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LOGICS OF TRANSDERMAL CONTROLLED DRUG ADMINISTRATION

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A) Pharmaceutical Industry's Research and Development Productivity

As the first speaker for this symposium on "Transdermal Controlled Release Medication," it seems to be very logical to begin the presentation with a brief discussion of some historic background and statistics on the Research and Development producticity and expenditure of our pharmaceutical industry in the past two decades. This discussion may provide the audience the justifications, from the business standpoints of view, about the needs to invest more of our Research and Development efforts into the development of Drug Delivery Systems for Controlled Drug Administration through various routes (or parts) of administration, the skin as the example, to maximize the bioavailability, to optimize the therapeutic efficacy, and/or to minimize any side effects of the drug.

In the year of 1975, the pharmaceutical industry in this nation alone spent more than one billion dollars in research and produced only fifteen (15) new drug entities (Table I). In summary, it took an average cost of 68 million dollars and a time frame of ten to fifteen years to develop

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TABLE I

RESEARCH EXPENDITURE and DEVELOPMENT PRODUCTIVITY

In U.S. PHARMACEUTICAL INDUSTRY

	1960	1965	1975
Research expenditure (in million dollars)	<100	351	1,028
Development productivity (Number of new drug entity successfully developed and marketed)	50	25	15
R & D effectiveness:			
1) Cost (million dollars/new drug entity)	<2	14	68
2) Time (years)	2	--	10-15

SOURCE: REFERENCE 1.

a new drug entity.[1] As the comparison, we invested in 1960 less than 100 million dollars in research, and, with this amount of research investment, we were able to develop fifty (50) new drug entities. It translates into a Research and Development effectiveness of two million dollars in research cost and two years in development time for the discovery of every new drug entity, as compared to 14 million in 1965 and 68 million in 1975. The decline in pharmaceutical Research and Development productivity has become a very alarming fact in recent years, as research expenditure is skyrocketing every year and longer time is needed to receive the regulatory approval on a new drug product.

The birth of a new drug is an extremely long journey. By conventional research approach of isolation and synthesis, the pharmaceutical industry in the United States in 1970 alone generated 126,060 drug substances with therapeutic potential and initiated 703,900 submissions for various pharmacology testing (Table II). Only 1,013 drug substances were found

TABLE II

THE BIRTH PANGS OF A NEW DRUG

(U.S. Pharmaceutical Industry in 1970)

	Drug Substances
1. Results from extraction, isolation and synthesis for therapeutic purposes	126,060 (100%)
2. Submission for pharmacology testing	703,900 (558%)
3. Selection for clinical testing	1,013 (0.8%)
4. NDA approval	16 (0.013%)

SOURCE: REFERENCE 1.

useful and were selected for further clinical evaluations, and sixteen (16) of them finally passed the new drug applications (NDA) review and received FDA's approval for marketing. It translates into a storming statistic fact: Only one new drug product was successfully developed and marketed from every 8,000 drug substances discovered by the traditional Research and Development approaches in the year of 1970. What a pang for the birth of a new drug product!

Development of a new drug product requires a coordinated team effort of a large group of researchers and scientists in various physical, chemical and biomedical disciplines working closely together for several years. A survey conducted in 1979 [1] suggested that development of, for example, an orally-administered, systemic-acting drug for long-term therapy requires an average investment of 24 million dollars for a duration of twelve years if it intends to be marketed worldwide, in which 50 percent of the investment, in terms of dollars and time, goes to Phases I, II and III of clinical testings required for regulatory submission (Table III).

TABLE III

Year	0	2	4	6	8	10	12 years
Stage / Discipline	Research	Pre-ind	Phase I	Phase II	Phase III	NDA Wait	Total $(000)
Chemistry	500	300	400	300	200	300	$2,000
Biology Animal Pharmacology	400	400	300	200	100	100	$1,500
Toxicology	0	400	1,000	1,600	1,000	0	$4,000
Pharmacy	0	500	700	800	600	400	$3,000
Clinical Medicine	0	200	1,300	5,700	3,700	1,100	$12,000
Marketing Regulatory Project Mgmt.	100	200	300	400	400	100	$1,500
Total $(000)	$1,000	$2,000	$4,000	$9,000	$6,000	$2,000	$24,000

*Development of an orally-administered systemic-acting drug for long-term therapy; marketing is to be worldwide.

[a] D. Graham & M. Katz
April 14, 1979

SOURCE: REFERENCE 1.

The high cost of new drug development (Tables I and III), the lack of FDA-approved drug products (Table II), coupled with the expiration of patents to the existing drugs have caused many pharmaceutical firms to be faced with a decreasing number of patent-protected drug products from which they may generate revenue for continuing growth.

In early 1970s, several pharmaceutical companies recognized the dilemma and began to reorganize their Research and Development strategy. Instead of a constant search for new drugs using the traditional random, hit-or-miss approaches, the new Research and Development stratagem called for the development of novel and patentable methods of drug administration. The idea is to apply the concepts and techniques of controlled drug administration into the designing of Drug Delivery Systems, which make clinically-already-established drugs do their therapeutics best. In addition to the biomedical benefits gained, the new Research and Development programs also produce an additional 17-year patent protection on the existing drugs with the combination of novel, patentable drug delivery systems. Several encouraging progresses have been made in the past years. It is one of the objectives set in organizing this symposium; that is, it intends to review various aspects of one of the most productive drug delivery system development programs: Transdermal Controlled Release Medication.

Many of you may have already learned an exciting news in the past two or three months, that three (3) new transdermal therapeutic systems were developed and successfully received NDA approvals from FDA for marketing. These drug delivery systems all contain a 100-year-old grandfather drug, called nitroglycerin, and are designed to be applied directly onto the surface of the skin for transdermal controlled administration of nitroglycerin for the prevention and/or treatment of angina pectoris for a duration of at least twenty-four (24) hours.

Now, let us analyze the logics behind the use of skin as the port for the controlled administration of drugs, through the topical application of a novel drug delivery system, for long-term systemic medication of various chronic illnesses.

