroglycerin, which is in radiolabeled form and dissolved in a volatile organic solvent, onto a controlled skin surface area of rhesus monkeys (19). Analysis of the urinary recovery data indicated that the rate of skin permeation (dQ/dt) increases with the increase in nitroglycerin dose (C_d) applied on a unity surface area of the skin (Figure 10). It appears that a maximum rate of skin permeation (1.585 mg/cm^2/day) is achieved when the applied dose of nitroglycerin reaches the level of 4.786 mg/cm^2 or greater.

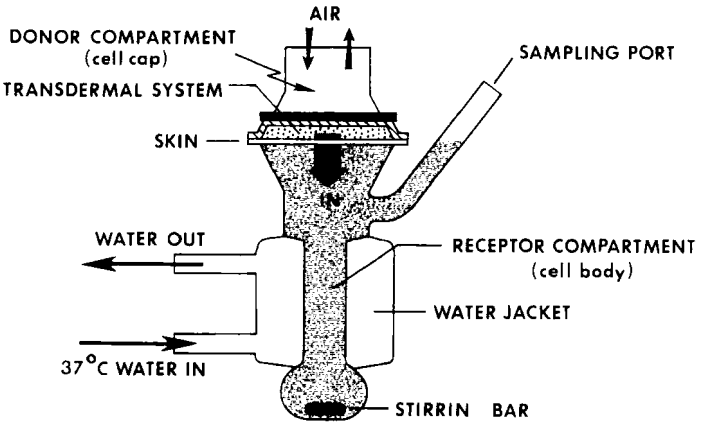


Figure 11: Diagrammatic illustration of the in vitro skin permeation system, in which one unit of the commercially available 8-cell Franz diffusion apparatus is shown with TDD system in intimate contact with the stratum corneum surface (Reproduced from Y. W. Chien, 1984).

The kinetics of skin permeation can be more precisely analyzed by studying the permeation profiles of drug across a freshly excised skin specimen mounted on a diffusion cell, such as the Franz diffusion cell (Figure 11). A typical skin permeation profile is shown in Figure 12 for nitroglycerin. Results indicated that nitroglycerin penetrates through the freshly-excised abdominal skin of hairless mouse at a zero-order rate of 19.85 (±1.71) mcg/cm^2/hr, as expected from Equation 4, when the pure nitroglycerin, in oily liquid form, is directly deposited on the surface of stratum corneum (in this case the skin permeation of drug is under no effect from either an organic solvent or a rate-controlled drug delivery system)(20). Using a hydrodynamically well-calibrated horizontal skin permeation cell, the same observations were also made in a series of long-term skin permeation kinetic studies for estradiol (21), which provides a critical analysis of the relationships among skin permeation rate, permeability coefficient, partition coefficient, diffusivity, and solubility. The effects of skin uptake, binding, and metabolism kinetics of estradiol on its skin permeation profiles were also evaluated and illustrated (22).

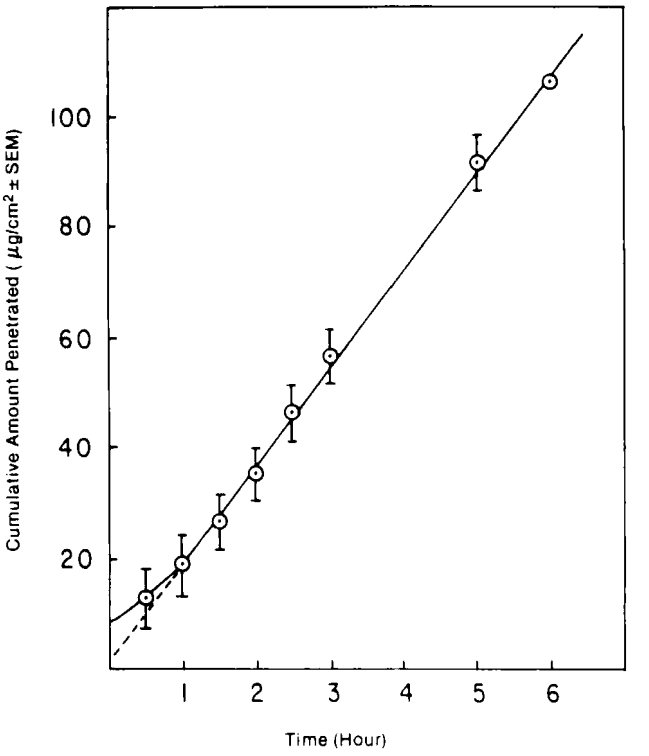


Figure 12: Permeation profile of pure nitroglycerin across the abdominal skin of hairless mouse mounted on Franz diffusion cell at 37°. A constant skin permeation profile was obtained with a permeation rate of 19.85 (±1.71) mcg/cm^2/hr (From Keshary et al., 1984).

To gain a fundamental understanding of the skin permeation kinetics of drugs and to assist the formulation development of transdermal drug delivery systems, the in vitro skin permeation studies, using a freshly-excised skin sample mounted in a hydrodynamically well-calibrated skin permeation cell, are considered to be a must prior to conducting any in vivo evaluations in human volunteers.

VI. TECHNOLOGIES FOR DEVELOPING TRANSDERMAL DRUG DELIVERY SYSTEMS

Several technologies have been successfully developed to provide a rate-control over the release and skin permeation of drugs. These technologies can be classified into 4 basic approaches as outlined as follows:

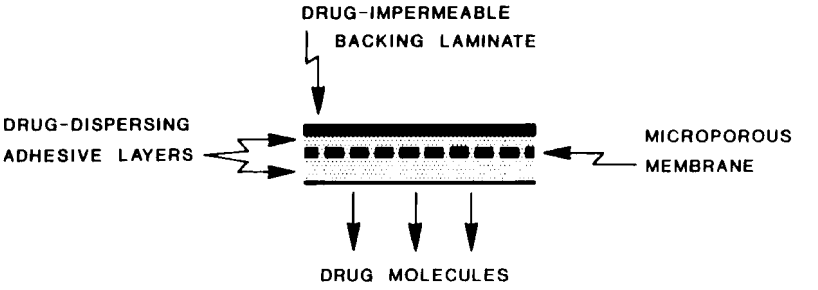


Figure 13: Cross-sectional view of a membrane permeation-controlled TDD system, showing various major structural components (Reproduced from Y. W. Chien, 1985).

A. Membrane Permeation-controlled TDD Systems

In this system, the drug reservoir is sandwiched between a drug-impermeable metallic plastic laminate and a rate-controlling polymeric membrane (Figure 13). The drug molecules are permitted to release only through the rate-controlling polymeric membrane. In the drug reservoir compartment, the drug solids are either dispersed homogeneously in a solid polymer matrix (e. g. polyisobutylene adhesive), suspended in an unleachable, viscous liquid medium (e.g., silicone fluid) to form a paste-like suspension, or dissolved in a releasable solvent (e.g., alkyl alcohol) to form a clear drug solution. The rate-controlling membrane can be either a microporous or a non-porous polymeric membrane, e.g., ethylene-vinyl acetate copolymer, with a specific drug permeability. On the external surface of the polymeric membrane, a thin layer of drug-compatible, hypoallergenic pressure-sensitive adhesive polymer, e.g., silicone or polyisobutylene adhesive, may be applied to provide an intimate contact of the TDD system with the skin surface. The rate of drug release from this TDD system can be tailored by varying the composition of drug reservoir formulation, the permeability coefficient and/or thickness of the rate-controlling membrane. Several TDD systems have been successfully developed from this technology and approved by FDA for marketing, such as the Transderm-Nitro® system, for once-a-day medication of angina pectoris (24, 25), Transderm-Scop® system for 3-day protection of motion sickness (2), Catapres-TTS® system for weekly therapy of hypertension (26-28), and Estraderm® system for twice-a-week treatment of postmenopausal syndromes (5, 29, 30).

The intrinsic rate of drug release from this type of drug delivery system is defined by:

$$\frac{dQ}{dt} = \frac{K_{m/r}K_{a/m} \cdot D_a \cdot D_m}{K_{m/r}D_m h_a + K_{a/m}D_a h_m} C_R \qquad (5)$$

Where C_R is the drug concentration in the reservoir compartment; $K_{m/r}$ and $K_{a/m}$ are, respectively, the partition coefficients for the interfacial partitioning of drug from the reservoir to the membrane and from the membrane to the adhesive; D_m and D_a are the respective diffusion coefficients in the rate-controlling membrane and in the adhesive layer; h_m and h_a are, respectively, the thickness of the rate-controlling membrane and the adhesive layer. In the case of microporous membrane, the porosity and tortuosity of the membrane should also be taken into consideration in the calculation of the D_m and h_m values.

The membrane permeation-controlled transdermal drug delivery technology has also been applied to the development of TDD systems for the rate-controlled percutaneous absorption of prostaglandin derivative (31).

B. Adhesive Dispersion-type TDD Systems

This type of drug delivery system can be viewed as a simplified version of the membrane-moderated drug delivery system, in which the release of drug molecules from the drug-dispersing reservoir is metered by permeation through a rate-controlling membrane. In this system, the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer, e.g., polyisobutylene or polyacrylate, and then spreading the medicated adhesive, by solvent casting or hot melt, onto a flat sheet of drug-impermeable backing support to form a single or multiple layers of drug reservoir (Figure 14). The release profiles of drug from this type of TDD systems will not be constant, as expected from the matrix diffusion process (See Section VI-C).

This type of TDD system is best illustrated by the development and marketing of the isosorbide dinitrate-releasing TDD system, named Frandol® tape, by Toaeiyo/Yamanouchi in Japan and of nitroglycerin-releasing TDD system, named Nitro-Dur® II system, by Key in the United States for once-a-day medication of angina pectoris. Frandol tape is currently under clinical evaluations in the United States for regulatory approval, while Nitro-Dur® II system has recently received FDA approval for marketing.

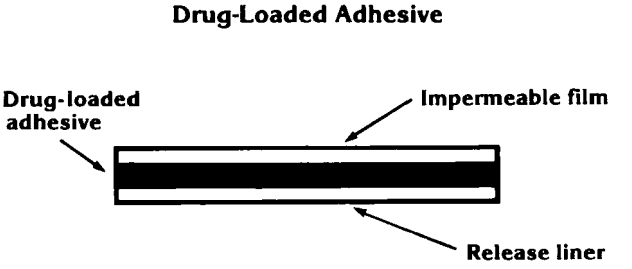


Figure 14: Cross-sectional view of an adhesive dispersion-type TDD system, showing various major structural components.

To overcome the non-constant drug release profiles, this type of TDD system can be modified to have the drug loading level varied at increment manner to form a gradient of drug reservoir along the multilaminate adhesive layers (Figure 15). The rate of drug release from this drug reservoir gradient-controlled TDD systems can be expressed by:

$$\frac{dQ}{dt} = \left(\frac{K_{a/r} D_a}{h_a(t)}\right) A\ (h_a) \qquad (6)$$

In Equation (6), the thickness of adhesive layer for drug molecules to diffuse through is increasing with time [$h_a(t)$]. To compensate this time-dependent increase in diffusional path as a result of drug depletion by release, the drug loading level is also increased proportionally [$A\ (h_a)$]. A constant drug release profile is thus produced. This type of TDD system is best illustrated by the development of a nitroglycerin-releasing TDD system, named Deponit® system, and marketed by PharmaSchwartz/Lohmann in Europe. U. S. Food and Drug Administration has recently approved its NDA for marketing in the United States.

C. Matrix Diffusion-controlled TDD Systems

In this approach, the drug reservoir is formed by homogeneously dispersing the drug solids in a hydrophilic or lipophilic polymer matrix and the medicated polymer formed is then molded into medicated discs with a defined surface area and controlled thickness. This drug reservoir-containing polymer disc is then mounted onto an occlusive baseplate in a compartment fabricated from a drug-impermeable plastic backing (Figure 16). Instead of applying the adhesive polymer directly on the surface of the medicated disc as shown earlier in the first two types of TDD

DRUG RESERVOIR GRADIENT-CONTROLLED
TRANSDERMAL DRUG DELIVERY SYSTEMS

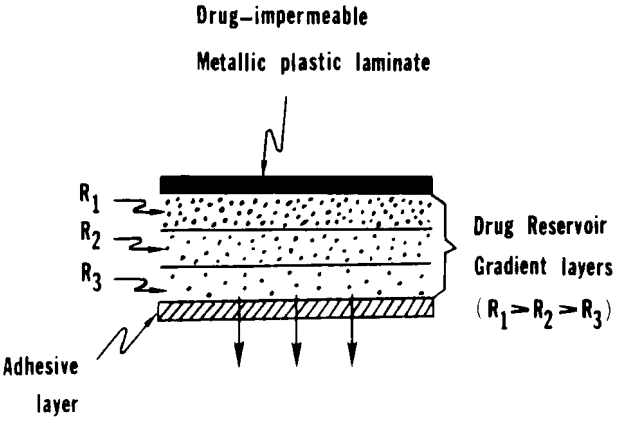


Figure 15: Cross-sectional view of a drug reservoir gradient-controlled TDD system, showing various major structural components.