B) The Potential of Skin as Port of Drug Administrations

The skin is one of the most extensive and readily accessible organs of the human body. The skin of an average adult covers over 20,000 cm^2 of

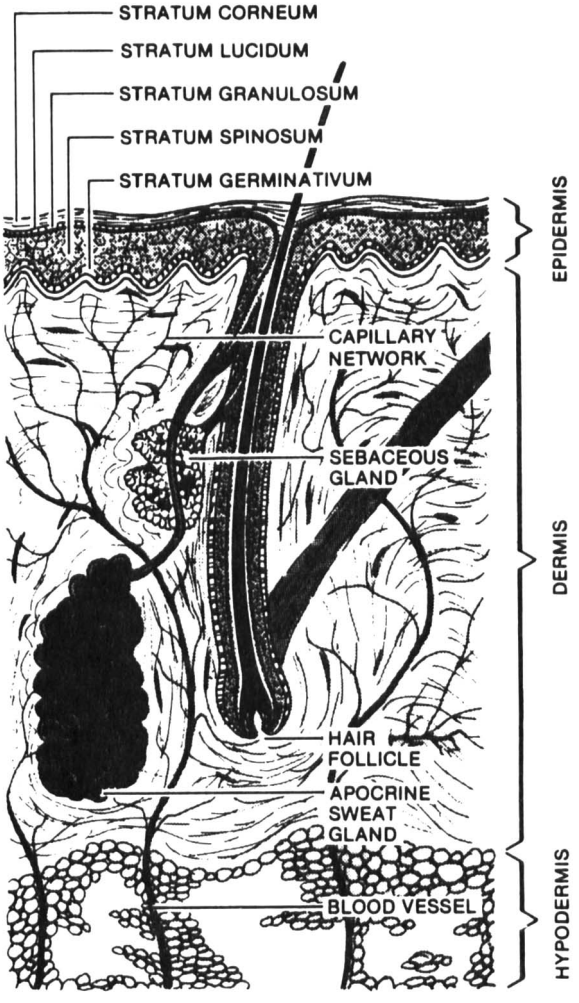
surface area and receives about one-third of all blood circulating through the body. It is a multilayered organ composing of many histological layers and is generally described in terms of three tissue layers: the epidermis, the dermis, and the hypodermis (or subcutaneous fat layer) (Figure 1).

Microscopic section of the epidermis shows that it can be further divided into five (5) tissue layers with stratum corneum, which consists of many layers of compacted, flattened, keratinized cells, exposing to the environment as a physical barrier to protect the human body from the invasion of any foreign agents. The effect of physiologic/pathologic factors on percutaneous drug absorption will be discussed in Professor Kligman's chapter.

Although each cm^2 of human skin surface contains an average of 40 to 70 hair follicles and 200 to 250 sweat ducts, these skin appendages actually occupy only 0.1 percent of the total skin surface area. Hence, the transdermal permeation of most neutral molecules can be viewed as, primarily, a process of passive diffusion through the intact stratum corneum in the interfollicular region. Therefore, the skin barrier can be represented, for the sake of simplicity in mechanistic analysis, by a simplifistic multilayer model shown in Figure 2. It illustrates all the tissues involved, to different degrees, in the course of transdermal permeation of drugs.

The skin is the common site of administration for dermatological drugs to achieve a localized pharmacologic action. In this case, the drug molecule is considered to diffuse to a target tissue in the skin to produce its action before it is distributed to the blood circulation for elimination (Figure 3). Hydrocortisone is an example.

Most recently, the potential of skin serving as the port of administration for a number of systemically-active drugs has also been recognized. It is exemplified by scopolamine and nitroglycerin. In this case, the systemically-active drug applied topically will be absorbed first into the



Source: P. Zanowiak, in Handbook of Nonprescription Drugs (AphA, Ed.), American Pharmaceutical Association, Washington, D. C., Chapter 27, 5th edition, (1977)

Figure 1

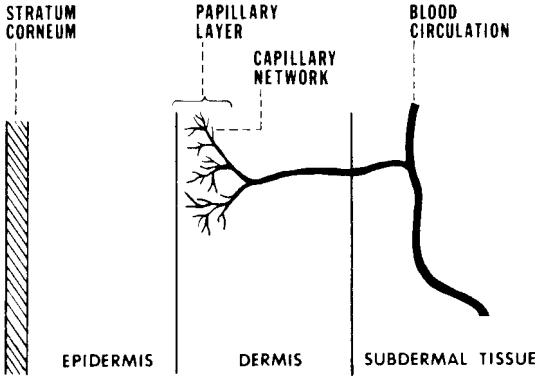


Figure 2

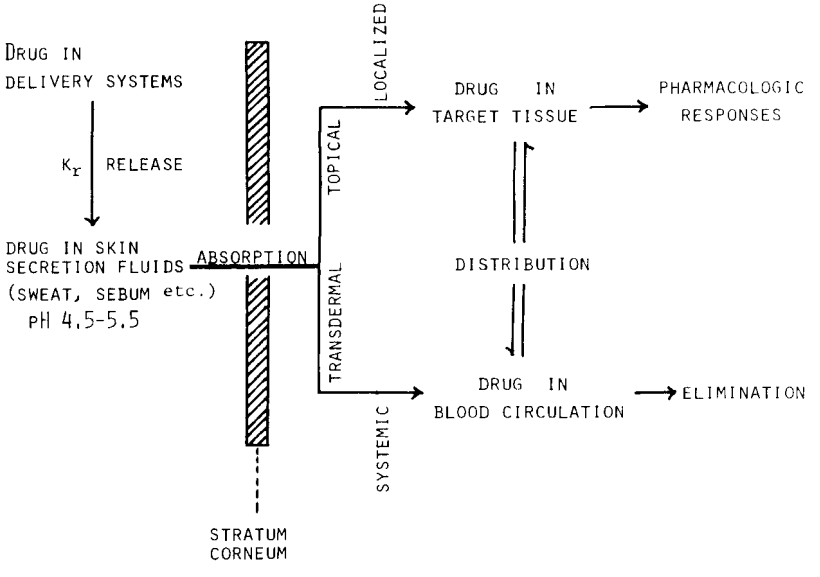


Figure 3

blood circulation and then be transported to target tissues to achieve its therapeutic purposes. This presentation will center in the area of transdermal permeation of systemically-active drugs.