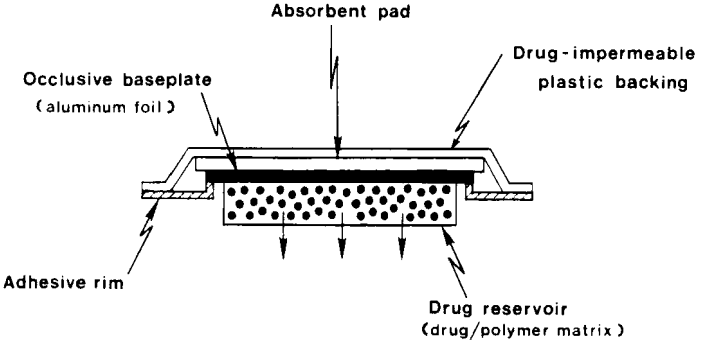


Figure 16: Cross-sectional view of a matrix diffusion-controlled TDD system, showing various major structural components (Reproduced from Y. W. Chien, 1985).

systems, in the present system the adhesive polymer is spread along the circumference of the patch to form a strip of adhesive rim around the medicated disc. The rate of drug release from this matrix dispersion-type TDD system is defined as:

$$\frac{dQ}{dt} = \left(\frac{ACpDp}{2t}\right)^{\frac{1}{2}} \tag{7}$$

where A is the drug loading dose initially dispersed in the polymer matrix; and Cp and Dp are the solubility and diffusivity of the drug in the polymer, respectively. In view of the fact that only the drug species dissolved in the polymer can release, so, Cp is practically equal to C_R.

At steady state, a $\underline{Q \text{ vs. } t^{\frac{1}{2}}}$ drug release profile is obtained (32) as defined by:

$$\frac{Q}{t^{\frac{1}{2}}} = [(2A - Cp)CpDp]^{\frac{1}{2}} \tag{8}$$

This type of TDD system is exemplified by the development and marketing of Nitro-Dur® system (33) and NTS system, which have been approved by FDA for once-a-day medication of angina pectoris.

D. Microreservoir Dissolution-controlled TDD Systems

This type of drug delivery system can be considered as a hybrid of the reservoir- and matrix dispersion-type drug delivery systems. In this approach, the drug reservoir is formed by first suspending the drug solids in the aqueous solution of a water-soluble polymer, e.g., polyethylene glycol, and then dispersing homogeneously the drug suspension in a lipophilic polymer, by high-shear mechanical force, to form thousands of unleachable microscopic drug reservoirs (Figure 17). This thermodynamically unstable dispersion is quickly stabilized by immediately cross-linking the polymer chains *in situ*, which produces a medicated polymer disc with a constant surface area and a fixed thickness. A TDD system is then produced by forming the medicated disc at the center of an adhesive pad. This technology has been successfully utilized in the development and marketing of Nitrodisc® system, which has been approved by FDA for once-a-day treatment of angina pectoris (19, 34-38).

The rate of drug release from the microreservoir-type drug delivery system is defined (32, 38) by:

$$\frac{dQ}{dt} = \frac{D_p D_s \alpha' K_p}{D_p \delta_d + D_s \delta_p \alpha' K_p} \left[\beta S_p - \frac{D_1 S_1 (1-\beta)}{\delta_1} \left(\frac{1}{K_1} + \frac{1}{K_m}\right)\right] \tag{9}$$

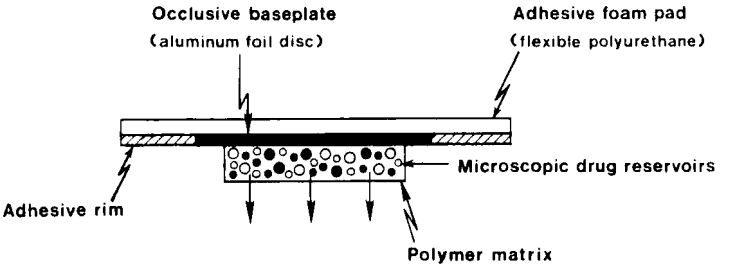


Figure 17: Cross-sectional view of a microreservoir dissolution-controlled TDD system, showing various major structural components (Reproduced from Y. W. Chien, 1985).

where $\alpha' = \frac{\partial'}{\beta'}$. ∂' is the ratio of the drug concentration in the bulk of elution solution over the drug solubility in the same medium and β' is the ratio of the drug concentration at the outer edge of the polymer coating membrane over the drug solubility in the same polymer composition; K_l, K_m and K_p are the partition coefficients for the interfacial partitioning of drug from the liquid compartment to the polymer matrix, from the polymer matrix to the polymer coating membrane, and from the polymer coating membrane to the elution solution (or skin), respectively; D_l, D_p, and D_s are the drug diffusivities in the liquid compartment, polymer coating membrane, and elution solution (or skin), respectively: S_l and S_p are the solubilities of the drug in the liquid compartment and in the polymer matrix, respectively; δ_l, δ_p and δ_d are the thicknesses of the liquid layer surrounding the drug particles, the polymer coating membrane around the polymer matrix, and the hydrodynamic diffusion layer surrounding the polymer coating membrane, respectively; β is the ratio of the drug concentration at the inner edge of the interfacial barrier over the drug solubility in the polymer matrix.

Release of drugs from the microreservoir-type drug delivery system can follow either a partition control- or matrix diffusion-control process depending upon the relative magnitude of S_l and S_p (38). So, a Q vs. t or Q vs. $t^{\frac{1}{2}}$ release profile is resulted (40, 41).

Development of other types of drug delivery systems are also underway for possible applications in the transdermal controlled delivery of drugs. It is exemplied by the disposition of drugs in a poroplastic membrane

(42) and the formation of a hydrophilic polymeric reservoir (43). Both of them may be viewed as a drug solution-saturated porous polymer matrix.

VII. EVALUATIONS OF TRANSDERMAL DRUG DELIVERY KINETICS

The release and skin permeation kinetics of drug from these technologically-different TDD systems can be evaluated, using a two-compartment diffusion cell assembly, under identical conditions. It is carried out by mounting, individually, a skin specimen, which has been freshly excised from either a human cadaver or an animal model (44), on a diffusion cell, such as Franz diffusion cell (Figure 11). Each unit of the TDD systems is then applied with its drug-releasing surface in intimate contact with the stratum corneum surface of the skin (41). The skin permeation profile of drug is followed by sampling the receptor solution at predetermined intervals until the steady state flux is established and assaying drug concentrations in the samples by a sensitive analytical method, such as the high performance liquid chromatographic (HPLC) method. The release profiles of drug from these TDD systems can also be investigated, using the same experimental setup with no skin.

In actual determination of drug release and skin permeation kinetics studies, the rate profiles obtained could be well below the intrinsic rates calculated from Eq. (5), (6), (8) and (9) due to the effect of mass transfer across the hydrodynamic diffusion layer on the surface of drug delivery system or dermis. The magnitude of reduction is related to the thickness of hydrodynamic diffusion layer and the physicochemical properties of the drugs (45, 46). It is rather important to take these effects into consideration for accurate determination of drug release and skin permeation rate profiles.

A. In Vitro Drug Release Kinetics

Using Franz diffusion cell assembly, the mechanisms and the rates of drug release from these technologically-different TDD systems can be evaluated and compared (20). The results indicated that nitroglycerin is released at a constant rate profile (Q vs. t) from the TDD systems like Transderm-Nitro system (a membrane permeation-controlled TDD system) and Deponit system (a drug reservoir gradient-controlled TDD system) (Figure 18). The release rate of nitroglycerin from the Transderm-Nitro system (0.843 ± 0.035 mg/cm^2/day) is almost 3 times greater than that from the Deponit system (0.324 ± 0.011 mg/cm^2/day). It suggests that the diffusion through the rate-controlling adhesive layers in the Deponit

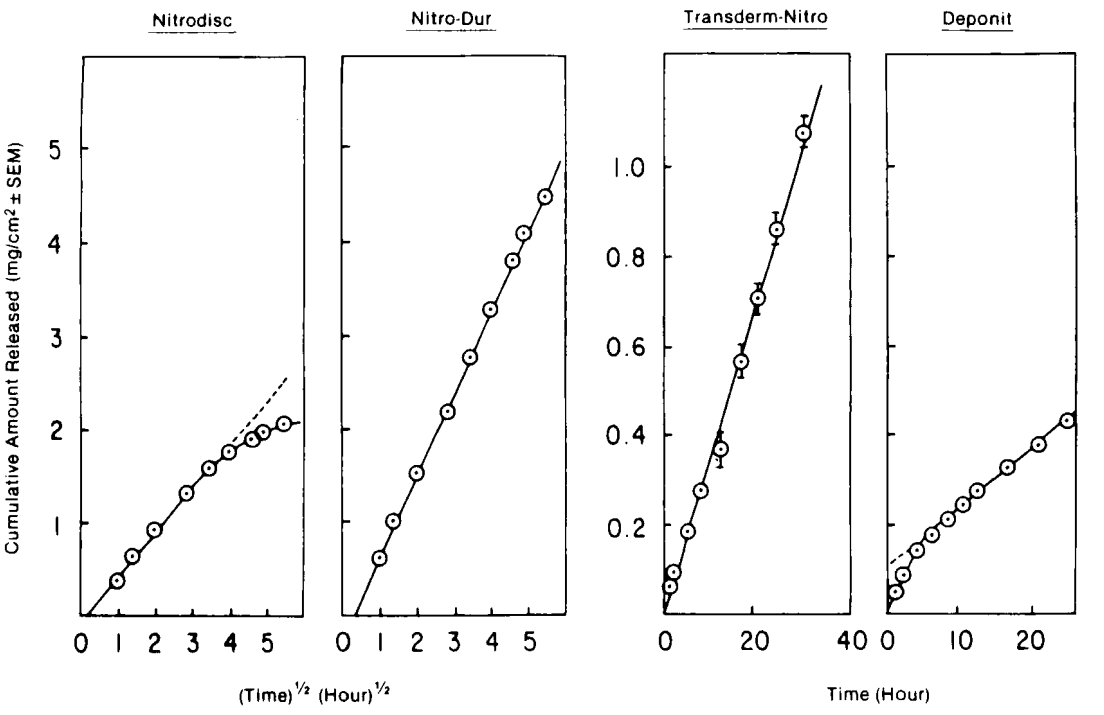


Figure 18: Comparative release profiles of nitroglycerin from various TDD systems into saline solution under sink conditions at 37°C. The release flux of nitroglycerin is: Nitrodisc system (2.443 ± 0.136 mg/cm^2/day^{½}), Nitro-Dur system (4.124 ± 0.047 mg/cm^2/day^{½}), Transderm-Nitro system (0.843 ± 0.035 mg/cm^2/day), and Deponit system (0.324 ± 0.011 mg/cm^2/day) (From Keshary et al., 1984).

system plays a greater rate-limiting role over the release of nitroglycerin than does the permeation across the rate-controlling membrane in the Transderm-Nitro system.

On the other hand, the release profiles of nitroglycerin from Nitrodisc and Nitro-Dur systems are not constant, but are observed to follow a linear Q vs. $t^{½}$ pattern as expected from the matrix diffusion-controlled drug release kinetics (32). The release flux of nitroglycerin from the Nitro-Dur system (a matrix diffusion-controlled TDD system) is almost twice greater than that from the Nitrodisc system (a microreservoir dissolution-controlled TDD system)(4.124 ± 0.047 vs. 2.443 ± 0.136 mg/cm^2/day^{½}).

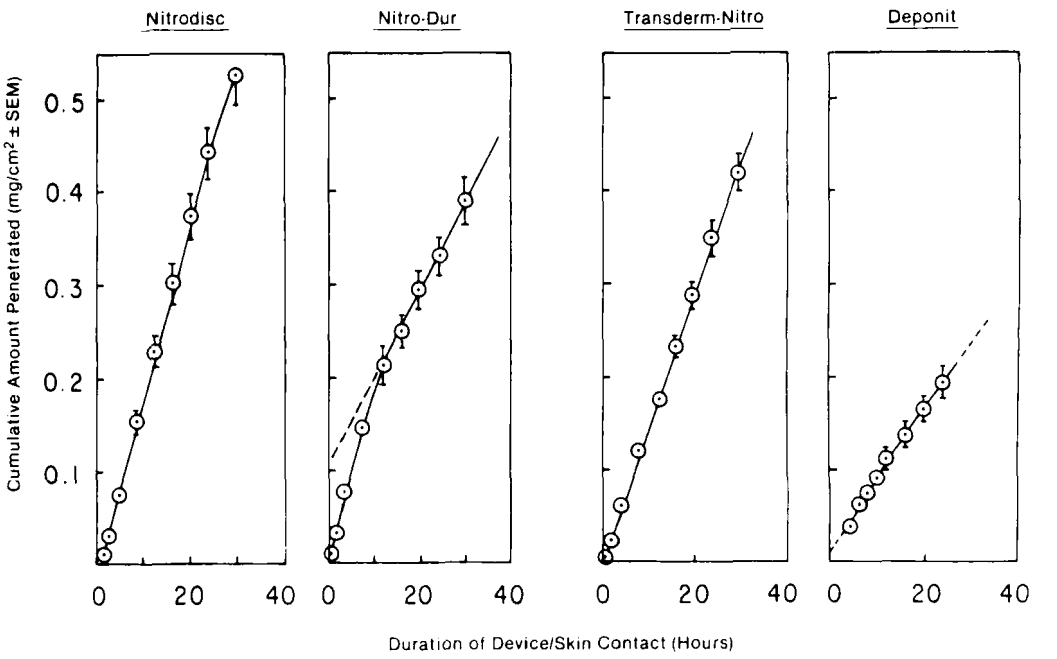


Figure 19: Comparative permeation profiles of nitroglycerin from various TDD systems through the hairless mouse abdominal skin at 37°C. The rate of skin permeation is: Nitrodisc system (0.426 ± 0.024 mg/cm^2/day), Nitro-Dur system [0.408 ± 0.024 mg/cm^2/day (<12 hrs); 0.248 + 0.018 mg/cm^2/day (>12 hrs)], Transderm-Nitro system (0.338 ± 0.017 mg/cm^2/day), and Deponit system (0.175 ± 0.016 mg/cm^2/day) (From Keshary et al., 1984).

Apparently, the mechanisms and/or rates of nitroglycerin release from these 4 TDD systems are quite different from one another, as expected from Eq. (5), (6), (8) and (9).

B. In Vitro Skin Permeation Kinetics - Animal Model

The skin permeation studies of these TDD systems suggested that all 4 systems give a constant rate of skin permeation (Figure 19) as expected from Equation 3. Highest rate of skin permeation was observed with Nitrodisc system (0.426 ± 0.024 mg/cm^2/day), which is, however, statistically no different from the rate of skin permeation for pure nitroglycerin (0.476 ± 0.041 mg/cm^2/day, Figure 12). For Nitro-Dur system,

practically the same rate of skin permeation (0.408 ± 0.024 mg/cm^2/day) was obtained initially and 12 hours later, however, the rate became slowed down to 0.248 (±0.018) mg/cm^2/day. On the other hand, the rate of skin permeation of nitroglycerin from Transderm-Nitro system (0.338 ± 0.017 mg/cm^2/day) was found to be 30% lower than the rate achieved by pure nitroglycerin (0.476 mg/cm^2/day) or 21% slower than that by Nitrodisc system (0.426 mg/cm^2/day). Lowest rate of skin permeation was observed with Deponit system (0.175 ± 0.016 mg/cm^2/day), which achieved only one-third of the skin permeation rate for pure nitroglycerin.

Comparing the rate of skin permeation (Figure 19) with the rate of release (Figure 18) suggest that, under the sink conditions, all TDD systems deliver nitroglycerin at a rate which is greater than its rate of permeation across the skin ($R_d > R_a$, Figure 9). For example, nitroglycerin was delivered by Transderm-Nitro system, which is a membrane permeation-controlled drug delivery system, at a rate (0.843 mg/cm^2/day) that is 2.5 times greater than its rate of permeation across the skin (0.338 mg/cm^2/day); Likewise, the rate of delivery by the Deponit system, which is a multilaminate adhesive dispersion-type drug delivery system having the slowest rate of nitroglycerin delivery (0.324 mg/cm^2/day), was found almost two folds faster than the rate of skin permeation (0.175 mg/cm^2/day). The same observations were also true for Nitrodisc and Nitro-Dur systems. This phenomenon is indicative of the rate-limiting role that the stratum corneum plays in the skin permeation of drugs as a result of its extremely low permeability.

C. In Vitro Skin Permeation Kinetics - Human Cadaver

The permeation of nitroglycerin across the skin of human cadaver was also investigated for Transderm-Nitro system, the membrane permeation-controlled TDD system, and for Nitro-Dur system, the matrix diffusion-controlled TDD system (47). The results (Figure 20) indicated that the skin permeation of nitroglycerin through the abdominal epidermis of human cadaver also follows the same zero-order kinetic profile as observed with hairless mouse abdominal skin (Figure 19). It is interesting to note that the rates of skin permeation generated from the freshly excised skin specimen of hairless mouse agree fairly well with the data obtained from human cadaver skin (Table IV), suggesting that hairless mouse skin could be an acceptable skin model for humans in the skin permeation kinetics studies of nitroglycerin. This finding is substantiated by the data recently generated in the transdermal permeation studies of estradiol

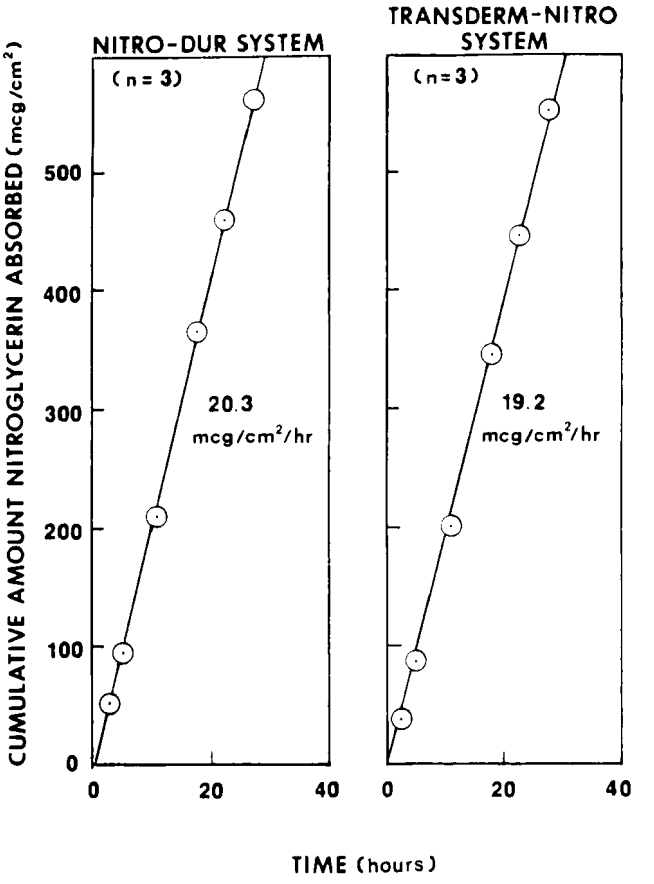


Figure 20: Comparative permeation profiles of nitroglycerin from Nitro-Dur and Transderm-Nitro systems across the human cadaver abdominal epidermis. The rate of skin permeation is: Nitro-Dur system (20.3 mcg/cm^2/hr) and Transderm-Nitro system (19.2 mcg/cm^2/hr) (plotted from the data by D. E. Magnuson, 1983).

from Estraderm system and of clonidine from Catapres-TTS system (50). It has been found that the difference in the type and the thickness of skin specimen and in the hydrodynamics of in vitro skin permeation cells could affect the inter-species correlation in skin permeation rates. For a better correlation, a skin model with controlled source and a skin permeation cell with well-calibrated hydrodynamics should be used in the skin permeation kinetics studies (Figure 21). The transdermal perme-

TABLE IV: INTER-SPECIES CORRELATION IN THE IN VITRO TRANSDERMAL CONTROLLED ADMINISTRATION OF DRUGS FROM TDD SYSTEMS

Drugs	TDD System	Skin Permeation Rate ($mcg/cm^2/hr$)	
		Human Cadaver	Hairless Mouse
Nitroglycerin	Transderm-Nitro	19.23	14.55[a)]
	Nitro-Dur	20.33	16.67[a)]
Estradiol	Estraderm	0.27[b)]	0.40[b)]
Clonidine	Catapres-TTS	2.05[b)]	3.62[b)]

a) Determined in Franz diffusion cells (Figure 11) at 37°C (haq = 0.0338 cm) (Chien et al., 1983)

b) Determined in Valia-Chien skin permeation cells (Figure 31) at 37°C (haq = 0.0054) (Chien et al., 1986)

c) Calculated from clinical bioavailability data reported in the literature

ation rates across the skin of human cadaver and hairless mouse can be better correlated by correcting the difference in the thickness of skin specimen used (Table V).

D. In Vivo Transdermal Bioavailability in Humans

The transdermal bioavailability of nitroglycerin resulted from the 24- to 32-hr topical applications of various TDD systems in human volunteers, as indicated by the plasma levels of nitroglycerin, is shown in Figures 22-25. Results suggested that a prolonged, steady-state plasma level of nitroglycerin is achieved within 1-2 hours and maintained for a duration of at least 24 hrs as a result of continuous transdermal infusion of drug, at controlled rate, from the TDD systems.

A comparative systemic bioavailability study was initiated and the results demonstrated that there is no statistically significant difference among the plasma profiles of nitroglycerin delivered by Transderm-Nitro, Nitrodisc, and Nitro-Dur systems (26).

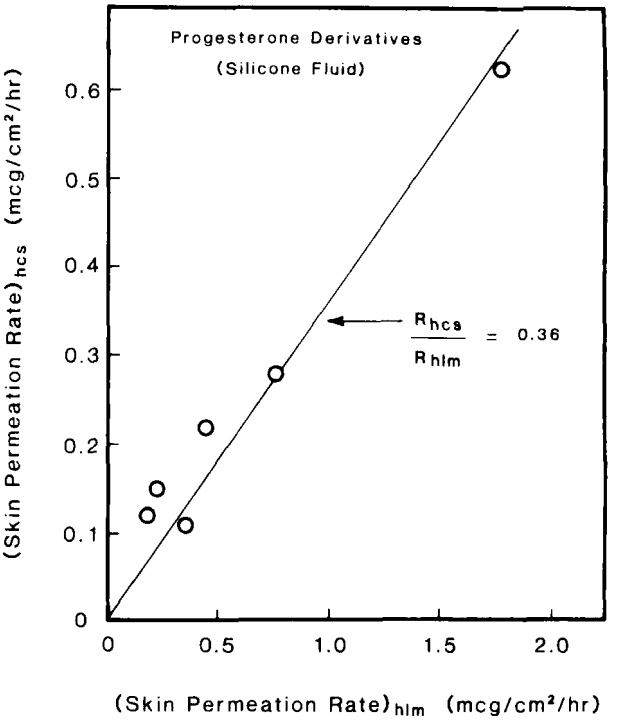


Figure 21: Correlation in the permeation rates of progesterone and its hydroxyl derivatives across the skin of human cadaver (hcs) and of hairless mouse (hlm) with approximately same thickness.

The plasma level was found to be linearly proportional to the area of the drug releasing surface of TDD systems in contact with the skin (Figure 26). So, the plasma drug level can be easily tailored to reach a target therapeutic concentration by simply controlling the surface area of drug-releasing device applied to the skin.

Further investigations demonstrated that the transdermal bioavailability of nitroglycerin-releasing TDD systems is independent of the site of application (24). The results of repeat daily applications also showed an excellent day-to-day reproducibility, whereas no drug accumulation was detected (24).

E. Correlations in In Vitro and In Vivo Skin Permeation Kinetics

To further examine the feasibility of using freshly excised hairless mouse skin as the model skin for studying the transdermal controlled

TABLE V: INTER-SPECIES AND BETWEEN-SEX CORRELATION IN SKIN PERMEATION RATES OF CLONIDINE[1)]

Skin Specimen		Skin Permeation Rate (± S.D.)	
Species	Source	Actual[2)] (mcg/cm^2/hr)	Normalized[3)] (mcg/cm/hr x 10^2)
Human cadaver	Black female Left anterior leg (620 μm)	2.05 (± 0.28)	12.71 (± 1.74)
Hairless mouse	Female Abdominal (450 μm)	3.99 (± 0.58)	17.96 (± 2.61)
	Male Abdominal (450 μm)	3.62 (± 0.68)	16.29 (± 3.06)

1) Delivered from Catapres-TTS.

2) Measured in Valia-Chien skin permeation cells (Figure 31) at 37°C (Chien et al., 1986)

3) Corrected for the difference in the thickness of skin specimen used.

permeation kinetics of drugs across the human skin, the *in vivo* rate of skin permeation $(Q/t)_{i.v.}$ can also be determined for comparison. It can be calculated from the steady-state plasma level $(C_p)_{ss}$ data (Figures 22-25), using the following relationship (53):

$$\left(\frac{Q}{t}\right)_{i.v.} = (C_p)_{ss} \cdot K_e \cdot V_d \,/\, A_s \qquad (10)$$

where K_e is the first-order rate constant for the elimination of drug, V_d is the apparent volume of distribution for the drug, and A_s is the surface area of drug-releasing device in contact with the skin.