For a systemically-active drug to reach a target tissue away from the site of drug administration on the skin surface, it has to possess some physicochemical properties which are capable of facilitating the permeation of the drug through various skin tissues, the stratum corneum in particular,

and also the uptake of the drug molecules by the capillary network in dermal papillary layer. The effect of physicochemical properties on transdermal permeation of drugs will be discussed in depth in Professor Zatz's chapter.

Along the course of skin permeation, a drug molecule will encounter a number of diffusional resistances which counteract its penetration through various skin tissue layers (Figure 4). The total diffusional resistance (R_s) that a drug molecule has to overcome during the course of permeation across the skin tissues and the subsequent uptake by the capillary network for transport to the general circulation is described mathematically by:

$$R_s = R_{sc} + R_e + R_{pd} + R_t \qquad \text{(Eq. 1-A)}$$

$$= \frac{H_{sc}}{D_{sc}K_m} + \frac{H_e}{D_e K_e} + \frac{H_{pd}}{D_{pd}K_{pd}} + \frac{1}{F_{cn}H_s} \qquad \text{(Eq. 1-B)}$$

Where R, H, D and K stand for the diffusional resistance, thickness, diffusivity and partition coefficient, respectively; and the subscripts s, sc, e and pd refer to the skin, stratum corneum, epidermis and the

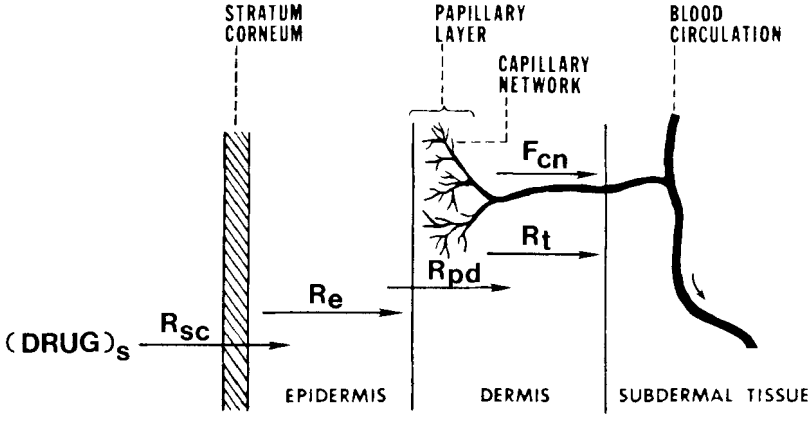


Figure 4

papillary layer in the dermis, respectively; and R_t and F_{cn} represent the transfer resistance and the peripheral blood flow rate in the capillary network, respectively.

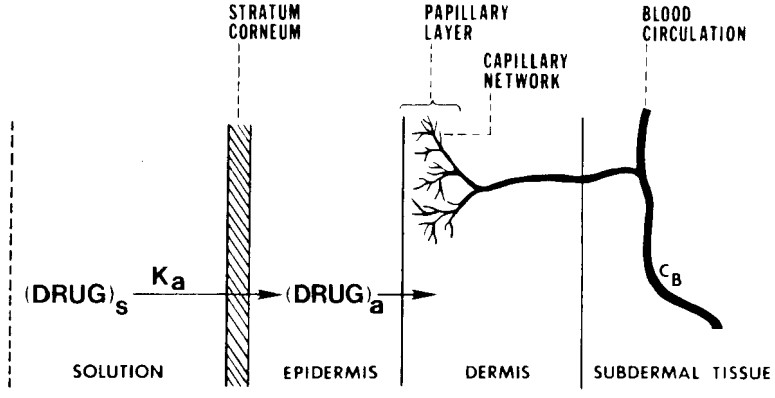
For most drugs, the principal diffusional resistance has been found to reside in the stratum corneum cell layers. That is, the stratum corneum plays a rate-limiting role in the overall transdermal permeation process.(2)

The rate-limiting stratum corneum can be described as a dispersion of hydrophilic protein gel in a continuous lipid matrix, through which the penetrating drug molecules migrate by dissolution and Fickian diffusion.(3) The transdermal permeability coefficient (P_{sc}), which is the reciprocal of the diffusional resistance, across the biphasic stratum corneum can be defined by the following mathematical expression:

$$P_{sc} = \frac{1}{R_{sc}} = \frac{K_{pa}D_{pg}}{H_{sc}} \left(\frac{1.16}{\left(\frac{0.16}{K_{pl}} \cdot \frac{D_{pg}}{D_{lm}}\right) + 1} + 0.0017\, K_{pl} \frac{D_{lm}}{D_{pg}} \right) \qquad \text{(Eq. 2)}$$

Where K_{pa} is the distribution coefficient of the penetrant molecules between the protein gel and the applied penetrant solution at equilibrium, D_{pg} is the diffusion coefficient of the penetrant molecules in the protein gel; H_{sc} is the thickness of stratum corneum, K_{pl} is the distribution coefficient of the penetrant molecules between the lipid matrix and protein gel; D_{lm} is the diffusion coefficient of the penetrant molecules in the lipid matrix. Equation (2) suggests that the permeability coefficient (P_{sc}) of stratum corneum to any penetrant molecule is determined by two physicochemical parameters: $K_{pa}\, D_{pg}/H_{sc}$ and $K_{pl}\, D_{lm}/D_{pg}$.

If a drug applied onto the skin surface is in a simple solution formulation (i.e., no physicochemical interactions occur between the drug molecules and the formulation composition), the concentration of the drug (C_B) absorbed into the body can be described by a simple mathematical



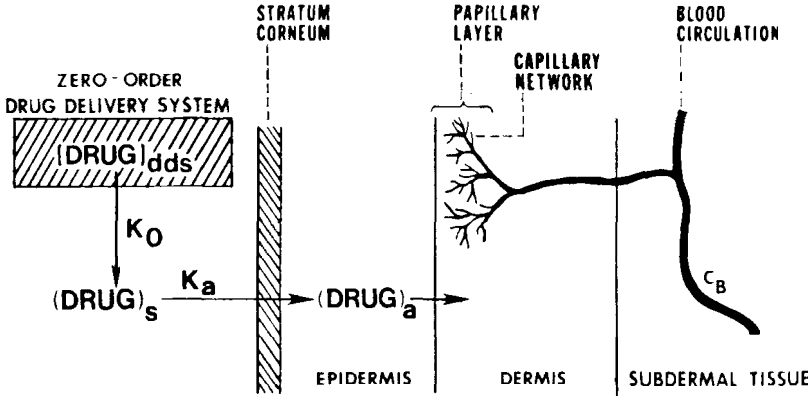
$$C_B = \frac{(DRUG)_a}{V_d} \frac{K_a}{K_a - K_e} (EXP^{-K_e t} - EXP^{-K_a t}) \qquad EQ\ 3$$

Figure 5

expression (Equation 3) if the pharmacokinetic pattern of the drug is known to follow a simple one-compartment open model (Figure 5).