Results in Table VI indicated that the *in vivo* skin permeation rates calculated on the basis of Eq. (10) show a reasonably good agreement with the *in vitro* data determined from either human cadaver epidermis

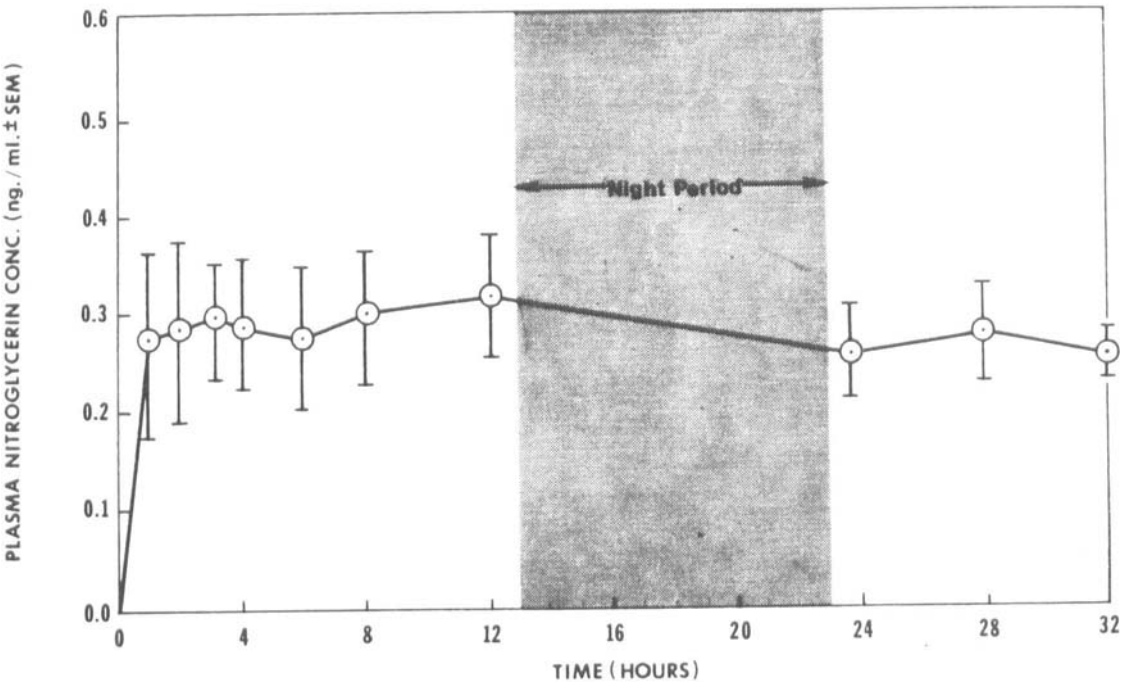


Figure 22: Plasma profiles of nitroglycerin in 12 healthy male volunteers, each received one unit of Nitrodisc system (16 cm^2) on the chest for 32 hours. A mean steady-state plasma level, (Cp)ss, of 280.6 ± 18.7 pg/ml was obtained (plotted from the data by Karim, 1983).

or hairless mouse full-thickness skin. This *in vivo-in vitro* agreement provides additional evidence that hairless mouse skin could be an acceptable skin model for studying the skin permeation kinetics of systemically-effective drugs in humans.

VIII. OPTIMIZATION OF TRANSDERMAL CONTROLLED DRUG DELIVERY

To formulate a TDD system one should take into consideration the relationship between the rate of drug delivery (R_d) to the skin surface and the maximum achievable rate of drug absorption (R_a) by the skin tissue (Figure 9). It is particularly important since the stratum corneum is known to be highly impermeable to most drugs. Ideally, a TDD system should be so designed to have a skin permeation rate which is determined by the rate of drug delivery from the TDD system, not by the skin permeability; In such case, the transdermal bioavailability of a drug becomes

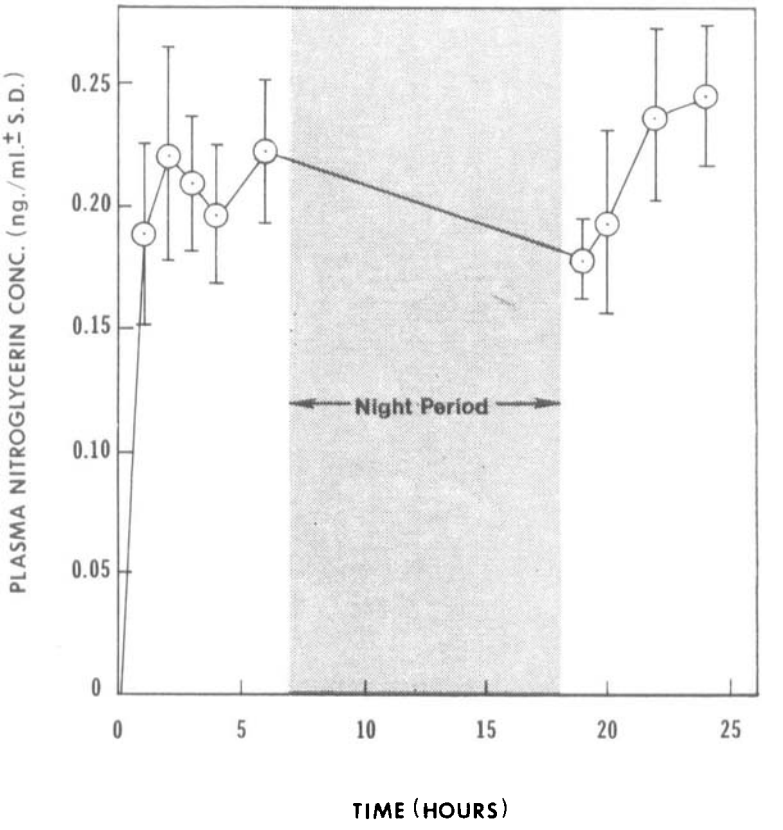


Figure 23: Plasma profiles of nitroglycerin in 14 healthy human subjects, each received one unit of Transderm-Nitro system (20 cm^2) for 24 hours. A (Cp)ss value of 209.8 ± 22.8 pg/ml was yielded (plotted from the data by Gerardin et al., 1981).

less dependent upon any possible intra- and/or inter-patient variabilities in skin permeability.

The rate of skin permeation of a drug at steady state, $(R_p)_{ss}$, is mathematically related to the actual rate of drug delivery from a TDD system, $(R_d)_a$, to the skin surface and the maximum achievable rate of skin absorption, $(R_a)_m$, by the following relationship (54):

$$\frac{1}{(R_p)_{ss}} = \frac{1}{(R_d)_a} + \frac{1}{(R_a)_m} \qquad (11)$$

And, the actual rate of drug delivery from a TDD system to the skin sur-

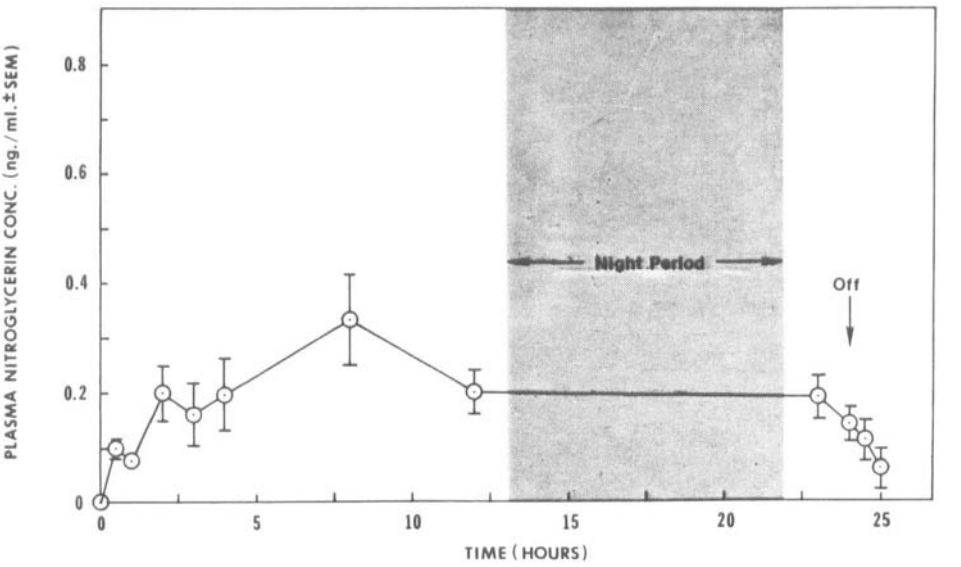


Figure 24: Plasma profiles of nitroglycerin in 6 normal male volunteers each received one unit of Nitro-Dur system (20 cm^2) over the chest for 24 hours. A (Cp)ss value of 201.4 ± 60.7 pg/ml was achieved (plotted from the data by Keith, 1983).

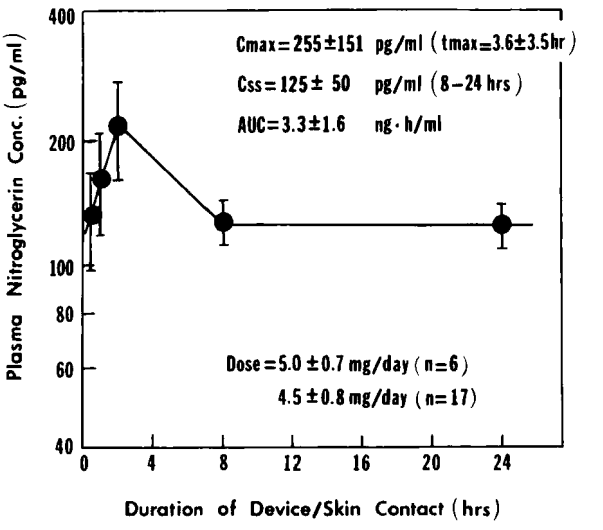


Figure 25: Plasma profiles of nitroglycerin in 6 healthy male volunteers, each received one unit of Deponit system (16 cm^2) over the chest for 24 hours. A (Cp)ss value of 125 ± 50 pg/ml was obtained (plotted from the data by Wolff et al., 1985).

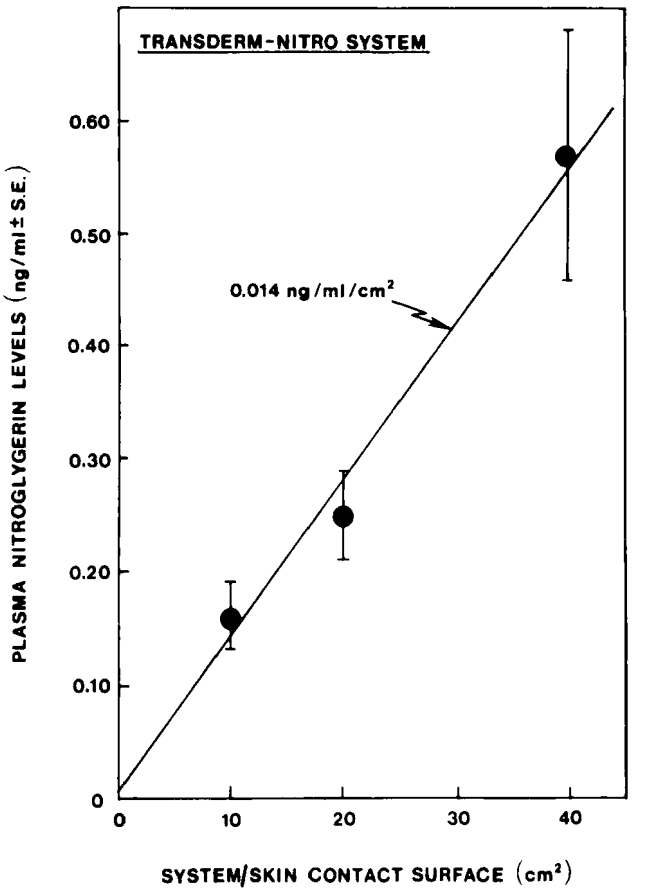


Figure 26: Linear relationship between the steady-state plasma nitroglycerin levels in humans and the drug-releasing surface of Transderm-Nitro system in contact with the skin. A plasma nitroglycerin level of 14 pg/ml was achieved for every cm^2 of drug-releasing surface applied (plotted from the data by W. R. Good, 1983).

face, which acts as the receptor medium in the clinical applications, can thus be determined from:

$$\frac{1}{(R_d)_a} = \frac{1}{(R_p)_{ss}} - \frac{1}{(R_a)_m} \qquad (12)$$

If we consider the rate of skin permeation for pure nitroglycerin, which is freed from any effect by the formulation or vehicle, as the

TABLE VI: COMPARISON IN IN VITRO AND IN VIVO SKIN PERMEATION RATES

Drugs	Delivery Systems	Skin Permeation Rates ($mcg/cm^2/day$)		
		In Vitro		In Vivo[g]
		Hairless Mouse	Human Cadaver	
Nitroglycerin	Nitrodisc	435.6[a]	-	713.0
	Nitro-Dur	400.1[a]	487.9[d]	411.6
	Transderm-Nitro	349.2[a]	461.5[d]	427.9
	Deponit	269.5[b]	-	282.5
Estradiol	Estraderm	9.6[c]	6.5[c,e]	5.0
Clonidine	Catapres-TTS	86.9[c]	49.2[c,f]	38.9

a) Determined in Franz diffusion cells (Figure 11) at 37°C (haq = 0.0304 cm) (Chien et al., 1983)

b) Determined in Keshary-Chien diffusion cells (Figure 31) at 37°C (haq = 0.0108 cm) (Keshary and Chien, 1984)

c) Determined in Valia-Chien diffusion cells (Figure 37) at 37°C (haq = 0.0054 cm) (Chien et al., 1986)

d) Determined from skin permeation studies at 37°C using the epidermis isolated from human cadaver abdominal skin (D. E. Magnuson, 1983)

e) Determined from skin permeation studies at 37°C using the human cadaver skin (male, 381 μm)

f) Determined from skin permeation studies at 37°C using the human cadaver skin (female, left anterior leg, 620 μm)

g) Calculated from steady-state plasma profiles using Equation (10)

value for $(R_a)_m$, the actual delivery rate of nitroglycerin from various TDD systems can be determined. The results in Table VII indicate that the delivery rates of nitroglycerin from Nitrodisc, Nitro-Dur, Transderm-Nitro and Deponit systems are all greater than its maximum achievable rate of skin permeation (0.621-4.058 vs. 0.476 $mg/cm^2/day$). The data suggest that the delivery rate of nitroglycerin from all 4 TDD systems has not been adequately optimized.