Equation (3) indicates that the drug concentration in the body is a function of the amount of drug absorbed into the skin tissues, $(Drug)_a$, the volume of drug distribution, V_d, the rate constant for skin absorption, K_a, the rate constant for drug elimination; K_e, and the duration of drug administration, t. The k_e term is replaced by a composite rate constant for drug elimination, β, if the pharmacokinetic pattern of the drug best described by a multiple compartment open model.

If the drug is administered topically via a controlled release drug delivery system which releases the drug molecules at a programmed rate of release; and the rate of drug release from the transdermal drug delivery system is significantly slower than the rate of percutaneous absorption, then the process of drug release will play the rate-controlling role to the blood level of a drug. For instances, suppose the drug is delivered to the skin surface through a zero-order drug delivery system (Figure 6). At steady-state, a constant blood level will be achieved, and it is simply



$$\text{INITIAL PHASE:} \quad C_B = \frac{K_o}{K_e V_d} (1 - \text{EXP}^{-K_e t}) \qquad \text{EQ 4}$$

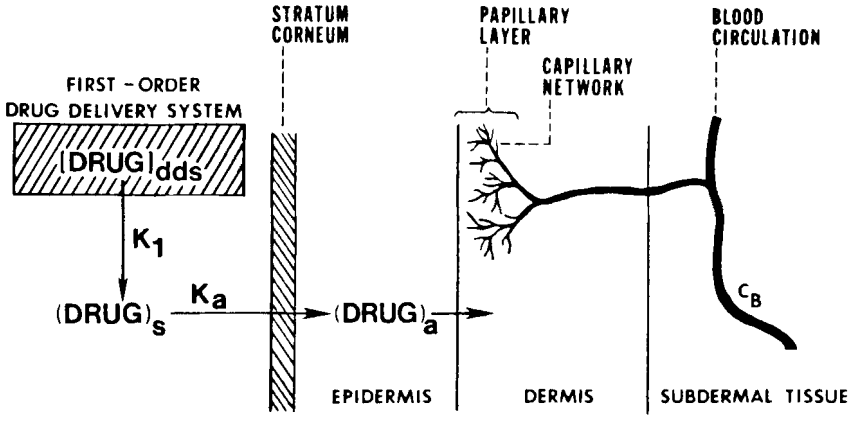
$$\text{STEADY-STATE PHASE:} \quad C_B = \frac{K_o}{K_e V_d} \qquad \text{EQ 5}$$

Figure 6

a linearly function of the rate of drug release (k_o) and is inversely proportional to the rate constant for drug elimination (K_e) and the volume of drug distribution (V_d). Equation 5 indicates that the blood levels of a drug can be controlled in a desired therapeutic range by programming the magnitude of k_o value of the delivery system (since both k_e and V_d terms are the intrinsic pharmacokinetic properties of the drug molecule).

On the other hand, if the drug is administered via a transdermal drug delivery system which releases the drug molecules at a first-order rate constant (k_1), the blood level of the drug will then be described by Equation (6) (Figure 7). In this case, the drug concentration in the blood circulation (C_B) will be dependent of the drug dose level in the drug delivery system, $(Drug)_{dds}$. Any change in the dose level will affect the blood level of the drug (Eq. 6).

Furthermore, if the transdermal drug delivery system administers the drug to the skin surface under a matrix diffusion-controlled process with the drug molecules release at a rate profile of Q versus $t^{\frac{1}{2}}$ (or $k_{\frac{1}{2}}$)



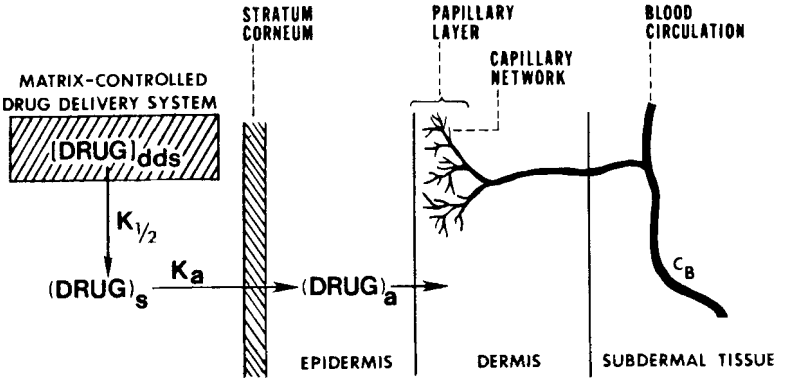
$$C_B = \frac{K_1 (DRUG)_{dds.}}{(K_1 - K_e)V_d} (EXP^{-K_e t} - EXP^{-K_1 t}) \qquad EQ\ 6$$

Figure 7

(Figure 8). In this case, the blood drug level will be in proportional to the square root of the drug dose level in the drug delivery system, $(Drug)^{\frac{1}{2}}_{dds}$ (Eq. 7).

In both cases (Figures 7 and 8), the drug concentration profiles in the blood circulation will also be dependent upon the relative magnitude between the rate of drug release (k_1 or $k_{\frac{1}{2}}$) and the rate constant for drug elimination (k_e) as well as the volume of drug distribution (V_d). The rate of drug release can be controlled at a magnitude which is substantially greater than k_e. Under this condition, Equations 6 and 7 can be simplified.

If the permeation thru the stratum corneum is the only rate-limiting step; that is, the rate of drug release from the drug delivery system is substantially higher than the rate of percutaneous absorption, then the drug level in the blood circulation will be defined by Equation 3. Under this condition, the drug delivery system does not play any controlled-drug-release function as desired for the transdermal controlled drug administration. In fact, the drug delivery system and the stratum corneum both likely play the rate-controlling role in the transdermal controlled drug administration.



$$C_B = \frac{K_{1/2}(DRUG)^{1/2}_{dds}}{(K_{1/2} - K_e)\,V_d}\,(EXP^{-K_e t} - EXP^{-K_{1/2} t}) \qquad EQ\ 7$$

Figure 8

The Systemic Bioavailability of a drug by transdermal permeation is determined largely by the permeability through the rate-limiting stratum corneum as discussed earlier. It is also possibly affected by the metabolic activities and/or any potential binding of the permeating drug molecules in the viable skin tissues (Figures 9 and 10).

The viable epidermis is known to contain a number of catabolic enzymes and is metabolically more active than the dermal tissue.[2] For example, it has been reported that 95 percent of the absorbed testosterone dose is metabolized by the steroid 5α - reductase in the epidermal tissue to anhydrostenediol, Δ^4 - androstenedione and 5α - dihydrotestosterone.[4, 5] Apparently, the cutaneous metabolism will affect the transdermal bioavailability of the intact drug if it is the therapeutically active moiety. The rate of metabolism is known to vary from one area of the skin to another.

The cutaneous drug metabolism can be utilized productively to improve the percutaneous absorption of some drugs. A drug with low skin permeability can be made to form a skin permeable pro-drug, which is then converted by cutaneous metabolism to regenerate the active drug species

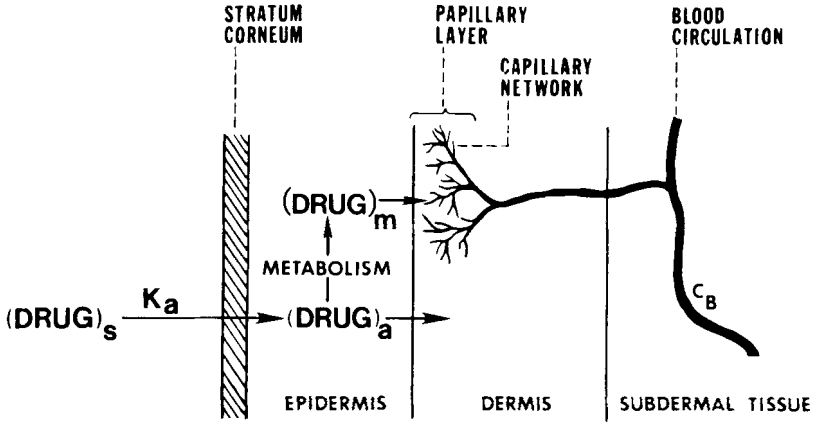


Figure 9

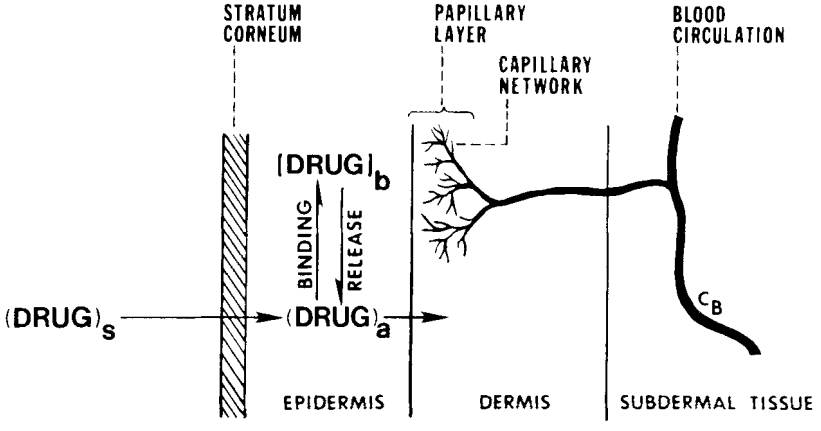


Figure 10

in the skin tissues (Figure 11). More discussions on this novel approach are presented in Dr. W. I. Higuchi's chapter.

Some drugs were reportedly bound to some binding sites in the skin tissues, resulting in a reservoir (or depot) effect.[2] Testosterone, for example, was found to be markedly bound to dermal tissue at a manner which can be described by a linear Freundlich Adsorption isotherm[6] and, on the other hand, scopolamine was observed to be irreversibly bound to the protein phase in stratum corneum by a non-linear sorption isotherm.[7]

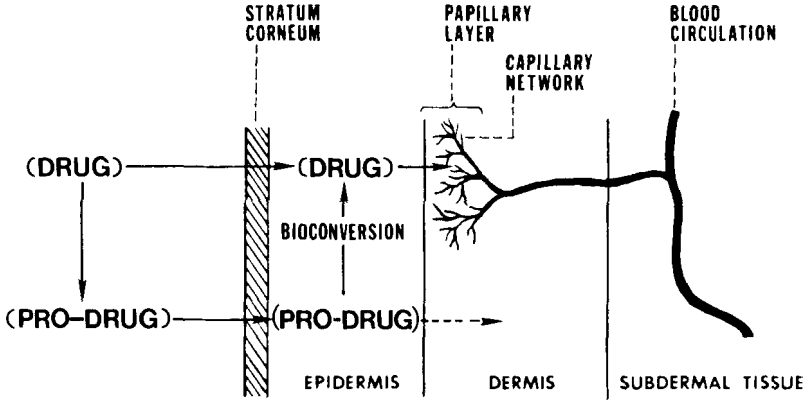


Figure 11

C) How To Achieve Transdermal Controlled Drug Administrations

Several approaches can be effectively utilized to control the release of systemically-active drugs for permeation at a programmed rate through the skin tissues. Three of the well-established techniques are outlined as follows:

1) Membrane permeation-controlled drug delivery systems

This type of drug delivery system is composed of, basically, a drug reservoir, which can be in a form of pure drug solid particles or a suspension of drug solid particles in a liquid medium, encapsulated in a compartment walled by an impermeable membrane laminate (Figure 12). This compartment is then enclosed by a constant surface of a permeation-controlled polymeric membrane, either microporous or nonporous, for metering the rate of drug release from the system. It is exemplified by the scopolamine-releasing Transderm-V System and the nitroglycerin-releasing Transderm-Nitro System. Both products will be discussed by Dr. S. K. Chandrasekaran and by Dr. W. R. Good, respectively, in their chapters.