TABLE VII: DELIVERY RATE OF NITROGLYCERIN FROM VARIOUS TDD SYSTEMS

TDD Systems	Delivery Rate* ($mg/cm^2/day$)
Nitrodisc	4.058
Nitro-Dur	2.857
Transderm-Nitro	1.166
Deponit	0.621

*Calculated from the hairless mouse data in Table VI using Equation (12) and $(R_a)_m$ = 0.476 $mg/cm^2/day$.

Using a matrix diffusion-controlled TDD system, the relationship between the rate of drug delivery from the TDD system and the rate of skin permeation can be established. The skin permeation rate of a drug at steady state, $(R_p)_{ss}$, is related to the drug delivery rate from the matrix-type TDD system, $(Q/t^{1/2})$, as follows (55):

$$(R_p)_{ss} = \frac{m\,(Q/t^{1/2})^2}{1 + n\,(Q/t^{1/2})^2} \tag{13}$$

in which m and n are composite constants and defined, respectively, as follows:

$$m = \frac{1}{2k} \tag{14}$$

$$n = \frac{R_{sc}}{2K_1kC_p}\left(1 + \frac{R_{vs}K_3 + R_{aq}}{K_2K_3R_{sc}}\right) \tag{15}$$

where k is a constant; K_1, K_2, and K_3 are the partition coefficients for the interfacial partitioning between stratum corneum and polymer matrix, between viable skin and stratum corneum, and between receptor solution and viable skin, respectively; C_p is the drug solubility in the polymer matrix; R_{sc}, R_{vs}, and R_{aq} are the diffusional resistances for stratum corneum, viable skin, and receptor solution on the dermis side, respectively.

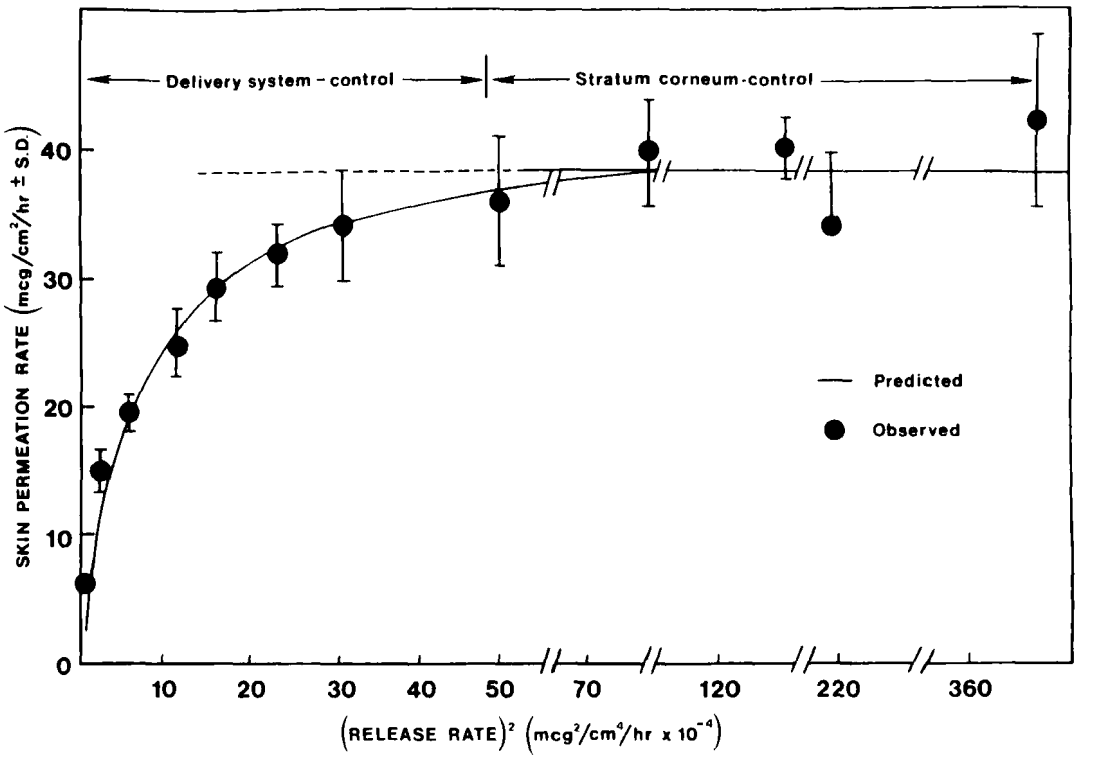


Figure 27: The hyperbolic relationship between the skin permeation rate and the square of the release flux of nitroglycerin delivered by the matrix diffusion-controlled TDD system, as prediced from Equation 13. It was observed that when $(Q/t^{\frac{1}{2}})^2$ value is equal to or less than 48 $mcg^2/cm^4/hr$, the skin permeation rate of nitroglycerin is controlled by the delivery system; when the $(Q/t^{\frac{1}{2}})^2$ value is greater than 48 $mcg^2/cm^4/hr$, the skin permeation rate becomes limited by the stratum corneum (Reproduced from Keshary et al., 1985).

Equation (13) indicates that a hyperbolic relationship should exist between $(R_p)_{ss}$ and $(Q/t^{\frac{1}{2}})^2$. When the rate of drug delivery from the TDD system is low, the skin permeation will be controlled by the delivery rate from the TDD system (Figure 27). As increasing the rate of drug delivery, the rate of skin permeation increases at hyperbolic manner and then reaches a plateau level, at which the rate of skin permeation becomes rate-limited by the inherent permeability of stratum corneum to the drug species delivered.

Using Equation (13), one can optimize the formulation and the design of a TDD system with the rate of skin permeation controlled by the rate of drug delivery from the TDD system.

IX. ADVANCES IN TRANSDERMAL CONTROLLED DRUG DELIVERY RESEARCH

It has been recognized that the transdermal rate-controlled drug delivery offers one or more of the following potential biomedical benefits:

1) To avoid the risks and inconveniences of intravenous therapy.
2) To prevent the variation in the absorption and metabolism associated with oral administration.
3) To permit continuous drug administration and the use of a drug with short biological half-life.
4) To increase efficacy through the bypass of hepatic first-pass elimination.
5) To reduce the chance of over- or under-dosing as the result of prolonged, preprogrammed delivery of drug at the required therapeutic rate.
6) To provide a simplified therapeutic regimen, leading to a better patient compliance.
7) To permit a rapid termination of the medication, if needed, by simply removing the TDD system from the skin surface.

The intensity of interests in the potential biomedical applications of the rate-controlled transdermal drug administration has been demonstrated by a substantial increase in the research and development activities in many health care institutions aiming to the development of viable TDD systems for prolonged continuous transdermal infusion of therapeutic agents (56-58). The drug candidates evaluated range from the anti-hypertensive, anti-anginal, anti-histamine, anti-inflammatory, analgesic, anti-arthritic, steroidal to contraceptive drugs. It has been estimated by marketing research experts that within the next 5 years, over 10% of the drug products will be marketed in TDD systems.

On the other hand, it has become increasingly recognized that not every drug can be administered transdermally at a rate which is high enough to achieve a blood level that is therapeutically beneficial for systemic medication. An increasing number of biomedical researchers working in the fields of transdermal drug delivery have cautioned the potential limitations of transdermal systemic medications (57, 59).

For instance, the smallest size of the nitroglycerin-releasing TDD systems (8 cm^2 for Nitrodisc, 10 cm^2 for both Transderm-Nitro and Nitro-Dur, and 16 cm^2 for Deponit) has been found capable of establishing a mean steady-state plasma level of less than 0.18 ng/ml (53), which is substantially lower than the plasma level (0.29-0.41 ng/ml) achieved by i.v. infusion of nitroglycerin at a rate of 3.4 mcg/min (i.e., a daily dose of 4.9 mg) (Figure 28). To achieve the same plasma level as the i.v. infusion, it is estimated that a transdermal patch with a nitroglycerin-releasing surface of 20-30 cm^2 will be needed, depending upon which type of TDD systems is used. The same requirement is also applied to the 2% ointment formulation, but at a more frequent dosing schedule (t.i.d.).

To achieve and to maintain a plasma drug concentration above the minimum therapeutic level, the barrier properties of the skin have to be overcome before an effective transdermal controlled delivery of drugs can be successfully accomplished. The following approaches have shown potentially promising for accomplishing the goals of reducing skin's barrier properties and, hence, of enhancing the transdermal permeation of drugs (61):

1) Physical approach:
   a) Stratum corneum stripping
   b) Stratum corneum hydration
   c) Iontophoresis
   d) Ultrasonic energy
   e) Thermal energy
2) Chemical approach:
   a) Synthesis of lipophilic analogs
   b) Delipidization of stratum corneum
   c) Co-administration of skin permeation enhancer
3) Biochemical approach:
   a) Synthesis of bioconvertible prodrugs
   b) Co-administration of skin metabolism inhibitors

Some examples of the successful approaches are discussed in the following sections:

A. Skin Permeation Enhancement by Bioconvertible Pro-drugs

Pro-drugs can be viewed as the therapeutically-inactive derivatives of a therapeutically-active drug which undergo a bioconversion, either by hydrolytical or enzymatic transformation, in a biological environment

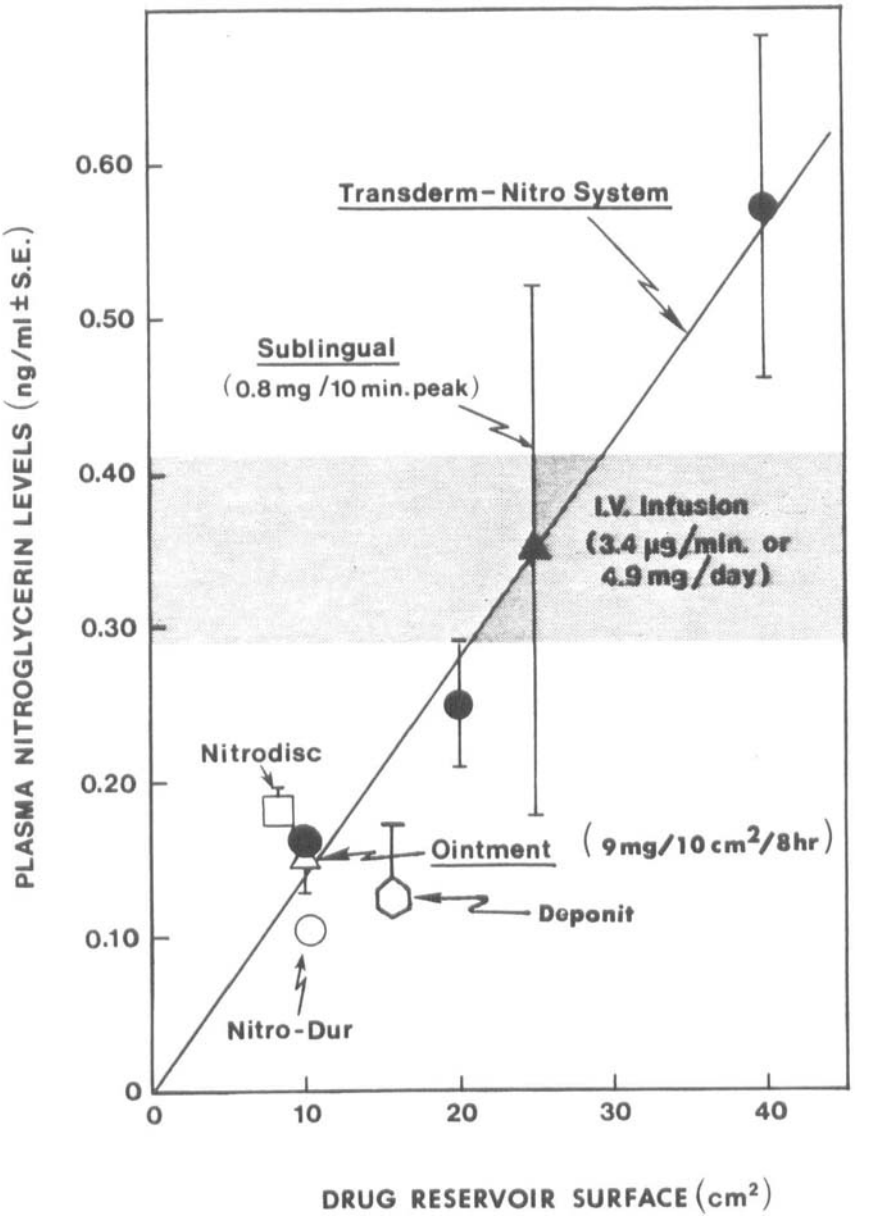


Figure 28: Comparison in the steady-state plasma levels of nitroglycerin achieved by various TDD systems in relation to those by sublingual administration and i.v. infusion (plotted from the data in Ref. 24-26, 37, 48, 49, 52, 60).