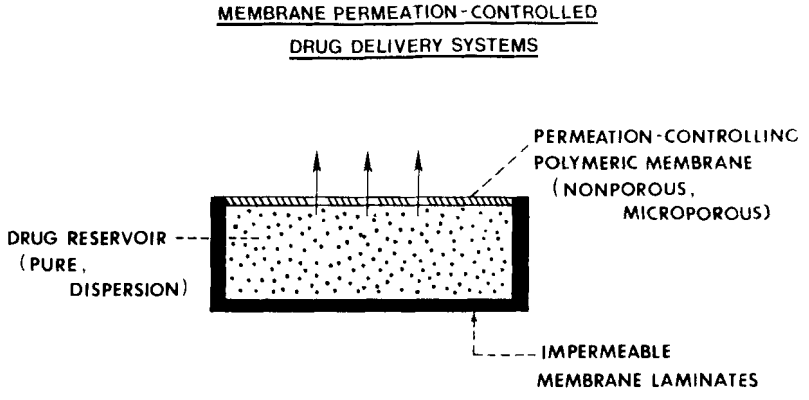


Figure 12

A sustained plasma nitroglycerin concentration profile can be achieved and maintained throughout the duration of twenty-four (24) hours with cutaneous application of one unit of Transderm-Nitro System on the chest of fourteen (14) human volunteers (Figure 13). The system has a surface area of 20 cm^2 with an in vitro release rate of 50 $\mu g/cm^2$ per hour and maintains a mean plasma level of 0.21 ± 0.16 ng/ml of nitroglycerin.(8)

2) Matrix diffusion-controlled drug delivery systems

This type of drug delivery system is manufactured by dispersing the solid drug particles in a diffusion-controlling matrix medium to form a drug reservoir. The drug reservoir is then encapsulated in a compartment walled by an impermeable membrane laminate (Figure 14). The compartment exposes a constant surface of medicated matrix to permit a continuous

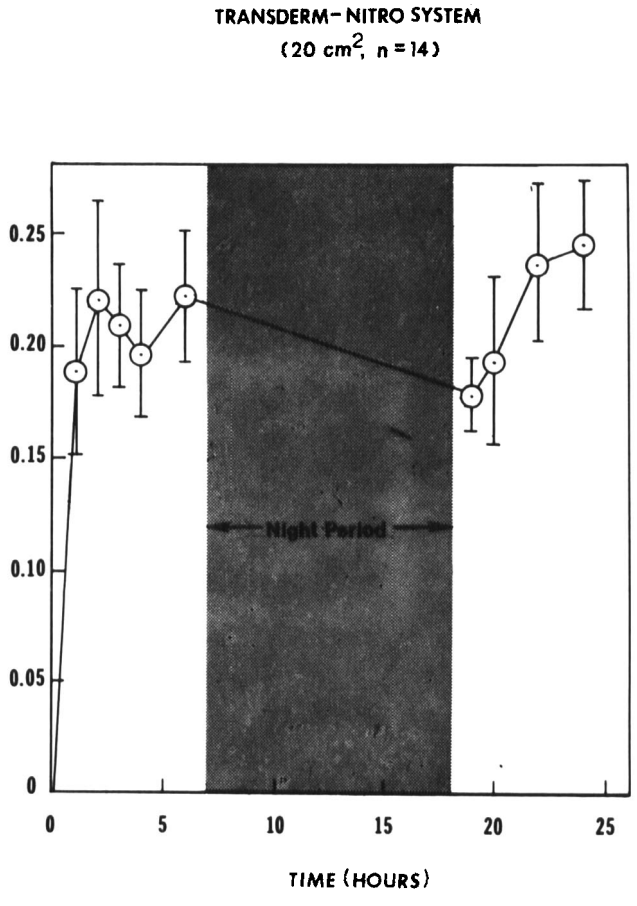


Figure 13

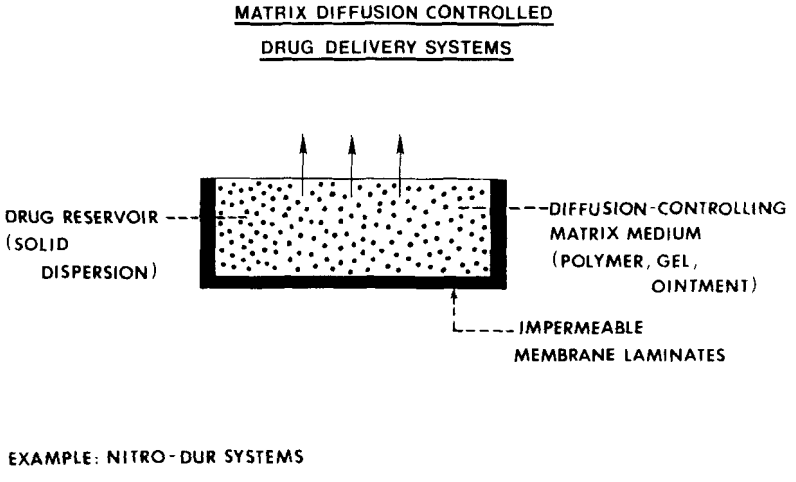


Figure 14

release of drug molecules from the diffusion-controlling matrix medium prepared from gel or polymer composition. It is exemplified by the development of nitroglycerin-releasing Nitro-Dur Transdermal Infusion System.(9)

Application of one 20 cm^2 unit of Nitro-Dur Transdermal Infusion System to the left upper chest of six (6) normal male volunteers was reported to produce a sustained plasma nitroglycerin concentration throughout the twenty-four (24) hour duration of medication (Figure 15). More detailed discussions can be found in Dr. A. Keith's chapter.