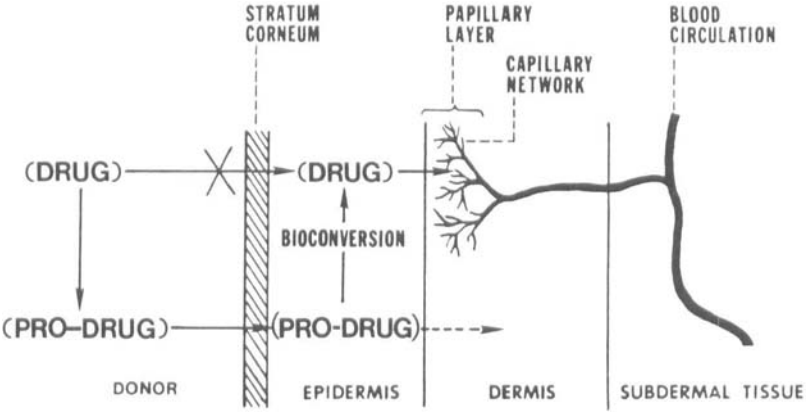


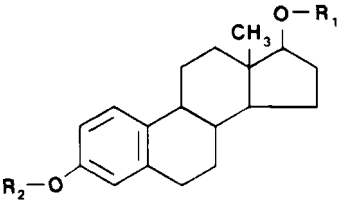
Figure 29: Multilayered skin model showing the enhancement in skin permeation of a drug by forming a more skin permeable pro-drug. In the viable epidermis layers, the pro-drug is metabolized and its parent drug is then regenerated.

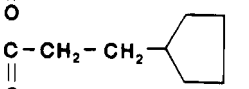
to regenerate the therapeutically-active parent drug prior to exhibiting their pharmacologic activities (62).

The objective of applying bioconvertible pro-drug concept in transdermal controlled drug delivery is to alter the skin permeability of a drug by modifying its physicochemical properties so as to greatly enhance its rate of transdermal permeation (63).

Pro-drugs of a poorly-skin-permeable drug may be synthesized to improve its percutaneous absorption characteristics. During the course of skin permeation, the pro-drugs are transformed, by the metabolic processes within the skin tissue, back to the active parent drug (Figure 29). In other words, if an active drug has a rather low affinity toward the skin and will, therefore, not easily partition into it to any significant extent for permeation. The partition behavior of this drug can be improved by simple chemical modification to form a lipophilic pro-drug; so, the transport of the drug across the stratum corneum is substantially enhanced. Upon absorption and penetration through the skin, the pro-drug is rapidly metabolized to regenerate the active parent drug. One typical example of such approach is the esterification of less-skin-permeable estradiol to form lipophilic estradiol esters (Table VIII).

TABLE VIII: CHEMICAL STRUCTURE OF ESTRADIOL AND ITS PRO-DRUG TYPE ESTERS



	R_1	R_2
Estradiol – 17 – β	–H	–H
Estradiol – 17 – Acetate	$-C(=O)-CH_3$	–H
Estradiol – 3,17 – Diacetate	$-C(=O)-CH_3$	$-C(=O)-CH_3$
Estradiol – 17 – Valerate	$-C(=O)-(CH_2)_3-CH_3$	–H
Estradiol – 17 – Heptanoate	$-C(=O)-(CH_2)_5-CH_3$	–H
Estradiol – 17 – Cypionate	$-C(=O)-CH_2-CH_2-$ 	–H

In vitro skin permeation studies (63) demonstrated that the 5 prodrug-type esters of estradiol are extensively metabolized during the course of skin permeation, by the esterase in the skin tissue, to regenerate estradiol (Figure 30) and the rate of regeneration of estradiol from its esters, by bioconversion, was observed to follow the order of: diacetate>valerate>heptanoate>cypionate>acetate. The metabolism of estradiol esters was found to follow a first-order kinetics and the rate constant for the enzymatic hydrolysis of the ester group at 3rd position was observed to be substantially greater than at 17-ester group (63, 64).

Based on the results of simultaneous skin permeation and bioconversion profiles, a Transdermal Bioactivated Hormone Delivery (TBHD) device was

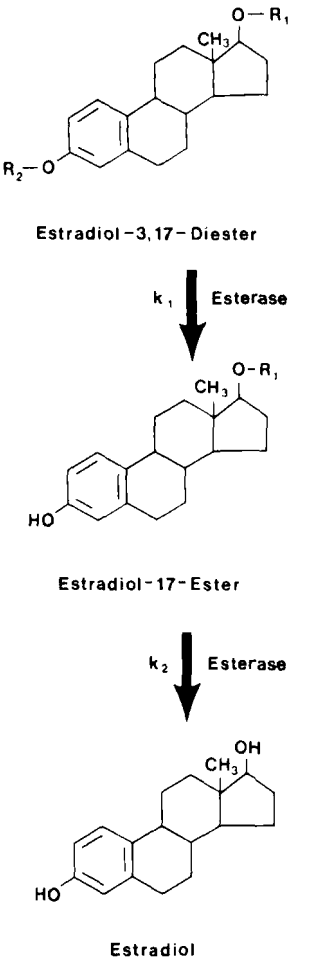


Figure 30: *Schematic illustration of the bioconversion of estradiol-3,17-diester, by the esterase in the cutaneous tissue, to estradiol-17-ester, as the intermediate, and then to the biologically-active estradiol (Reproduced from Valia et al., 1985).*

developed, using the microreservoir dissolution-controlled drug delivery system (Figure 17), for the transdermal controlled delivery of estradiol esters (65). Using a hydrodynamically well-calibrated horizontal-type skin permeation cell (Figure 31), the in vitro drug release and skin permeation profiles of estradiol and its esters were investigated simultaneously (Figure 32). Results demonstrated that estradiol and its esters are released from the TBHD device at a constant, zero-order rate profile

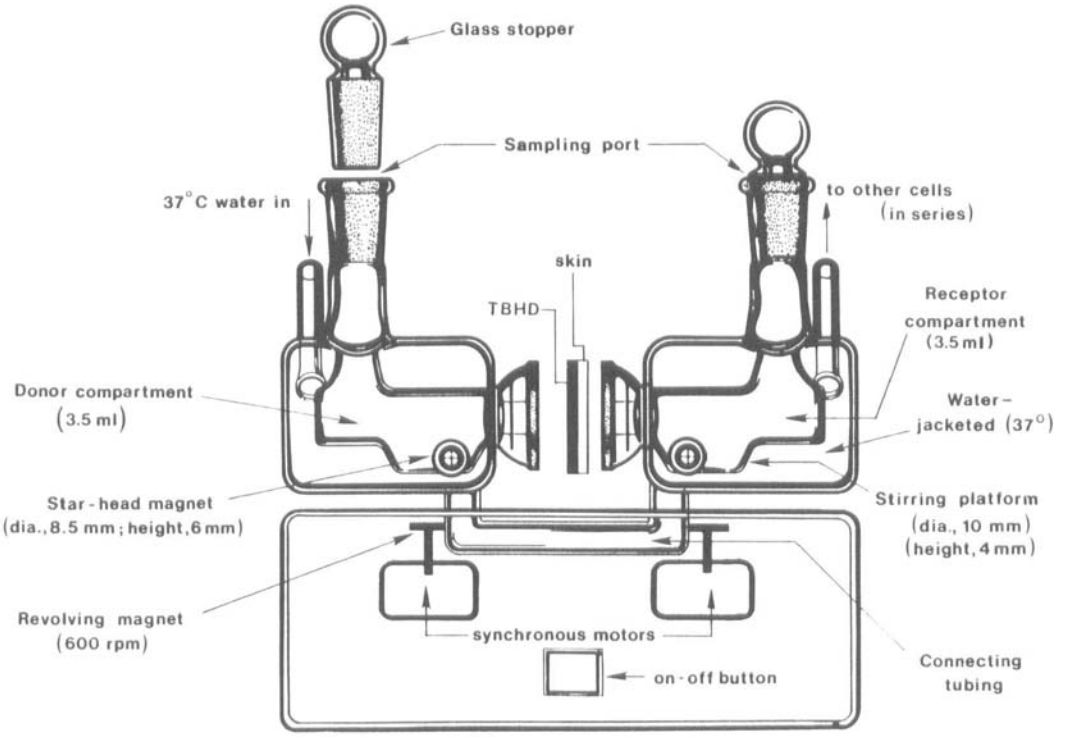


Figure 31: Diagrammatic illustration of the hydrodynamically well-calibrated horizontal-type skin permeation system used for the simultaneous study of the controlled release and the skin permeation of estradiol esters from transdermal bioactivated hormone delivery (TBHD) system (Reproduced from Chien et al., 1985).

and the rate of release increases as esterifying the hydrophilic OH groups at 3- and/or 17- positions to form a lipophilic ester (Figure 33). The release rate of estradiol-17-esters from the lipophilic TBHD device was found to be dependent upon the alkyl chain length of the esters at 17th position.

The skin permeation studies suggested that all the prodrug-type esters of estradiol, except extradiol-3-acetate and 3, 17-diacetate, are totally metabolized by the esterase in the viable skin to regenerate the biologically-active estradiol during the course of skin permeation (Figure 34). The rate of regeneration of estradiol from the esters was

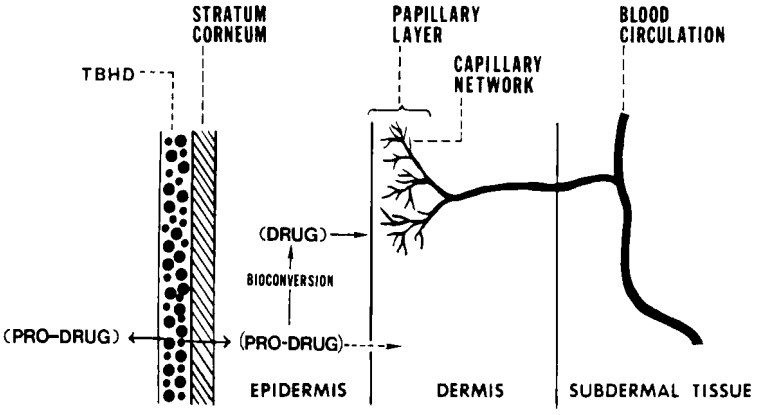


Figure 32: An expanded diagram to illustrate the simultaneous kinetics studies of the release and skin permeation of pro-drugs from TBHD system and of the regeneration of drug by the enzymatic metabolism of prodrugs (Reproduced from Chien et al., 1985).

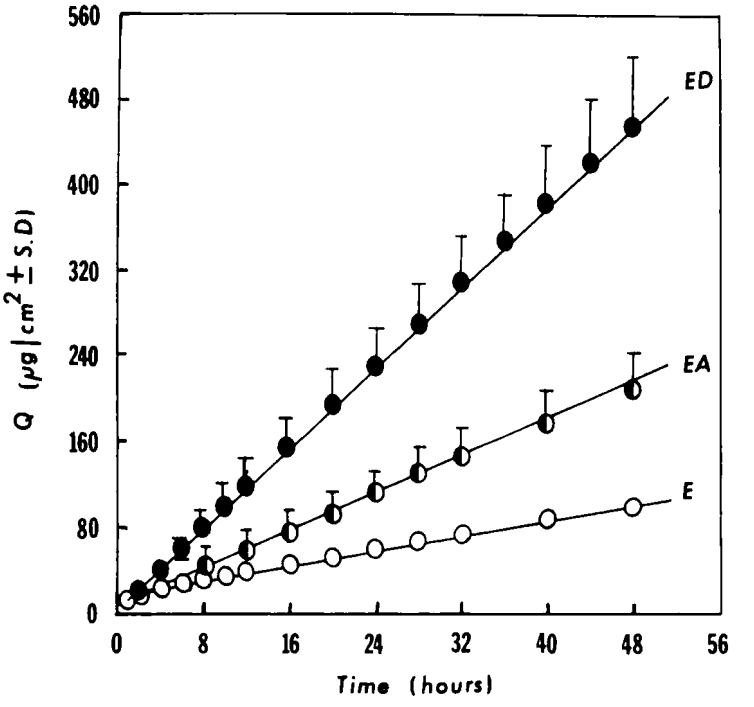


Figure 33: The cumulative release profiles of estradiol and its esters from TBHD system. Key: E(Estradiol); EA(Estradiol-17-acetate); ED(Estradiol-3, 17-diacetate) (Reproduced from Chien et al., 1985).

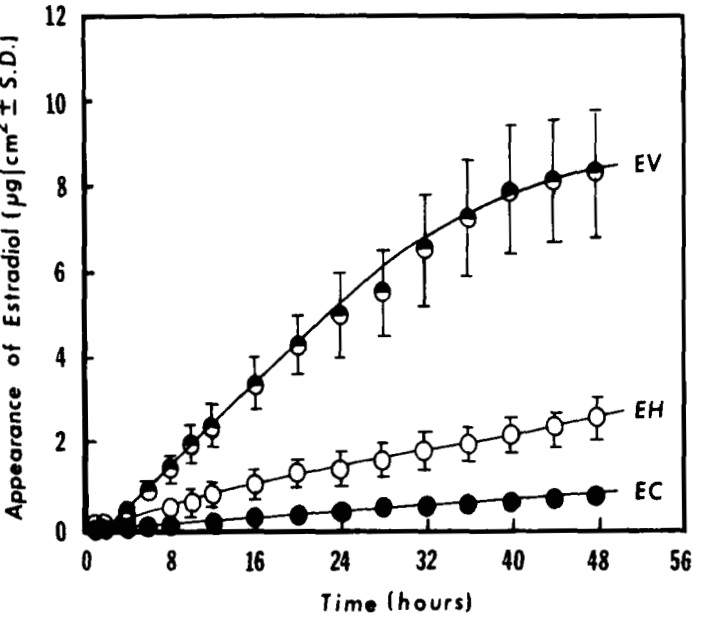


Figure 34: The time course for the regeneration of estradiol from various estradiol-17-esters, during the course of skin permeation, by metabolism following the transdermal controlled administration of various estradiol ester-releasing TBHD systems. Key: EV(Estradiol-17-valerate); EH(Estradiol-17-heptanoate); EC(Estradiol-17-cypionate). No unmetabolized ester was detectable in the dermal solution. (Reproduced from Chien et al., 1985).

also found to be dependent upon the alkyl chain length (Table IX). The appearance of estradiol from diacetate and valerate achieved a rate which is, respectively, 4- and 2- folds greater than the appearance rate of estradiol by skin permeation alone.

B. Skin Permeation Enhancement by Permeation Promotors

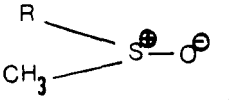
The skin permeability of drugs can also be greatly improved by treating the stratum corneum surface with an appropriate skin permeation promotor. Some representative classes of the potential skin permeation promotors are listed in Table X.

The concept of promoting the skin permeability of drugs by skin permeation enhancers has recently been applied in the practice of trans-

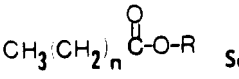
TABLE IX: APPEARANCE RATE PROFILES OF ESTRADIOL FOLLOWING TRANSDERMAL CONTROLLED ADMINISTRATION OF VARIOUS ESTRADIOL ESTERS FROM TRANSDERMAL BIOACTIVATED HORMONE DELIVERY SYSTEM

Species	Rate of Appearance ($\mu g/cm^2/hr \pm SD$)
Estradiol (E)	0.117 ± 0.027
Estradiol Esters	
E-Diacetate	0.490 ± 0.250
E-Acetate	0.057 ± 0.013
E-Valerate	0.227 ± 0.042
E-Heptanoate	0.061 ± 0.013
E-Cypionate	0.016 ± 0.002

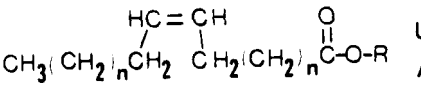
TABLE X: SOME REPRESENTATIVE CLASSES OF POTENTIAL SKIN PERMEATION PROMOTORS



Alkyl Methyl Sulfoxide



Saturated Fattyl Acid Alkyl Ester



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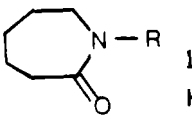

1- Alkyl Azacyclo-Heptan-2-One

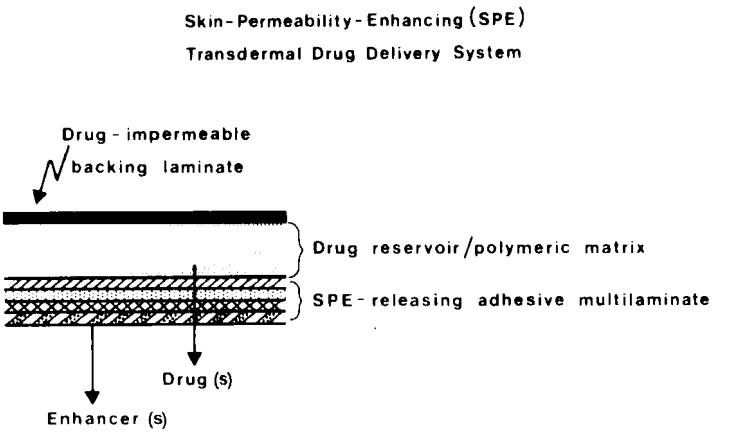

Figure 35: Cross-sectional view of a skin-permeability-enhancing TDD system, showing various major structural components (Reproduced from Chien and Lee, 1985).

dermal controlled drug delivery by developing a skin-permeation-enhancing (SPE) Transdermal Therapeutic System (Figure 35)(66). This new type of transdermal drug delivery system is capable of releasing one or a combination of two or more skin permeation enhancers to the surface of stratum corneum to modify the skin's barrier properties, prior to the controlled delivery of the active drug, and to render the skin more permeable to the drug (Figure 36). In vitro skin permeation studies in a hydrodynamically well-calibrated skin permeation cell (Figure 37) demonstrated that addition of simple pharmaceutical excipients, like capric acid, a straight-chain saturated fatty acid, can substantially enhance the transdermal permeation rate of progesterone and also significantly reduce the duration of time lag, while the zero-order skin permeation rate profile is still maintained (Figure 38). The extent of enhancement is dependent upon the type of enhancer used and its concentration in the adhesive coating (Figure 39).

In addition to progesterone, which is a relatively skin-permeable steroidal drug, the propyl esters of myristic acid, a long-chain saturated fatty acid, and of oleic acid, a long-chain unsaturated fatty acid (Table X), are also capable of promoting the rate of skin permeation for the less permeable steroidal anti-inflammatory agents, like hydrocortisone, nonsteroidal anti-inflammatory drugs, like indomethacin, and estrogenic

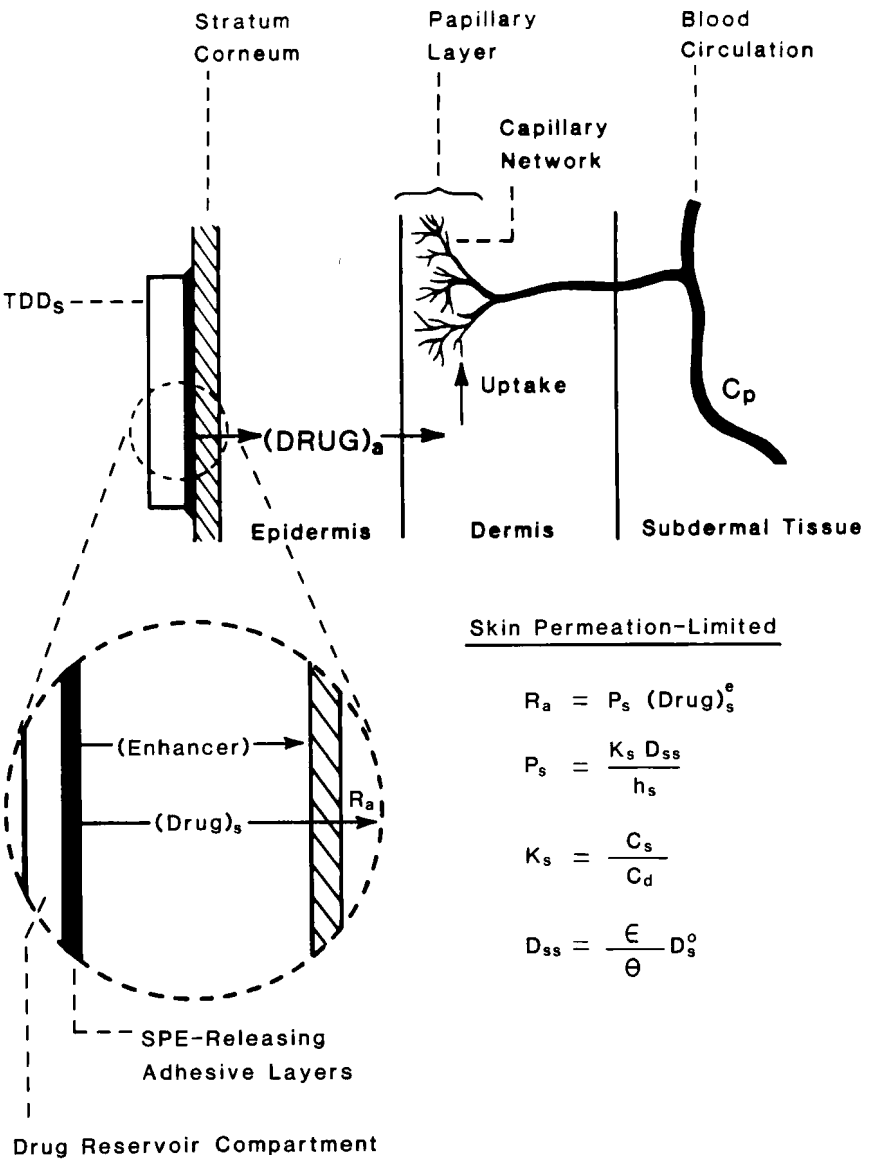

Figure 36: An expanded diagram which illustrates the concept of enhancing the skin permeation of drugs by first releasing one or more enhancers to skin surface to modify permeability characteristics of the stratum corneum prior to the controlled delivery of a therapeutically-active drug.

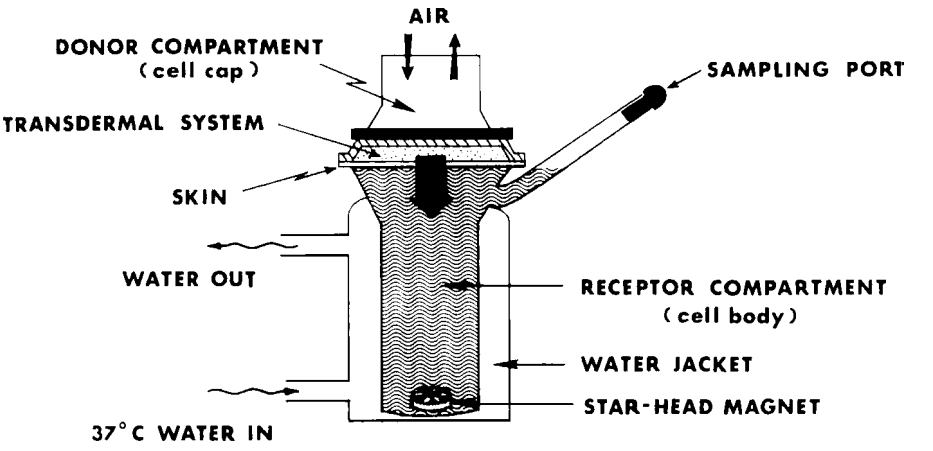

Figure 37: Diagrammatic illustration of a hydrodynamically well-calibrated vertical-type skin permeation cell. The cell consists of two compartments in vertical arrangement: A donor compartment, which is exposed to an ambient condition and a receptor compartment, which is maintained at 37°C by circulating a thermostated water through the surrounding water-jacket. The solution hydrodynamics in the receptor compartment is kept at constant by a Teflon-coated starhead magnet rotating at 600 rpm by a synchronous motor mounted directly underneath the cell mounting block. One unit of the skin-permeation enhancing (SPE) Transdermal Therapeutic System is mounted between the donor and receptor compartments with its SPE-releasing adhesive layer in intimate contact with the stratum corneum surface (Reproduced from Keshary et al., 1985).

steroids, like estradiol (Table XI). The enhancement in skin permeability appears to be dependent upon the alkyl chain length and the terminal carboxylic group of the straight-chain fatty acid (Figure 39).