3) Microsealed Drug Delivery Systems

This type of drug delivery system is manufactured by homogenously dispersing the drug reservoir, a

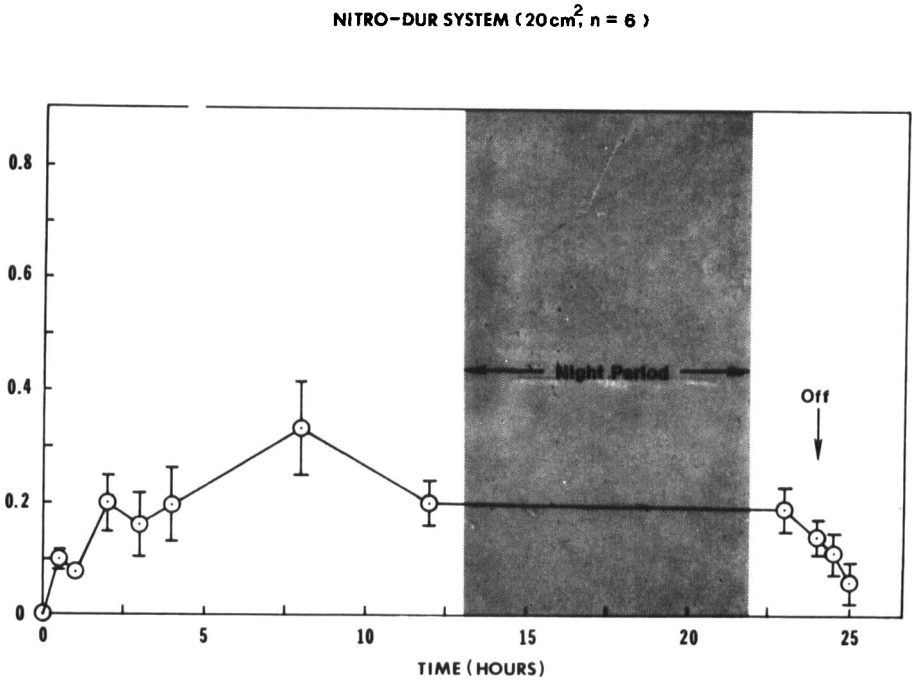


Figure 15

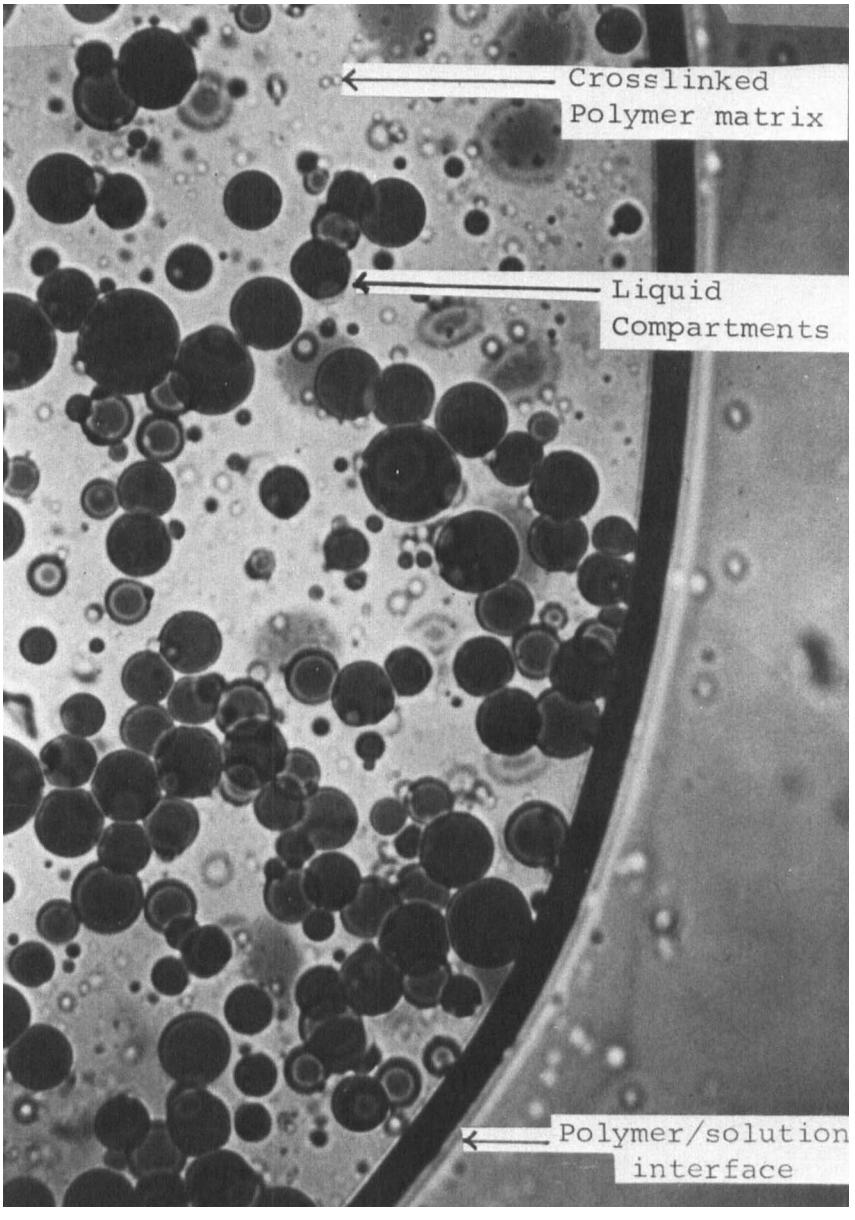
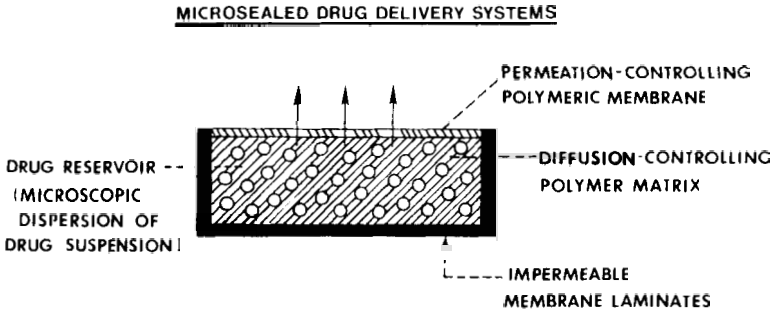


Figure 16



EXAMPLES: 1. Nitrodisc

2. Steroid - Releasing Transdermal Bandages

Figure 17

liquid suspension of solid drug particles in water-soluble liquid-type polymers, in a silicone elastomer before crosslinking the elastomer to form a stable dispersion of millions of unleachable microscopic liquid compartments of drug suspension in a solid polymer matrix (Figure 16). The medicated polymer matrix can be, depending upon the physicochemical properties and the desired release rates of the drug, molded into any shape of device walled with impermeable membrane laminates with an opening of a constant surface, which can be covered with a permeation-controlling polymeric membrane to provide an additional controlling step on the release of the drug molecules (Figure 17).