Not only the esters of saturated and unsaturated fatty acids, azone and decylmethyl sulfoxide are also very effective in improving the skin permeability of drugs (Table XI and Figure 40). Results appear to suggest the possible existence of a relationship between the skin permeability enhancement of a drug and its molecular structure as well as the type of promotor used. A synergistic effect in skin permeability enhancement

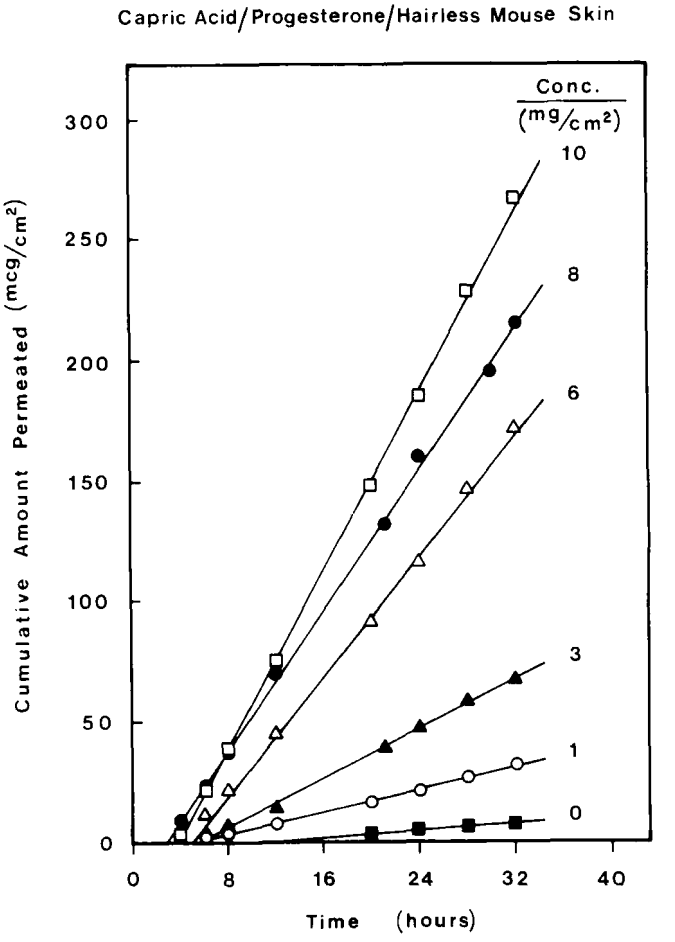

Figure 38: Enhancement in the skin permeation profiles of progesterone by various concentrations of capric acid, a straight-chain saturated fatty acid, released from the adhesive coating layer (Reproduced from Chien et al., 1986).

could be achieved by incorporating a combination of two or more enhancers in the adhesive layers.

The mechanisms of action of various skin permeation enhancers may be attributed to their activity on lipophilic lipid matrix and/or hydrophilic protein gel in the stratum corneum (61,67).

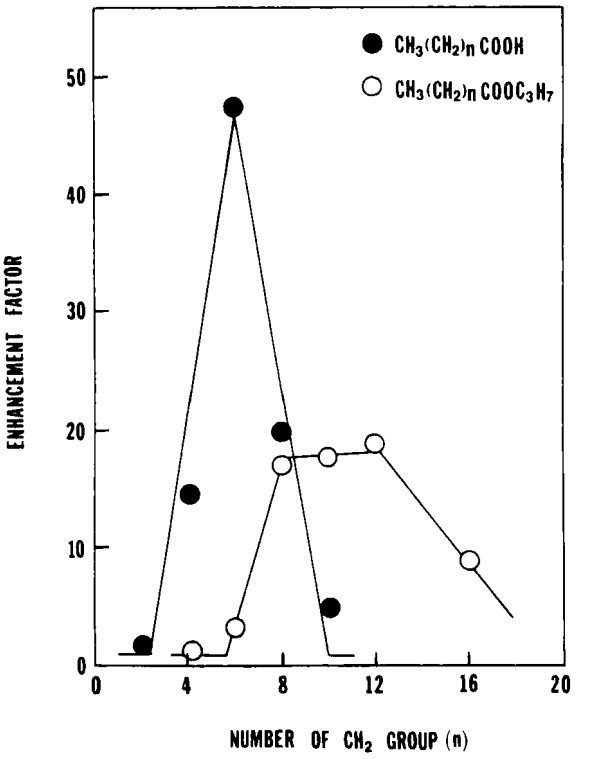

Figure 39: Dependency of the enhancement factor for the skin permeation of progesterone on the alkyl chain length (n) of the straight-chain saturated fatty acid and its propyl ester (Reproduced from Chien et al., 1986)

The enhancement factor is calculated from the following relationship:

$$\text{Enhancement Factor} = \frac{(\text{Normalized skin permeation rate})_{\text{enhancer}}}{(\text{Normalized skin permeation rate})_{\text{control}}}$$

C. Facilitated Transdermal Permeation by Iontophoresis

The transdermal permeation of peptide drugs received limited attention in the past. The reason for little research could be the result of the old belief that a drug with molecular mass as large as peptides or proteins in combination with their short biological half-life, polar properties and chemical instability, skin permeability would be insignificant (68).

TABLE XI: ENHANCEMENT OF SKIN PERMEABILITY OF VARIOUS DRUGS BY DIFFERENT TYPES OF PROMOTORS[a)]

Drugs	Skin Permeation Rate[b)] ($mcg/cm^2/day$)	Enhancement Factor[c)]			
		propyl myristate	propyl oleate	Azone	Decylmethyl sulfoxide
Progesterone	36.72 ± 10.32	4.56	5.36	5.96	11.04
Estradiol	29.29 ± 24.48	9.33	14.62	20.17	12.59
Indomethacin	9.36 ± 0.08	3.77	4.67	14.49	15.67
Hydrocortisone	1.10 ± 0.12	4.57	5.01	61.30	25.23

a) Compiled from the data by Chien and Lee (1985)

b) Basic skin permeation rate for the drug-releasing TDD systems containing no enhancer

c) Unit concentration of promotor in the adhesive layer = 3.2 mg/cm^2

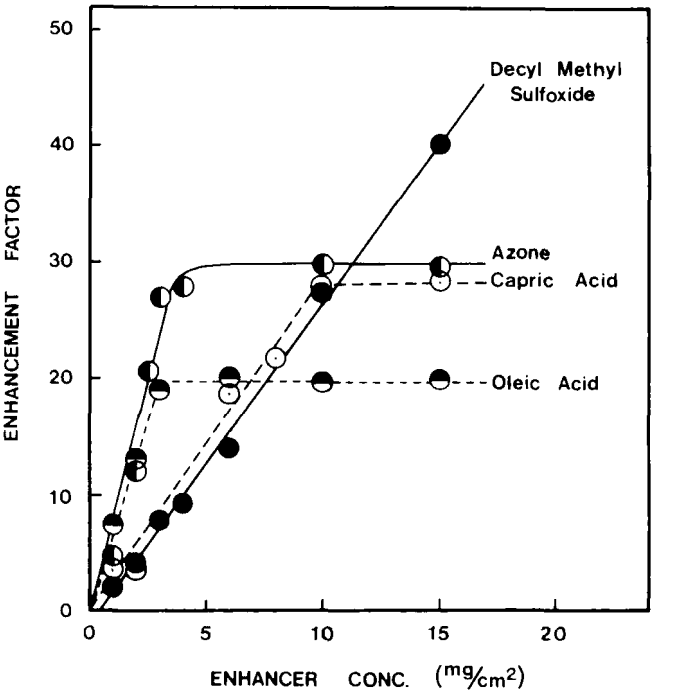

Figure 40: Dependency of the enhancement factor for the skin permeation of progesterone on the concentration of various skin permeation enhancers (Reproduced from Chien et al., 1986).

Most recently, the transdermal delivery of peptide drugs, like insulin, has become feasible by the application of iontophoresis (69). The research carried out in this Research Center has demonstrated that the rate-limiting function of stratum corneum can be overcome by iontophoresis and some of the polar and peptide drugs can be successfully delivered transdermally to produce a systemic therapeutic effect (70, 71). One typical result on the iontophoretic transdermal administration of polar and peptide drugs, like insulin, is shown in Figure 41. The mechanism of transdermal iontophoretic delivery of polar and peptide drugs is diagramatically illustrated in Figure 42.

X. Conclusion

The future of transdermal rate-controlled drug delivery in medicine is undoubtedly bright. The scope of the biomedical applications of this

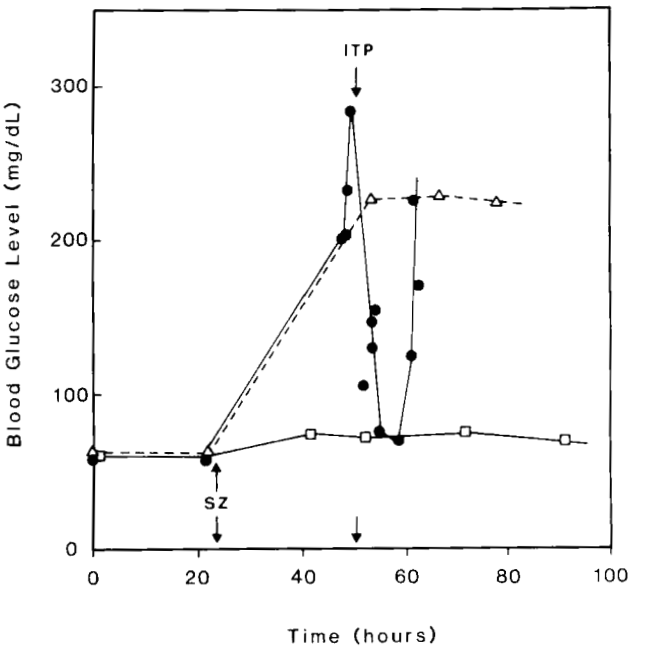

Figure 41: Blood glucose levels in the hairless rats before and after the injection of streptozotocin (sz) to induce diabetes. (□) healthy controls, (△) diabetic controls, (●) Diabetic hairless rats treated with insulin by transdermal iontophoretic delivery of insulin (4mA, 80 min.) (Reproduced from Siddiqui et al, 1986).

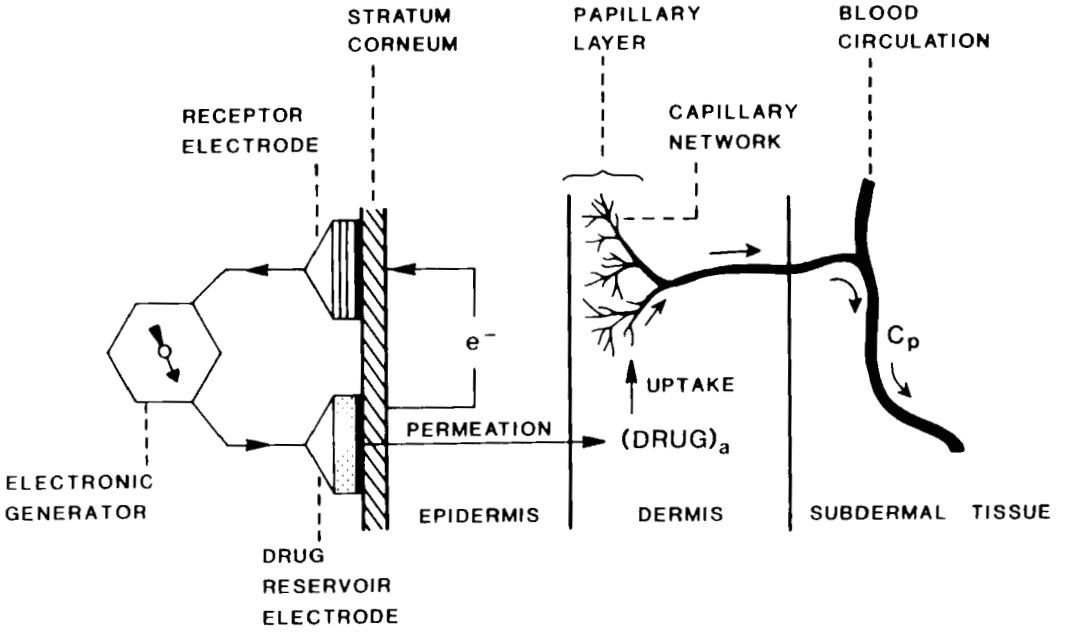

Figure 42: Schematic illustration of the mechanism involved in the transdermal iontophoretic delivery of polor or peptide drugs.

new form of drug administration will be increasingly expanded for many years to come, especially with the successful development of new approaches which are capable of enhancing the skin permeability of drugs (61, 63-71).

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