It is exemplified with the development of nitroglycerin-releasing Nitrodisc and steroid-releasing transdermal bandages. The clinical performance on maintaining a sustained therapeutic plasma level of nitroglycerin in humans over a thirty-two (32) hours duration of medication is illustrated in Figure 18. More discussions will be found in Dr. A. Karim's chapter.

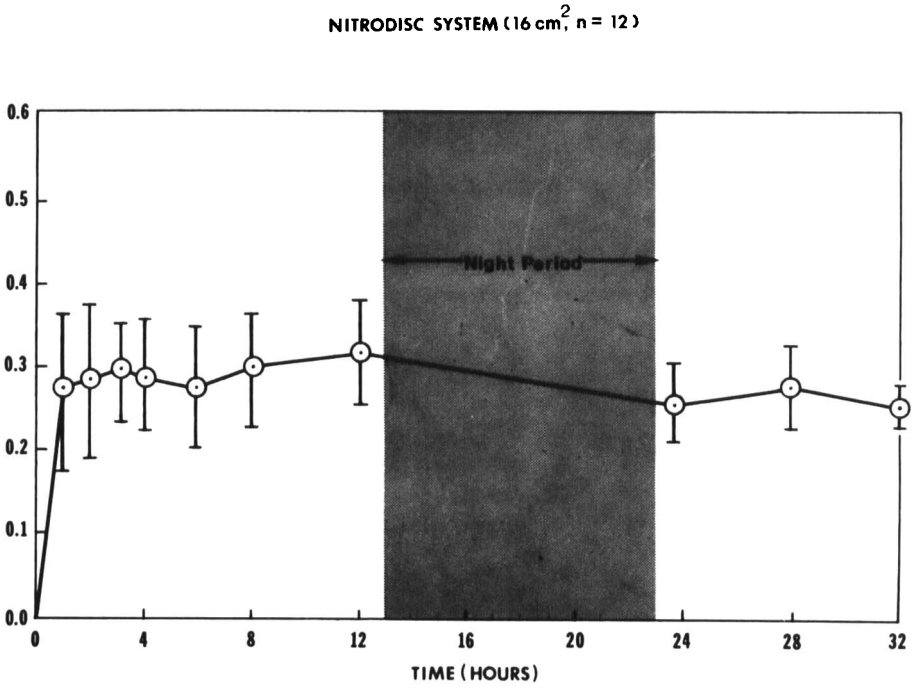


Figure 18

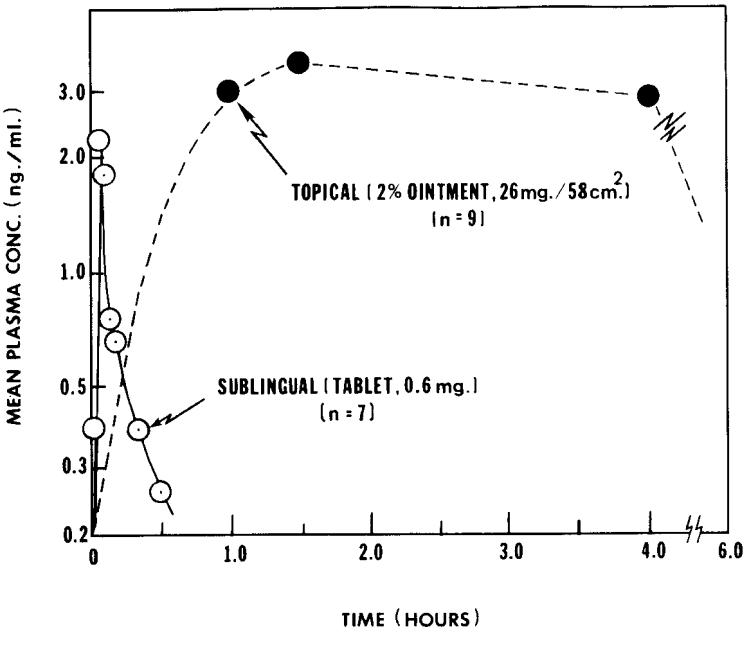


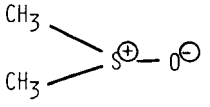
Figure 19

ENHANCEMENT OF TRANSDERMAL DRUG PERMEATION

SKIN PERMEATION PROMOTORS

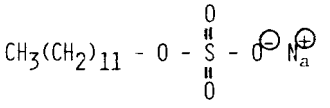
1) LIPOPHILIC SOLVENTS

e.g., DIMETHYLSULFOXIDE



2) SURFACE-ACTIVE AGENTS

e.g., SODIUM LAURYL SULFATE



3) NEW PENETRATION ENHANCER

e.g., AZONE

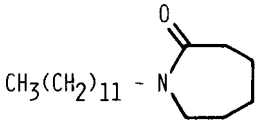


Figure 20

The sustained plasma nitroglycerin levels achieved by the daily applications of Transderm-Nitro, Nitro-Dur and Nitrodisc are very much similar. Apparently, these drug levels are much more prolonged than those maintained by topical application of 2 percent nitroglycerin ointment (four to six hours) and sublingual nitroglycerin tablets (Figure 19).[10, 11]

In conclusion, a well-designed transdermal controlled-release drug delivery system is expected to provide most of the benefits outlined as follows:

a) Bypass hepatic "first-pass" metabolism and gastrointestinal imcompatibility of drugs

b) Minimize inter- and intra-patient variations

c) Maintain steady drug concentration

d) Provide predictable, extented duration of drug action

e) Enhance therapeutic efficacy

f) Reduce frequency of drug dosing

g) Improve patient compliance

A number of solvents or agents have demonstrated the potential of promoting the permeation of different types of drugs through the skin tissues. Most of these skin permeation promotors have some common

structural features, as shown in Figure 20. Dr. W. O. McClure will discuss this area of research, Azone in particular, in his chapter.

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